Music and Surgery

The Effect of Perioperative Music on Patient Outcome and Surgical Performance

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Provided by thesis specialist Ridderprint, www.ridderprint.nl
Printing: Ridderprint
Layout and cover design: Dagmar van Schaik, persoonlijkproefschrift.nl

ISBN: 978-94-6416-889-1

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Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof. dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.
The public defence shall be held on April 13, 2022

At 3.30 pm
by

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Erasmus University Rotterdam

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"The professions music and surgery still often go hand in hand.
Both push manual skill to its limit; both mature with practice and age;
both depend on immediacy, precision and opposable thumbs."

Siddhartha Mukherjee on Theodor Billroth, the founding father
of abdominal surgery and an accomplished pianist and violist,
in *The Emperor of All Maladies: A Biography of Cancer*.

Music and Surgery: The Effect of Perioperative Music on Patient Outcome and Surgical Performance

Chapter 1

General Introduction and Outline of this Thesis

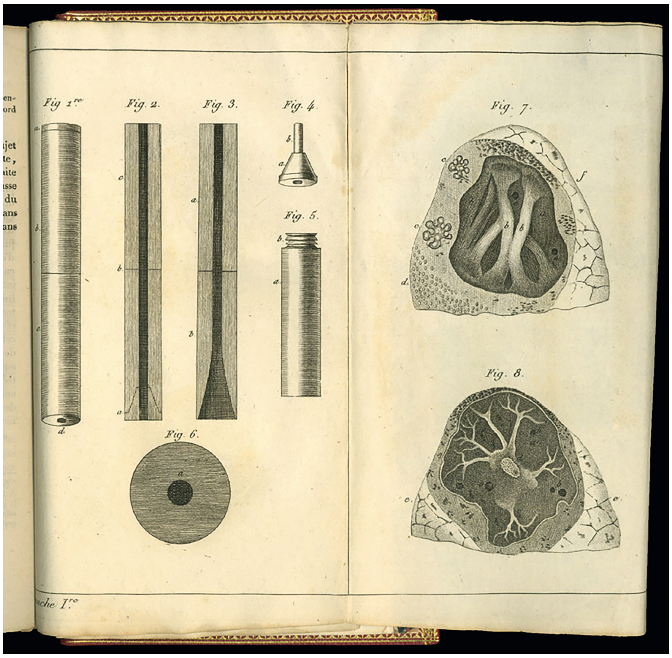
"Music is the universal language of mankind"

Henry Wadsworth Longfellow, 1835, poet.

Music as medicine throughout history

Music is universal among societies worldwide and has been part of our daily life since antiquity[1,2]. Different practical, theoretical and even philosophical definitions of music have been proposed. In general, music consists of vocal sound, instrumental sound, or both, containing the elements melody, harmony and rhythm. The concept of music as medicine dates back several millennia. Music therapy is described as a fundamental aspect of the Five-Element Theory of traditional Chinese medicine in Huangdi Neijing (黄帝内经, The Yellow Emperor's Classic of Medicine), an ancient Chinese medical textbook believed to have been written around 2600 BC[3]. In ancient Greece, prominent philosophers including Plato and Aristotle believed in the healing therapeutic effects of music, whilst Apollo is regarded as the Greek God of both music and medicine. In medieval Arab hospitals, music was employed in patient rooms to improve clinical outcome. Hence, music was a fundamental part of both society and medicine all over the world for centuries[4].

Figure 1.



Drawing of the Laennec stethoscope and lungs from 'De L'Auscultation Médiate' by René Laennec, 1819. Wikimedia Commons, Public Domain.

Musical knowledge has also shaped modern medicine. Josef Leopold Auenbrugger, an Austrian physician who was the first to describe percussion as a technique for examination of the chest, was also a gifted musician and composer[5]. He wrote the libretto for an opera by Antonio Salieri, and Joseph Haydn dedicated a set of six piano 'Auenbrugger sonatas' to his two daughters. The French physician René Laennec was an accomplished flutist[5]. This undoubtedly aided him in inventing the stethoscope, initially a mono-aural wooden hollow tube 25 centimetres long, which has forever changed modern medicine.

Perioperative music and patient care

The first report on the use of music in the operating room to benefit both patient and surgeon in modern times was published by Pennsylvanian surgeon Evan O'Neill Kane in JAMA in 1914[6]. He experienced surgery both as a surgeon and a patient by performing an auto-appendectomy in 1920, followed by performing an inguinal hernia repair on himself at the age of 70. Patients exposed to perioperative music were less anxious and better able to undergo anesthesia induction. Moreover, it was generally well-liked, with over 95% of patients desiring perioperative music[7].

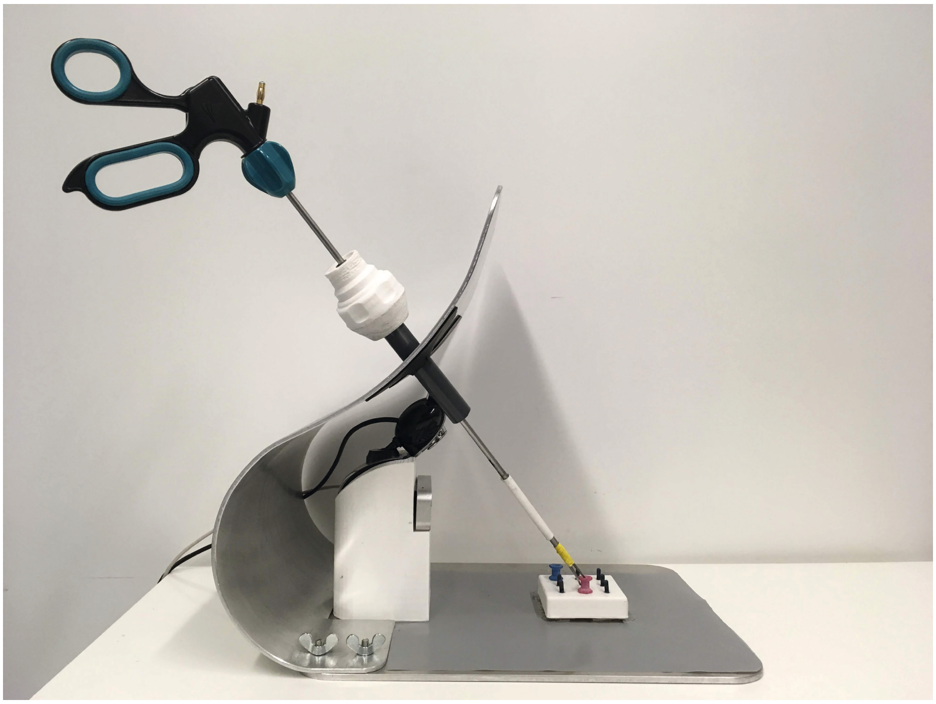
Current perioperative patient care consists of fast track recovery protocols, which emerged in the 1990's[8]. The most well-known are collectively bundled as the Enhanced Recovery After Surgery (ERAS) protocols, consisting predominantly of non-pharmacological, multidisciplinary interventions throughout the entire perioperative period. A wide range of surgical specialties have since embraced evidence-based fast track protocols for different surgical procedures by incorporating ERAS-specific components. The primary aim of current surgical patient care is to attenuate the physiological stress response to surgery, as a more vigorous response is associated with an increased postoperative complication rate[8-10]. Furthermore, reducing postoperative pain and lowering medication requirement are important aspects as well. Music has always been regarded as having a soothing, stress-reducing, therapeutic power. It can be provided through different methods, either as so-called music therapy or music medicine. Music therapy consists of an interactive process with the patient and requires a trained musical therapist, using patient-tailored and often improvised live music[11]. Not only is this relatively manpower intensive and therefore more expensive compared to music medicine, but reproducibility of the intervention is also not possible given that the intervention varies from patient to patient and day to day. Furthermore, the musical therapist may also influence the effect of music therapy. Music medicine on the other hand, as provided by Kane to surgical patients over a century ago[6], consists of recorded music[11], offered by using a music player. As an easily applicable, non-pharmacological intervention with no known adverse side effects that can be broadly used throughout the entire perioperative process, music medicine would in theory neatly fit into current surgical patient care.

Perioperative music and surgical performance

Stress during surgery can also affect the surgeon and surgical performance. The stress experienced by the surgeon in regard to performance can be evaluated by employing the theoretical concept of mental workload as a framework. Mental workload is defined as the amount of cognitive effort required to perform a specific task[12]. During surgery, mental workload is predominantly tasked by the cognitive effort needed for motor task execution and decision making[12]. If motor task demand increases during a technically difficult surgical procedure, mental workload can increase as well. Given that the total mental capacity available is more or less fixed during a specific moment[12], a higher workload leaves less spare cognitive capacity for decision making, potentially decreasing surgical performance. This does not necessarily mean that an increase in task demand automatically leads to a decrease in performance. A surgeon could compensate and reduce other stressors affecting mental workload; for example by turning off his pager, increasing availability of spare cognitive capacity, or involving an experienced surgical assistant, thereby easing cognitive attention for motor task execution[13]. Moreover, repetitive training can also reduce mental workload, as less cognitive attention is needed for motor execution[12].

Laparoscopic surgery has previously been identified as more taxing on mental workload compared to conventional open or robotic surgery[13,14]. A different skill set is required to perform laparoscopic surgery, due to the use of long surgical instruments and the fulcrum effect, two-dimensional screen visualization which can impair depth perception, and limited tactile feedback[15]. This has led to the rise of simulation-based training, as acquired competencies are seemingly transferable to the real world setting[16,17]. The simulated setting also allows for research. In the last decade, more attention has focused to reducing mental workload and stress, as they seem to correlate with surgical performance and patient outcome[13]. A range of subjective self-report questionnaires have been developed to measure mental workload[18]. The Surgery Task Load Index is a validated tool for the specific demands of surgery. A derivative of the NASA Task Load Index, the most widely used instrument assessing workload, it is easy in use and fast to fill out. Moreover, it assesses different domains, which have previously been identified as key surgical stressor domains[19]. Stress hormones levels in bodily fluids indicative of stress response activity are more difficult to collect and sometimes costly to analyse. Cardiovascular vital parameters as a measure for mental workload have led to assessment by using wearable devices, like chest straps, fingertip and earlobe sensors and smart watches[18]. Heart rate variability in particular has been identified as a potential accurate marker of surgical mental workload[18]. Defined as the variability between R waves in the electrocardiogram representing autonomic nervous system activity, a higher mental workload decreases heart rate variability. This has previously been associated with worse surgical performance[20,21]. However, the optimal method for measuring mental workload and stress is still unclear, and multiple methods may be used concurrently.

Figure 2. Custom made laparoscopic box trainer, used in the ENSEMBLE and OPTIMISE studies.



As noted over a century ago by Kane, the use of music reduced the need for the surgical team to continuously keep up conversation with the patient to keep the patient's mind of the surgical procedure[6]. As the surgeon could devote more attention to the surgical task, music was beneficial for surgical mental workload, although Kane did not use the exact phrasing. More famously, the reported so-called 'Mozart effect' showed that listening to music can be beneficial to spatial-temporal performance as well[22]. Therefore, perioperative music can potentially benefit both surgical patient outcome and surgical performance worldwide, as music is universal[1].

Music and surgery in recent years

In light of the previously described emergence of non-pharmacological interventions in order to benefit patients undergoing surgery, an increasing number of studies during the last decade have focused on perioperative music. Beneficial effects regarding postoperative pain and anxiety in patients undergoing surgery have been observed[23-25], as well as on analgetic medication requirement[26,27]. In the subsequent chapters of this thesis, these observations are placed in light of recent findings regarding perioperative music, their validity discussed, and the results projected in regard to use in daily perioperative practice.

In addition, the use of music in the operation room is further evaluated by encompassing surgical performance and the operation team.

Thesis outline

This thesis aims to evaluate the effect of perioperative music on the patient and the surgeon, using evidence-based medicine principles. The first part of this thesis focuses on the effect of perioperative music on patient outcome and recovery.

Chapter 2 is a systematic review and meta-analysis describing the effect of perioperative music on the physiological stress response to surgery.

Chapter 3 consists of a systematic review and meta-analysis of 55 randomized controlled trials on the effects of perioperative music on intraoperative sedative and postoperative opioid medication requirement in adult surgical patients, as well as its effect on length of stay.

Chapter 4 evaluates the effect of intraoperative auditory stimuli during general anaesthesia in surgical patients through a systematic review and meta-analysis of 53 randomized controlled trials in which patients, the surgical and operation room staff, as well as outcome assessors, are all blinded.

Chapter 5 is a randomized, placebo-controlled, multicentre double-blinded trial assessing whether intraoperative music during general anaesthesia can benefit postoperative recovery of esophageal and stomach cancer surgery patients.

Chapter 6 is a study protocol of a multicentre randomized controlled clinical trial evaluating the effect of perioperative music on postoperative delirium, recovery and self-sufficiency in elderly hip fracture surgery patients.

Chapter 7 contains a pilot study investigating implementation of perioperative music in day care surgery.

The second part of this thesis examines the effect of perioperative music on the surgeon and surgical performance.

Chapter 8 is a systematic literature review containing studies that have investigated the effects of music on surgical task performance.

Chapters 9 and 10 are two randomized crossover trials evaluating the effect of participant-selected music on mental workload and laparoscopic task performance in a simulated setting.

Chapter 11 consists of a systematic literature review on the effect of noise on both patient and surgeon. Also, the attitudes towards noise and music in the operation room are encompassed in this chapter.

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Part I

The Effect of Perioperative Music on Patient Outcome and Recovery

Chapter 2

The Effect of Perioperative Music on the Stress Response to Surgery: A Meta-analysis

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Journal of Surgical Research, 244: 444 – 455, 2019.

"The key pathogenic factor in postoperative morbidity, excluding failures of surgical and anaesthetic technique, is the surgical stress response with subsequent increased demands on organ function"

Henrik Kehlet, 1997, Professor of Surgery and founder of the Enhanced Recovery After Surgery protocols.

Abstract

Background: Current perioperative patient care aims to maintain homeostasis by attenuation of the stress response to surgery, as a more vigorous stress response can have detrimental effects on postoperative recovery. This systematic review and meta-analysis aims to assess the effect of perioperative music on the physiological stress response to surgery.

Methods: The Embase, Medline Ovid, Cochrane central, Web-of-science and Google Scholar databases were searched from inception date until February 5th, 2019, using a systematic literature search following the PRISMA guidelines for randomized controlled trials investigating the effect of music before, during and / or after surgery in adult surgical patients on the stress response to surgery. Meta-analysis was performed using a random effect model and pooled standardized mean differences were calculated with 95% confidence intervals. This study was registered in the PROSPERO database (CRD42018097060).

Results: The literature search identified 1076 articles. Eighteen studies (1301 patients) were included in the systematic review, of which eight were included in the meta-analysis. Perioperative music attenuated the neuroendocrine cortisol stress response to surgery (pooled SMD -0.30, [95% CI -0.53 to -0.07], $p = 0.01$, $I^2 = 0$).

Conclusion: Perioperative music can attenuate the neuroendocrine stress response to surgery.

Authorship

Each author certifies that he has made a direct and substantial contribution to the work reported in the manuscript. VF, PO and JJ contributed to study concept and design. VF, PO and DS collected the data. Analysis and interpretation of data was performed by all authors. Drafting of the manuscript was done by VF, PO, DS and JJ, with SB, RF and BW providing critical revisions that were important for the intellectual content. All authors approved the final version of the manuscript.

Abbreviation list

ACTH	Adrenocorticotropic hormone
CI	Confidence interval
ERAS	Enhanced recovery after surgery
HPA-axis	Hypothalamic-pituitary-adrenal axis
IgA	Immunoglobulin A
IL-6	Interleukin 6
PACU	Post Anaesthesia Care Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
RCT	Randomized controlled trial
SD	Standard deviation
SMD	Standardized Mean Difference
TNF-α	Tumor necrosis factor alpha

Introduction

The stress response to surgery is the adaptive physiological response of the body evoked by surgery leading to behavioral and physical adaptations[1]. The neuroendocrine stress response induces changes in metabolic activity through the sympathetic nervous system and hypothalamic-pituitary-adrenal axis (HPA-axis). The immune system is responsible for the inflammatory response through cytokines and other immunological mediators[2]. The activity of these systems can be assessed by measuring stress response hormones and cytokines in blood, urine and saliva[3]. An excessive or prolonged stress response to surgery can have negative metabolic, catabolic and cardiovascular consequences and has been associated with increased morbidity[2,4-7]. While the magnitude of the stress response will depend on the tissue trauma caused by the surgical procedure[8], many other factors can also modify it[9]. Therefore, perioperative care has recently focused on attempting to improve postoperative clinical outcome by attenuating the stress response to surgery using Enhanced Recovery After Surgery (ERAS) protocols[10,11], as well as the use of locoregional anesthesia[2,12].

Perioperative music has a significant beneficial effect on anxiety, postoperative pain and patient satisfaction[13-15]. This effect on pain can even be observed when the music intervention is solely applied intraoperatively during general anesthesia. The mechanism of action is unknown, but modulation of autonomic nervous system activity, the neurohormonal stress response and the immune system have all been proposed[13,16,17]. The aim of this systematic review and meta-analysis was to assess the effect of perioperative music on stress response biomarkers indicative for the stress response to surgery.

Methods

This systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and was registered with PROSPERO (CRD42018097060)[18,19].

Literature search strategy

A systematic literature search was performed with assistance of a biomedical information specialist on February 5th, 2019 with the keywords "music", "surgery", "stress response" and several stress response biomarkers, using the exhaustive literature search method[20]. The Embase, Medline Ovid, Cochrane central, Web-of-science and Google Scholar databases were searched. No time limit was used. The full search syntax is presented in Appendix A. In addition, manual cross-referencing of the included articles was performed.

Study screening and selection

Eligible studies were identified by three reviewers independently (VF, PO and DS). All papers identified by the literature search were screened by title and / or abstract and subsequently by screening of the full text if eligibility criteria were matched. Inclusion criteria for the systematic review were randomized controlled trials investigating the effect of recorded music before, during and / or after surgery in adult surgical patients ≥ 18 years old on the stress response to surgery by measuring stress response biomarker levels. Only full text, peer-reviewed published papers in the English language were included. Studies were excluded if the music intervention did not contain the elements melody, harmony and rhythm, if multiple, concomitant interventions were used, if live music with a musical therapist was investigated, or when the intervention consisted solely of nature sounds. Disagreements between the investigators were resolved through mutual discussion or by referring to the senior author (JJ).

Data extraction and quality assessment

Three reviewers (VF, PO and DS) independently extracted study characteristics and data. A custom, predesigned Microsoft Excel 2010 format was used. If data was only available in the form of plots or images, data was estimated using the online available data extraction software WebPlotDigitizer (version 4.1)[21]. This was done independently by two reviewers (VF and DS), with less than five percent interrater difference observed. Risk of bias was assessed independently using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials[22]. Disagreements between the investigators were resolved through mutual discussion or by referring to the senior author (JJ).

Statistical analysis

Data was analysed using OpenMeta-Analyst, an open-source R-based software[23]. Meta-analysis was performed using random effect models, since between study heterogeneity was assumed to be present as the participants, surgical procedures and music intervention varied in the included studies. Standardized mean differences were calculated with 95% confidence interval (CI). Studies were included for meta-analysis if stress response biomarkers were assessed before and after surgery and if the mean values and standard deviations were reported. If only medians were reported, these were used as an approximation of the mean. If interquartile ranges were reported, the width of the interquartile range was divided by 1.35 as an approximation of the standard deviation. If ranges were reported, the width of the range was divided by 4 as an approximation of the standard deviation[24]. Heterogeneity was analysed using the I^2-test. Statistical significance was inferred at p-value < 0.05. Studies were excluded from quantitative synthesis if the presented data could not be used for meta-analysis, if the stress response biomarkers differed significantly between the music and control group at baseline preoperatively, or if no preoperative baseline and only postoperative stress levels were presented.

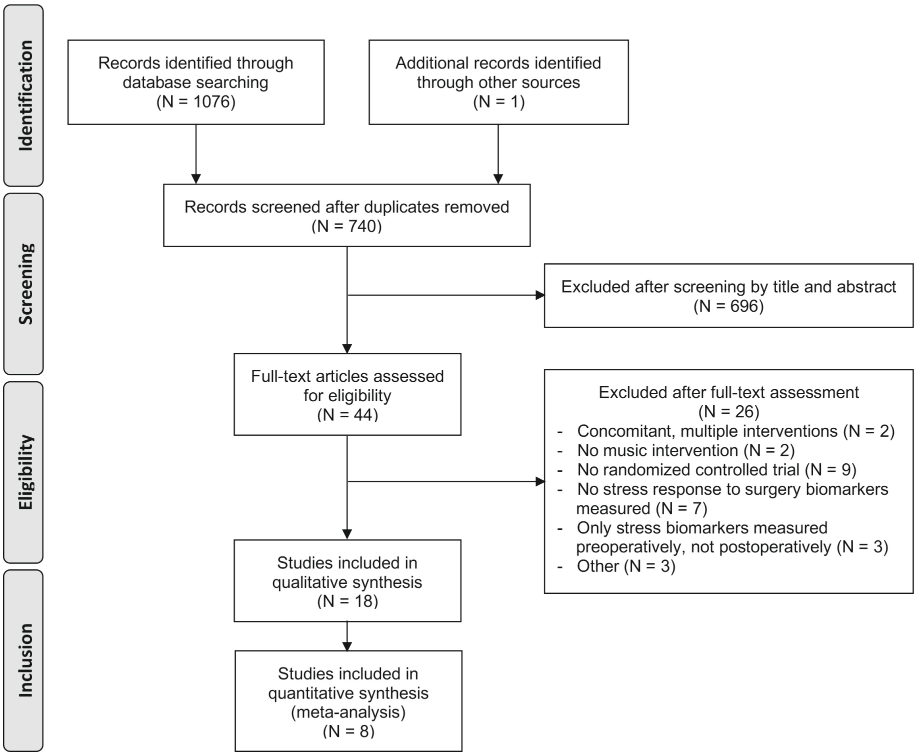
If studies included several music groups, the music group preferred for meta-analysis was the group that offered patients the choice to select from a preselected playlist, instead of the group with the patient's own favourite music or preselected music without patient choice, as this reportedly has the most beneficial effect[15]. If a study contained several music intervention groups based on the moment of music exposure (i.e. a study containing one group with only music exposure intraoperatively and one only postoperatively), the intraoperative music group would be preferred over the postoperative music group for meta-analysis. The beneficial effect has been observed to be larger when intraoperative compared to postoperative music was played[13]. Also, this allowed the largest number of studies to be pooled based on the moment of stress response measurement in the included studies, as stress response measured at the end of surgery cannot be used for meta-analysis if the postoperative music group is selected. Additionally, the means and standard deviations of the different music groups were pooled to an approximated mean and standard deviation in order to perform a separate meta-analysis. If studies included several control groups, data was used from the control group that represents current standard patient care. For example, if both a headphone without music group and a standard care group were presented as control groups in a study, the standard care group will be used for meta-analysis as the headphones without music can be seen as an intervention.

Results

The literature search yielded a total of 1076 articles and 740 remained after removal of duplicates. In addition, one full text publication of a conference abstract was retrieved through other sources[25]. There was a high percentage of interrater agreement of over 90 percent on exclusion and full-text screening of articles. Eighteen randomized controlled trials were included for qualitative synthesis (1301 patients: 689 in the music group and 612 in the control group) and eight of them were included in the meta-analysis (496 patients: 258 in the music group, 238 in the control group). The PRISMA flow diagram is presented in Figure 1.

2

Figure 1. PRISMA flow diagram



N = Number of studies

Study characteristics

Details of the study characteristics are presented in Table 1. The included studies contained a wide range of surgical procedures, varying from minor day care surgery to major surgery requiring postoperative intensive care stay. General anaesthesia was used in eight[25-32] and locoregional anaesthesia in eight studies[33-40]. One study contained different surgical procedures with different anaesthesia methods[41], while another did not specify the anaesthesia method used[42]. The music intervention varied in duration, moment of the intervention in relation to the surgical procedure and the selected music pieces. It was often not specified, but described as soft, soothing and relaxing. In one study, participating patients were allowed to bring their own music[32]. In all other studies, music selected by the research team was used. In five of these studies, patients were offered the possibility to choose music from a preselected list[28,36,37,42,40]. Music delivery was achieved in a majority of the studies through headphones (11 studies, 61%) or a music pillow (three studies, 17%)[27,30,31]. Most studies had a control group consisting of standard patient care (ten studies, 56%) or headphones without music (five studies, 28%), with one study having both[37].

Table 1. Study characteristics

Study	Surgical procedure	Anesthesia	Intervention	Moment	Music duration	N_M	Control	N_C	Outcome parameters
Conrad, 2007	Major pulmonary, abdominal, aortic and polytrauma surgery requiring ICU stay	General	Classical music (Mozart piano sonatas)	Postoperatively	60 min.	5	Headphones without music	5	Serum ACTH, cortisol, catecholamines, IL-6, prolactin
Finlay, 2016	Total knee arthroplasty	Spinal	32 tracks of pop, classical, jazz, folk and ethnic music	Postoperatively	15 min.	72	Headphones without music	17	Salivary cortisol
Graversen and Sommer, 2013[‡]	Laparoscopic cholecystectomy	General	Musicure using music pillow	Preoperatively Intraoperatively Postoperatively	Before surgery start until day care discharge	40	Standard care	35	Serum cortisol Serum CRP
Hepp, 2018	Primary caesarean section	Regional	Choice of 60 tracks of jazz, lounge, classical, meditation music	Intraoperatively	Procedure duration	154	Standard care	150	Salivary cortisol Salivary alpha-amylase
Jiménez-Jiménez, 2013	Varicose vein crossectomy with great saphenous vein stripping	Spinal	Classical music (Symphony no. 3 by Henryk Gorecki)	Intraoperatively	Procedure duration	20	Standard care	20	Plasma catecholamines Postoperative complications
Kar, 2015	Elective cardiac surgery under cardiopulmonary bypass	General	Raga Darbari (Indian classical music)	Preoperatively Intraoperatively	30 min. before surgery and procedure duration	17	Headphones without music	17	Serum cortisol levels

Table 1. Continued.

Study	Surgical procedure	Anesthesia	Intervention	Moment	Music duration	N_M	Control	N_C	Outcome parameters
Koelsch, 2011[‡]	Total hip arthroplasty	Spinal with propofol sedation	Joyful instrumental music	Preoperatively Intraoperatively	120 min. before surgery and procedure duration	20	Headphones with breaking sea waves	20	Serum ACTH Serum cortisol Serum IgA
Leardi, 2007[‡]	Day care surgery	Epidural or local	Relaxing new age music	Preoperatively Intraoperatively	60 min. before surgery and procedure duration	20	Standard care	20	Serum cortisol Natural killer lymphocytes
			Choice of country classical, pop, jazz			20			
Liang, 2017	*Not specified*	Spinal	Choice of hypnotic music list	Intraoperatively	Procedure duration	30	Standard care	30	Salivary cortisol
Lin, 2011	Elective spinal surgery	*Not specified*	Choice of pop, classical or sacred soft melody, Chinese music	Preoperatively Postoperatively	30 min. before and 90 min. after surgery	30	Bed rest	30	Urinary catecholamines Urinary cortisol
McRee, 2003[‡]	Different surgical procedures in "low risk" surgical patients	General, spinal, local and regional	Soft piano music	Preoperatively	30 min.	13	Standard care	13	Serum cortisol Serum prolactin
Migneault, 2004[‡]	Abdominal hysterectomy or (hystero)salpingo-oophorectomy	General	Choice of jazz, classical, new-age, popular piano music	Intraoperatively	Procedure duration	15	Headphones without music	15	Plasma ACTH Plasma catecholamines Plasma cortisol

2

Table 1. Continued.

Study	Surgical procedure	Anesthesia	Intervention	Moment	Music duration	N_M	Control	N_C	Outcome parameters
Nilsson, 2005‡	Open hernia repair (Lichtenstein)	General	Soft, relaxing, new age synthesizer melodies	Intraoperatively	Procedure duration	25	Standard care	25	Serum cortisol Serum IgA
				Postoperatively	60 min. after PACU arrival	25			
Nilsson, 2009a	Coronary artery bypass graft and/ or aortic valve replacement	General	Musicure using music pillow	Postoperatively	30 min. on postoperative day 1	20	Standard care	20	Serum oxytocin
Nilsson, 2009b	Coronary artery bypass graft or aortic valve replacement	General	Soft, relaxing, new age style music using music pillow	Postoperatively	30 min. on postoperative day 1	28	Standard care	30	Serum cortisol
Tabrizi, 2012‡	Urological or abdominal surgery	Spinal	Choice of relaxing Bach pieces	Intraoperatively	Procedure duration	30	Headphones without music	30	Serum cortisol
							Standard care	30	
Zengin, 2013‡	Port catheter placement	Local	'Acemişiran' (Turkish classical music)	Intraoperatively	Procedure duration	50	Standard care	50	Serum ACTH Serum cortisol

Table 1. Continued.

Study	Surgical procedure	Anesthesia	Intervention	Moment	Music duration	N_M	Control	N_C	Outcome parameters
Zhang, 2005	Total abdominal hysterectomy	General	Own choice	Intraoperatively	Procedure duration	55	Headphones without music	55	Serum IL-6

Table 1 legend: N_M = Number of patients in music intervention group; N_C = Number of patients in control group; ICU = Intensive Care Unit; min. = minutes; ACTH = Adrenocorticotropic hormone; IL-6 = Interleukin-6; IgA = Immunoglobulin A; ‡ = study included in meta-analysis
Conrad *et al*. (2007): surgical procedures included pneumonectomy and pulmonary wedge resection, esophagectomy, hemicolectomy, small bowel fistula and aortic graft surgery.
Finlay *et al*. (2016): four music intervention groups, with music differing in harmony and rhythmic music elements.
Leardi *et al*. (2007): surgical procedures included inguinal hernia repair with mesh, saphenous vein stripping, lateral internal sphincterectomy, carpal ligament incision and fracture stabilization surgery.
McRee *et al*. (2003): surgical procedures included cholecystectomy, hysterectomy, Hickman catheter placement, cystoscopy, orthopedic hardware removal and lipoma excision with different anesthesia methods.

Table 2. Risk of bias assessment

Study	Method of randomization	Allocation concealment	Blinding participants	Blinding surgical staff	Blinding assessors	Incomplete outcome addressed	Selective reporting	Other bias adequately addressed
Conrad, 2007	Unclear, not specified ('Randomized')	Unclear	No	Yes	Yes	Unclear, not specified	Unclear	Surgery duration and baseline stress response not specified.
Finlay, 2016	Unclear, computer-generated, pseudo-random numerical stratified schedule	Unclear	No	Yes	Yes	No, only 63.27% of participants provided cortisol samples	Unclear	Surgery duration and baseline stress response not specified.
Graversen and Sommer, 2013	Randomization by day by picking an envelope	No	No	No	Yes	Yes, exclusions unrelated to music intervention	Yes	Yes
Hepp, 2018	Computer-assisted randomization	Yes	No	No	Yes	Yes	Yes	Yes
Jiménez-Jiménez, 2013	Computer-generated randomized, 4-person block number sequence	Yes	No	No	Yes	Yes	Unclear	Surgery duration and baseline stress response not specified.
Kar, 2015	Computer-generated randomization chart	Yes	No	Yes	Yes	Yes	Unclear	Significant difference in baseline cortisol levels
Koelsch, 2011	Randomly chosen, identical looking mp3 player	Yes	No	Yes	Yes	No, 10/50 patients excluded due to study protocol deviation	Unclear	Surgery duration not specified
Leardi, 2007	List of randomized numbers	Unclear	No	No	Yes	Yes	Unclear	Yes
Liang, 2017	Not specified ('Randomly')	Unclear	No	No	Yes	Unclear	Unclear	Surgery duration not specified

Table 2. Continued.

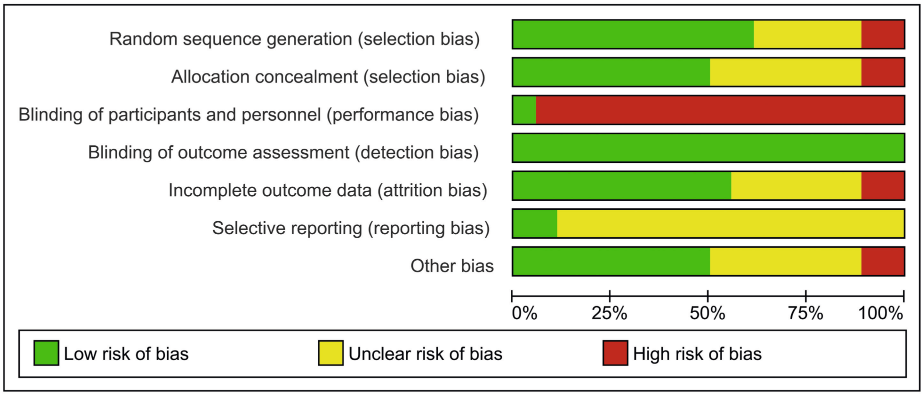
Study	Method of randomization	Allocation concealment	Blinding participants	Blinding surgical staff	Blinding assessors	Incomplete outcome addressed	Selective reporting	Other bias adequately addressed
Lin, 2011	Day of the week	No	No	No	Yes	Yes	Unclear	Surgery duration not specified
McRee, 2003	Drawing lots	Unclear	No	No	Yes	Unclear	Unclear	Surgery duration not specified
Migneault, 2004	Not specified ('Randomly assigned')	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes
Nilsson, 2005	Computer-generated randomization list	Yes	No	Yes	Yes	Unclear	Unclear	Yes
Nilsson, 2009a	Computer-generated randomization list	Yes	No	No	Yes	Yes	Unclear	Significant difference in surgery duration and oxytocin baseline levels
Nilsson, 2009b	Computer-generated randomization list	Yes	No	No	Yes	Yes	Unclear	Yes
Tabrizi, 2012	Not specified ('Randomly divided')	Unclear	No	No	Yes	Unclear	Unclear	Yes
Zengin, 2013	Computer-generated random numbers	Yes	No	No	Yes	Yes	Unclear	Yes
Zhang, 2005	Computer-generated randomization list	Yes	No	Yes	Yes	Yes	Unclear	Yes

Table 2 legend: Yes = Yes, low risk of bias; No = No, high risk of bias; Unclear = Unclear risk of bias

Risk of bias assessment

A summary of the risk of bias assessment can be found in Figure 2. A detailed description can be found in Table 2. Several studies provided insufficient details to assess all quality domains. In 5 studies (28%), the exact randomization method was not specified[26,28,33,36,37]. Risk of performance bias was high, as it is difficult to achieve adequate blinding to the music intervention. Blinding of participants is only possible if the music intervention is done solely intraoperatively during general anaesthesia. Blinding of personnel is possible if all participating patients in the music intervention and control group wear headphones. However, it is difficult to keep personnel blinded to the group assignment in practice, if patients for example request the music volume or track to be changed. One study (5.6%) employed a design in which participants, personnel and outcome assessors were all blinded[28]. In seven studies (39%), measures were taken to blind the surgical team and nursing staff[25,26,28,29,32,33,35]. Detection bias was low, as it is highly unlikely that stress response biomarker levels would be influenced even if the outcome assessor was not adequately blinded. Studies were classified as high risk of bias in the 'other risk of bias' category if there was a significant difference in surgery duration or baseline stress response levels between the music intervention and control group. If surgery duration or baseline stress response levels were not reported, the category 'other bias' was classified as unclear. Two studies (11%) had a significant difference in baseline stress response levels, even though a computer-generated randomization sequence was used[25,30]. Publication bias was not assessed, as less than ten studies were included in the meta-analysis.

Figure 2. Summary Risk of Bias



Neuroendocrine stress response to surgery

Fifteen studies assessed the effect of perioperative music on the neuroendocrine stress response to surgery by measuring cortisol. Cortisol levels were generally assessed on three moments: before anaesthesia induction (Cortisol 1, baseline), during skin closure at the end of surgery (Cortisol 2), and postoperatively in the Post Anaesthesia Care Unit (PACU) or surgical ward (Cortisol 3) (Table 3). Cortisol levels did not differ significantly between the music and control group at baseline (8 RCT's, pooled SMD 0.03, [95% CI -0.17 to 0.22], $p = 0.79$, $I^2 = 0$, N = 421 patients). Perioperative music exposure did not lead to a statistically significant difference in cortisol levels measured at the end of surgery (5 RCT's, pooled SMD -0.14, [95% CI -0.57 to 0.28], $p = 0.50$, $I^2 = 60.15$, N = 246 patients), but led to significantly lower cortisol levels postoperatively in the music group compared to the control group (6 RCT's, pooled SMD -0.30, [95% CI -0.53 to -0.07], $p = 0.01$, $I^2 = 0$, N = 295 patients) (Figure 3). For meta-analysis, the group in which patients could choose from a preselected playlist in the study of Leardi *et al.* (2007) and the intraoperative music group of Nilsson *et al.* (2005) were used.

Table 3. Neuroendocrine cortisol stress response assessment moment and analyzation method

Study	Analyzation method	Assessment moment cortisol 1	Assessment moment cortisol 2	Assessment moment cortisol 3
Graversen and Sommer, 2013	*Not specified*	Before start of surgery		2 hours after surgery
Koelsch, 2011	Enzyme-linked immunosorbent assay	2 hours prior to start of surgery	End of surgery	3 hours after surgery
Leardi, 2007	Fluoroimmunoassay	Before start of surgery		3 hours after surgery
McRee, 2003	Chemiluminescence immunoassay	Before start of surgery	End of surgery	
Migneault, 2004	Chemiluminescence immunoassay	Preoperatively during arterial line insertion	End of surgery	30 min. after PACU arrival
Nilsson, 2005	Radioimmunoassay	30 min. before anesthesia induction	End of surgery	2 hours after PACU arrival
Tabrizi, 2012	Enzyme-linked immunosorbent assay	30 min. before start of surgery		30 min. after surgery
Zengin, 2013	*Not specified*	Operating room arrival	End of surgery	

Table 3 legend: min. = minutes; PACU = Post Anesthesia Care Unit

When the approximated results of the different music groups of these two studies were pooled and used for meta-analysis, cortisol levels were still significantly lower postoperatively in the music group compared to the control group (6 RCT's, pooled SMD -0.27, [95% CI -0.49 to -0.05], $p = 0.01$, $I^2 = 0$, N = 340 patients) (Figure 4). Four studies that all observed a statistically significant attenuation of cortisol levels when comparing the music and control group were excluded from meta-analysis because no means were reported[26], baseline levels differed significantly between groups[25] or the moment of stress response measurement did not allow data to be pooled[31,42]. Three studies assessed the effect of perioperative music on salivary cortisol levels. While the data could not be pooled because of the way it was presented, all reported a statistically significant attenuation in the music group[33,40,36].

The effect of perioperative music on adrenocorticotropic hormone (ACTH) levels was assessed in four studies, of which three could be included for meta-analysis. ACTH levels did not differ at baseline (3 RCT's, pooled SMD 0.08, [95% CI -0.31 to 0.46], $p = 0.70$, $I^2 = 31.07$, N = 170 patients). Perioperative music did not lead to a change in ACTH levels at the end of surgery (3 RCT's, pooled SMD -0.24, [95% CI -0.89 to 0.42], $p = 0.48$, $I^2 = 74.24$, N = 170 patients) or postoperatively (2 RCT's, pooled SMD -0.26, [95% CI -0.73 to 0.21], $p = 0.28$, $I^2 = 0$, N = 70 patients).

In four studies (140 patients), the effect of music on catecholamine levels was assessed. Increase in catecholamine levels during elective varicose vein crossectomy surgery was significantly lower when music was played[34], while epinephrine levels decreased by an average of 55% after music exposure solely postoperatively on the intensive care in another study[26]. No significant difference in catecholamine levels was observed in 24 hours urine analysis[42], nor when music was played solely intraoperatively during general anaesthesia[28]. Perioperative music did not influence prolactin levels[26,41], while it significantly increased oxytocine levels[30].

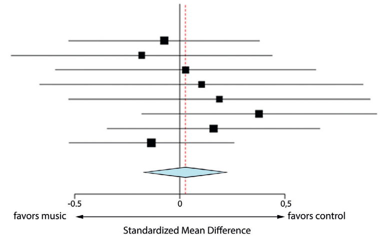
Inflammatory stress response

The effect of perioperative music on the inflammatory stress response was assessed in 6 studies by measuring different markers. Serum interleukin-6 (IL-6) levels were measured in two studies, but the reported outcomes could not be pooled for meta-analysis as no means and standard deviations were reported. In one study, IL-6 levels decreased statistically significantly with 83% after patients were exposed to postoperative music on the intensive care[26]. Zhang *et al.* (2005) reported that IL-6 levels were lower at the end of surgery compared to preoperative baseline values, but this was not significantly different compared to the control group[32]. Perioperative music did not influence serum immunoglobulin A (IgA) levels in the music intervention group (2 RCT's, pooled SMD 0.15 [95% CI -0.27 to 0.56], $p = 0.49$, $I^2 = 0$, N = 90 patients)[29,35], nor did it influence serum C-reactive protein (CRP) levels assessed two hours after surgery[27] or levels of natural killer lymphocytes three hours after surgery[39].

Figure 3. Summary forest plot for the neuroendocrine cortisol response to surgery

Cortisol 1: Baseline

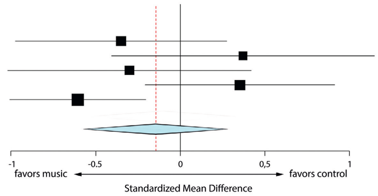
Study	N	Music Mean	SD	N_M	Control Mean	SD	N_C
Graversen and Sommer, 2013	75	428.5	207.6	40	443.5	185.8	35
Koelsch, 2011	40	387.1	119.0	20	416.8	192.5	20
Leardi, 2007	40	14.84	3.64	20	14.73	4.39	20
McRee, 2003	26	16.1	8.09	13	15.2	8.91	13
Migneault, 2004	30	383	181	15	351	148	15
Nilsson, 2005	50	548	213	25	480	134	25
Tabrizi, 2012	60	33.43	16.72	30	30.75	16.47	30
Zengin, 2013	100	16.44	4.24	50	16.95	3.16	50
Total	**421**			**213**			**208**



Pooled SMD 0.03 [95% CI -0.17 to 0.22], *p*=0.79, I^2=0

Cortisol 2: End of surgery

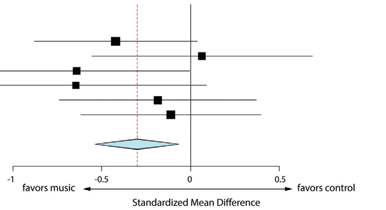
Study	N	Music Mean	SD	N_M	Control Mean	SD	N_C
Koelsch, 2011	40	285.3	189.0	20	363.6	245.1	20
McRee, 2003	26	21.99	19.42	13	14.70	18.72	13
Migneault, 2004	30	817	199	15	871	147	15
Nilsson, 2005	50	471.4	223.8	25	390.0	231.1	25
Zengin, 2013	100	14.02	4.01	50	16.36	3.64	50
Total	**246**			**123**			**123**



Pooled SMD -0.14 [95% CI -0.57 to 0.28], *p*=0.50, I^2=60.15

Cortisol 3: Postoperatively

Study	N	Music Mean	SD	N_M	Control Mean	SD	N_C
Graversen and Sommer, 2013	75	348.0	376.7	40	512.0	395.1	35
Koelsch, 2011	40	615.7	259.1	20	593.7	385.1	20
Leardi, 2007	40	8.63	2.72	20	12.08	6.96	20
Migneault, 2004	30	903	204	15	1050	239	15
Nilsson, 2005	50	300.6	207.0	25	343.6	229.3	25
Tabrizi, 2012	60	33.61	18.5	30	35.57	16.44	30
Total	**295**			**150**			**145**



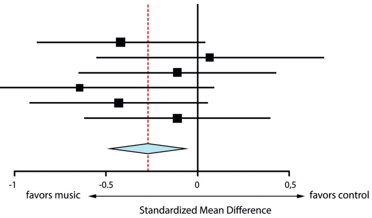
Pooled SMD -0.30 [95% CI -0.53 to -0.07], *p*=0.01, I^2=0

Figure 3 legend. Pooled standardized mean difference with 95 percent confidence intervals of cortisol values at baseline, end of surgery and postoperatively.
N = number of total patients in study; N_M = number of patients in the music group; N_C = number of patients in the control group; Mean = mean cortisol level; SD = standard deviation of cortisol level; SMD = standardized mean difference; CI = confidence interval

Figure 4. Summary forest plot for the neuroendocrine cortisol response to surgery with multiple music study arms.

Cortisol 3: Postoperatively (pooled approximated results of multiple music study arms)

Study	N	Music Mean	SD	N_M	Control Mean	SD	N_C
Graversen and Sommer, 2013	75	348.0	376.7	40	512.0	395.1	35
Koelsch, 2011	40	615.7	259.1	20	593.7	385.1	20
Leardi, 2007	60	11.42	5.284	40	12.08	6.96	20
Migneault, 2004	30	903	204	15	1050	239	15
Nilsson, 2005	75	261.1	167.6	50	343.6	229.3	25
Tabrizi, 2012	60	33.61	18.5	30	35.57	16.44	30
Total	**340**			**195**			**145**



Pooled SMD -0.27 [95% CI -0.49 to -0.05], *p*=0.01, I^2=0

Figure 4 legend. Pooled standardized mean difference with 95 percent confidence intervals of cortisol values postoperativel, the cortisol values of multiple music study arms of Leardi *et al.* (2007) and Nilsson *et al.* (2005) have been pooled to an approximated mean and standard deviation.
N = number of total patients in study; N_M = number of patients in the music group; N_C = number of patients in the control group; Mean = mean cortisol level; SD = standard deviation of cortisol level; SMD = standardized mean difference; CI = confidence interval

Discussion

Current perioperative care aims to maintain the homeostasis of the body by attenuation of the stress response, as there is increasing evidence that a more vigorous response may be detrimental for postoperative recovery[2,43,9]. This systematic review and meta-analysis is the first to assess the effect of perioperative music on the stress response to surgery. Our results indicate that perioperative music attenuates the neuroendocrine stress response to surgery, as postoperative cortisol levels were significantly lower when patients were exposed to music. Higher cortisol levels leading to insulin resistance and hyperglycemia negatively correlate with wound healing speed and increase the risk of wound infection[44,45]. Furthermore, it has been incriminated in the development of postoperative delirium, postoperative cognitive dysfunction and memory impairment[5,46-49]. High noise levels are common in the operating room and are recognized as a harmful stressor that can lead to higher cortisol levels and wound infection rates[50-52]. Therefore, some might argue that part of the beneficial observed effect might be due to noise reduction by the headphones. However, several included studies had a headphone without music group acting as a control. In one study with three patient groups, cortisol levels increased significantly compared to preoperative levels in both the standard patient care group and headphone without music group, while cortisol levels did not increase in the music group[37]. While no effect of music was found on plasma ACTH levels, it should be noted that ACTH is released in a pulsatile fashion and net changes in overall ACTH production cannot be detected with only a few measurements as performed in the three studies in this meta-analysis[53].

Music might also influence the inflammatory stress response to surgery[26]. In healthy participants exposed to 20 minutes of classical music, IL-6 levels were significantly lower when compared to participants resting in silence[54]. Preliminary presented results of a double-blind study in laparoscopic cholecystectomy patients suggest that intraoperative music attenuates IL-6 and TNF-α responses[55]. Higher postoperative IL-6 levels have been associated with the occurrence of postoperative pulmonary complications and a longer hospital length of stay[6,7,56]. Although Zhang *et al.* (2005) did not report a significant difference, this might be due to moment of interleukin levels assessment being too early and before a peak rise in IL-6 levels could occur[32,8,57]. IL-6 is an important stimulus for cortisol production in the systematic inflammatory response and may partly explain the attenuation of the cortisol response[58].

The clinical implications of our findings are unclear. Our original literature search included the effect of perioperative music on postoperative complications and clinical outcome, which none of the included studies adequately assessed. In one study, it was only mentioned that the ratio of complications was insignificant in both groups after crossectomy with striping of the greater saphenous vein, without further details[34]. The lack of studies assessing the effect on postoperative complications is in line with an earlier meta-analysis by Hole *et al.* (2015), in which no included studies reported wound infection or serious adverse event rates.

Strong points of this meta-analysis were the conducted exhaustive literature search using well-defined variables. Moreover, a predefined definition of what was considered as a music intervention was used, while studies involving live music, a musical therapist and solely nature sounds were excluded. However, this meta-analysis also has several limitations and results should therefore be interpreted with some caution. Most included studies in the meta-analysis had a relatively small number of patients. The patients, surgical procedures, anesthesia method used and perioperative care offered differed substantially and these factors can affect the stress response to surgery. It is therefore unclear whether music could attenuate the stress response to surgery during all operations. Because of the limited number of studies included in the meta-analysis, a dose-response analysis, comparison between the use of general versus locoregional anaesthesia, and whether the patient's own music is more beneficial than preselected music by the research team could not be assessed. Serum cortisol in the included studies was measured using different immunoassay methods. Direct comparison of plasma cortisol levels obtained with different immunoassays should preferably be avoided as they have different reference ranges and cut-off levels[59,60]. Therefore, no absolute mean cortisol reduction was calculated. The authors of the included studies did not substantiate the chosen moments in their study to measure the stress response. Khoo *et al*. (2017) observed that peak cortisol levels were observed at two, four and eight hours for minor, moderate and major surgical procedures, respectively[61]. In our meta-analysis, cortisol levels were all measured within three hours of surgery ending, while only four of the eight studies contained minor surgical procedures. As peak cortisol levels would not yet be reached, it could be that our results do not reflect the full beneficial effect of perioperative music on the stress response to surgery.

In recent years, newly developments in surgical patient care have attempted to modify the physiological stress response to surgery in order to improve patient outcome, with the most well-known being the ERAS protocols. While perioperative music seems to attenuate the neurohormonal stress response to surgery, the clinical implications are not yet totally clear as the occurrence of postoperative complications and clinical outcome were not adequately assessed. Further research should focus on the effect of perioperative music on postoperative complications, clinical outcome and recovery.

Conclusion

Perioperative music can attenuate the physiological, neuroendocrine stress response to surgery. As none of the included studies assessed postoperative complications or patient outcome, the clinical implications are not yet totally clear.

Author Disclosure Statement

No external funding was received for this study. The authors declare no conflicts of interest.

Acknowledgements

The authors would like to thank W. Bramer, biomedical information specialist at the Medical Library of the Erasmus University Medical Centre, for his aid and expertise with the literature search.

Appendix A. Literature search

Database	Years of Coverage	Before deduplication	After deduplication
Embase.com	1971 – February 5, 2019	347	365
Medline Ovid	1946 – February 5, 2019	178	51
Web of Science	1900 – February 5, 2019	237	140
Cochrane Central	1992 – February 5, 2019	87	20
Google Scholar	Not applicable	200	56
Total		**1076**	**740**

Embase.com
(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 'surgical stress'/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) AND (stress/de OR 'surgical stress'/de OR 'cytokine'/de OR 'interleukin 8'/de OR 'interleukin 6'/de OR 'interleukin 1'/de OR 'tumor necrosis factor'/de OR 'hydrocortisone'/de OR 'hydrocortisone blood level'/de OR corticotropin/de OR 'growth hormone'/de OR 'growth hormone blood level'/de OR 'prolactin'/de OR 'prolactin blood level'/de OR 'blood level'/exp OR 'saliva level'/de OR 'urine level'/exp OR 'urinalysis'/exp OR 'blood analysis'/exp OR (stress OR interleukin-6 OR il-6 OR interleukin-8 OR il-8 OR interleukin-1 OR il-1 OR cytokine* OR 'tumor necrosis factor' OR tnf OR cortisol* OR hydrocortison* OR corticotropin* OR adrenocorticotrop* OR adrenocorticaltrop* OR ACTH OR 'growth hormone*' OR prolactin* OR ((blood OR serum OR saliva* OR urin*) NEAR/3 (level OR concentrat* OR analy* OR value*)) OR urinalys*):ab,ti)

Medline Ovid
(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.) AND (Stress, Physiological/ OR Cytokines/ OR Interleukin-8/ OR Interleukin-6/ OR Interleukin-1/

OR exp Tumor Necrosis Factor-alpha/ OR Hydrocortisone/ OR Adrenocorticotropic Hormone/OR exp Growth Hormone/ OR exp Prolactin/ OR blood.fs. OR exp Urinalysis/ OR Hematologic Tests/ OR (stress OR interleukin-6 OR il-6 OR interleukin-8 OR il-8 OR interleukin-1 OR il-1 OR cytokine* OR tumor necrosis factor OR tnf OR cortisol* OR hydrocortison* OR corticotropin* OR adrenocorticotrop* OR adrenocorticaltrop* OR ACTH OR growth hormone* OR prolactin* OR ((blood OR serum OR saliva* OR urin*) ADJ3 (level OR concentrat* OR analy* OR value*)) OR urinalys*).ab,ti.)

Web of Science
TS=(((music OR musical OR musicotherap*)) 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*)) AND ((stress OR interleukin-6 OR il-6 OR interleukin-8 OR il-8 OR interleukin-1 OR il-1 OR cytokine* OR "tumor necrosis factor" OR tnf OR cortisol* OR hydrocortison* OR corticotropin* OR adrenocorticotrop* OR adrenocorticaltrop* OR ACTH OR "growth hormone*" OR prolactin* OR ((blood OR serum OR saliva* OR urin*) NEAR/2 (level OR concentrat* OR analy* OR value*)) OR urinalys*)))

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) AND ((stress OR interleukin-6 OR il-6 OR interleukin-8 OR il-8 OR interleukin-1 OR il-1 OR cytokine* OR 'tumor necrosis factor' OR tnf OR cortisol* OR hydrocortison* OR corticotropin* OR adrenocorticotrop* OR adrenocorticaltrop* OR ACTH OR 'growth hormone*' OR prolactin* OR ((blood OR serum OR saliva* OR urin*) NEAR/3 (level OR concentrat* OR analy* OR value*)) OR urinalys*):ab,ti)

Google Scholar
music|musical|musicotherapy rgery|surgical|peroperative|perioperative|preoperative|postoperative|operative|interoperative|intraoperative|anesthesia|anaesthesia stress|"blood|serum concentration|level|levels"

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Chapter 3

The Effect of Perioperative Music on Medication Requirement and Hospital Length of Stay: A Meta-analysis

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Annals of Surgery, 272(6): 961 – 972, 2020.

"Perioperative music reduces both intraoperative sedative and postoperative opioid medication requirement, leading to high patient satisfaction"

Abstract

Objective: To assess and quantify the effect of perioperative music on medication requirement, length of stay and costs in adult surgical patients.

Summary Background Data: There is an increasing interest in non-pharmacological interventions to decrease opioid analgesics use, as they have significant adverse effects and opioid prescription rates have reached epidemic proportions. Previous studies have reported beneficial outcomes of perioperative music.

Methods: A systematic literature search of eight databases was performed from inception date to January 7, 2019. Randomized controlled trials investigating the effect of perioperative music on medication requirement, length of stay or costs in adult surgical patients were eligible. Meta-analysis was performed using random effect models, pooled standardized mean differences (SMD) were calculated with 95% confidence intervals (CI). This study was registered with PROSPERO (CRD42018093140) and adhered to the PRISMA guidelines.

Results: The literature search yielded 2414 articles, 55 studies (N=4968 patients) were included. Perioperative music significantly reduced postoperative opioid requirement (pooled SMD-0.31 [95%CI -0.45 to -0.16], $p<0.001$, $I^2=44.3$, N=1398). Perioperative music also significantly reduced intraoperative propofol (pooled SMD-0.72 [95%CI -1.01 to -0.43], $p<0.00001$, $I^2=61.1$, N=554) and midazolam requirement (pooled SMD-1.07 [95%CI -1.70 to -0.44], $p<0.001$, $I^2=73.1$, N=184), while achieving the same sedation level. No significant reduction in length of stay (pooled SMD-0.18 [95%CI -0.43 to 0.067], $p=0.15$, $I^2=56.0$, N=600) was observed.

Conclusions: Perioperative music can reduce opioid and sedative medication requirement, potentially improving patient outcome and reducing medical costs as higher opioid dosage is associated with an increased risk of adverse events and chronic opioid abuse.

Abbreviation list

CI	Confidence interval
ERAS	Enhanced recovery after surgery
ICU	Intensive care unit
mg	Milligram
ME	Morphine equivalents (1 mg ME = 1 mg parenteral morphine)
NSAIDs	Non-steroidal anti-inflammatory drugs
PACU	Post Anesthesia Care Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
RCT	Randomized controlled trial
SD	Standard deviation
SMD	Standardized Mean Difference

Introduction

A majority of patients continues to experience moderate to severe postoperative pain[1], which is a risk factor for delayed hospital discharge[2] and the occurrence of postoperative complications[3,4], persisting chronic pain, as well as the predominant factor for the immediate post-surgical quality of life[5]. Opioid analgesics are the primary treatment modality for acute postoperative pain, which is the second most common reason to prescribe opioids[6]. However, opioid-related side effects are common[7,8]. Opioid use is considered a risk factor for pruritus, nausea, vomiting, drowsiness, urinary retention and the development of delirium[9]. Higher opioid doses also increase the incidence of postoperative ileus and respiratory depression[10,11]. Moreover, persistent opioid use in surgical patients is quite prevalent. Earlier studies reported that 5.9% of patients still filled an opioid prescription 3 to 6 months after minor surgical procedures[12], while over half of the patients receiving 90 days of continuous opioid medication still use opioid analgetics one year later[13]. Both opioid prescription dosage and duration of use are important predictors for chronic opioid use[6]. The concomitant use of benzodiazepines can potentially increase the risk of adverse effects, delirium and prolonged opioid misuse even more[11].

Despite these common adverse events and an increase in opioid-related deaths, opioid prescription rates have currently reached epidemic proportions[6]. Therefore, there is an increasing interest in non-pharmacological interventions in order to reduce both postoperative pain and opioid consumption. Recently, several studies have reported beneficial effects of perioperative music[14-16]. The purpose of this systematic review and meta-analysis is to assess and quantify the effect of perioperative music as a non-pharmacological intervention on medication requirement before, during and after invasive, surgical procedures. Secondary outcomes are the effect of perioperative music on length of stay and cost reduction.

Methods

This systematic review and meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and has been registered with PROSPERO (CRD42018093140).

Literature search strategy

A literature search using the exhaustive literature search method was performed with a biomedical information specialist[17]. The databases Embase, Medline Ovid, Web-of-science, Scopus, Cochrane central, Cinahl, PsychINFO Ovid and Google Scholar were searched from date of inception until January 7th, 2019. The full search terms and number of search results of each database are detailed in Appendix A. In addition, manual cross-referencing of the included studies was performed.

Study screening and selection

Three reviewers (VF, PO and VE) independently identified eligible studies using a two-stage approach. First, title and abstract of all identified papers screened, followed by reading of the full text if eligibility criteria were matched. Inclusion criteria for this systematic review were all available, peer-reviewed, full text articles of randomized controlled trials in the English language, containing adult patients ≥ 18 years old undergoing an inhospital or outpatient invasive, surgical procedure, investigating the use of recorded music before, during and / or after surgery with either medication requirement, hospital length of stay or direct medical costs as outcome measures. As these predefined outcome measures were often secondary outcomes and therefore not always mentioned in titles or abstracts, the three reviewers screened all studies full text for potential review inclusion if during the title and abstract screening process music as perioperative intervention in adult patients was investigated. The music intervention was predefined as vocal sound, instrumental sound or both, containing the elements melody, harmony and rhythm. Therefore, studies investigating solely nature sounds were excluded. Studies investigating live music with a music therapist were also excluded, because of the possibility that the effect is caused by the presence of the musical therapist and the irreproducibility of the study. Finally, studies investigating music with an additional, concomitant intervention were excluded, except if this additional intervention was used in both the intervention and control group (for example, the music intervention occurred during bed rest, and the control group received only bed rest). Disagreements between the investigators were resolved by referring to the supervisor (JJ).

Data extraction

Study data was independently extracted by the three reviewers (VF, PO, VE) using a custom, predesigned Microsoft Excel 2010 document. Risk of bias was also independently assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials[18]. Authors of included studies were contacted for additional information if necessary. All data was mutually discussed and disagreements between the investigators were resolved by referring to the supervisor (JJ).

Statistical analysis

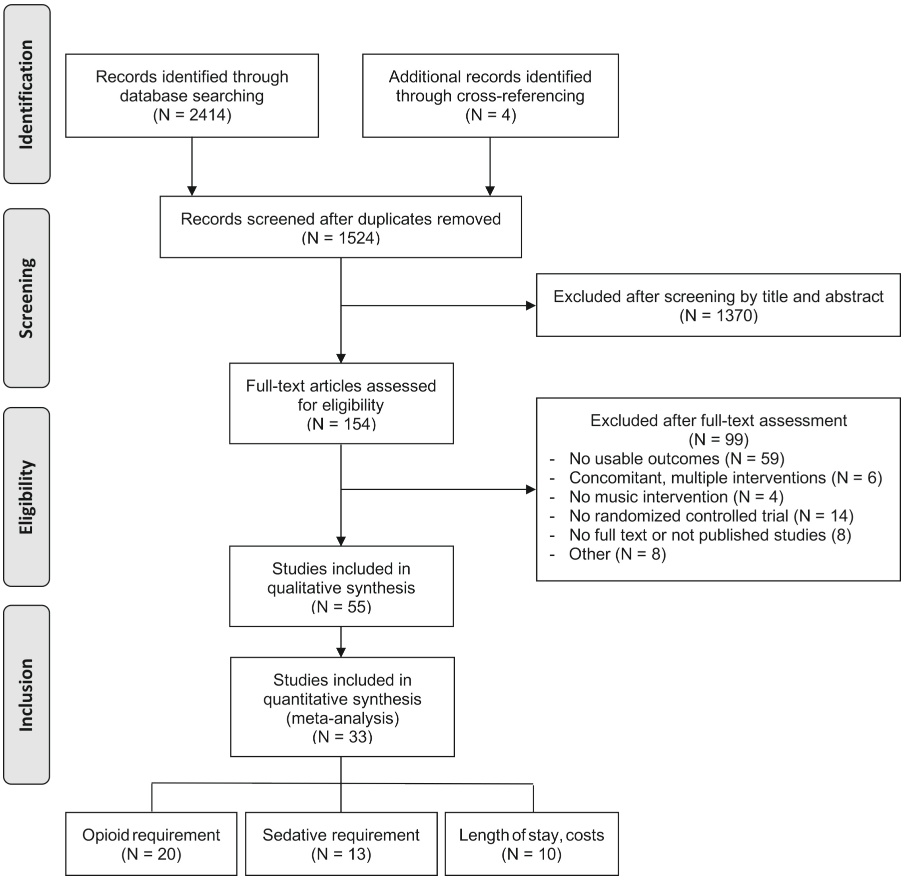
Data was analyzed with the open-source, meta-analysis software OpenMeta-Analyst, which uses R as the underlying statistical engine[19]. Random effect models were used, since heterogeneity between the included studies was assumed to be present. Standardized mean differences (SMD) and absolute mean differences were calculated with 95% confidence interval (CI). Studies were included for meta-analysis if mean values and standard deviations of the outcome measures were reported. Opioid doses were converted to milligrams (mg) of morphine equianalgesics (ME), with 1 mg ME being equivalent to 1 mg parenteral morphine. If interquartile ranges or ranges were reported, an approximation of the standard deviation was calculated by dividing the interquartile range by 1.35 and the range by 4. When the standard error of mean (SEM) was reported, standard deviations were calculated by multiplying the SEM with the square root of the number of patients[18]. Publication bias was visually assessed using funnel plots, if more than ten studies were included in the meta-analysis. Heterogeneity was analysed using the I^2-test. Statistical significance was inferred at p-value < 0.05.

If studies included several music groups, the means and standard deviations of the music groups were pooled to an approximated mean and standard deviation of the entire group[18]. If this was not appropriate, the music group that offered patients the choice to select from a preselected music list was preferred for meta-analysis. Choosing music from a preselected playlist has been observed to have a more beneficial effect on postoperative pain, compared to the own favorite music of the patient or preselected music without offering any choice[16]. If studies included several control groups, only the group which resembled standard perioperative patient care the most was included for meta-analysis.

Results

The literature search yielded 2414 results. A total of 1524 titles and abstract were screened after removal of duplicates and 154 articles were assessed full text. Fifty-five studies (4968 patients) were included in the qualitative synthesis and 33 studies (2390 patients)[20-53] in the meta-analysis (Figure 1). There was a high agreement rate of over 85 percent between the three reviewers on study inclusion, risk of bias assessment and data extraction, and all disagreements could be resolved through mutual discussion.

Figure 1. PRISMA Flow diagram



N = number of studies

Study characteristics

A detailed overview of study characteristics is presented in Table 1. The music intervention was assessed in a wide range of different surgical procedures. General anesthesia was the most commonly used anesthesia method during surgery in 36 studies (65%), while locoregional anesthesia was used in 8 studies (15%). Eight studies (15%) did not report the anesthesia method used and 3 studies (5.5%) contained different surgical procedures with different anesthesia methods. The moment of music intervention varied. Music was played solely preoperatively in 3 (5.5%), intraoperatively in 10 (18%), postoperatively in 25 (45%) and on multiple moments in 15 studies (27%). Two studies by the same author contained both an intraoperative music intervention group and a second music intervention group in which the intervention was solely applied postoperatively.

Table 1. Study characteristics

Study ID	Surgical procedure	Anesthesia	Intervention	Moment	Duration	N	Control	N	Outcome parameters
Allred, 2010	Total knee arthroplasty	General or spinal with femoral block	Choice of easy listening, non-lyrical music	Postoperatively	POD 1, 20 min. before and after first ambulation	28	Quiet rest period	28	Postoperative opioid requirement
Ames, 2017	Surgical procedures requiring ICU stay	General	MusiCure	Postoperatively	POD 1-2, 50 min., 1-8 times	20	50 min. quiet rest	21	Postoperative opioid requirement
Ayoub, 2005‡	Urological procedures	Regional	Own favorite music	Intraoperatively	Procedure duration	31	Headphones with operation noise recording	28	Intraoperative propofol requirement PACU length of stay
Bansal, 2010‡	Abdominal, urological, or lower extremity surgery	Spinal	Choice of folk, classical, religious, soothing music	Intraoperatively	*Not specified*	50	Occlusive headphones	50	Intraoperative midazolam requirement
Binns-Turner, 2011	Mastectomy	General	Choice of classical, easy-listening, new age, inspirational music	Preoperatively Intraoperatively Postoperatively	*Not specified*	15	Blank iPOD with occlusive headphones	15	Intraoperative opioid requirement Postoperative opioid requirement PACU length of stay
Blankfield, 1995‡	Coronary artery bypass surgery	General	Dreamflight II by Herb Ernst	Intraoperatively Postoperatively	Procedure duration and 2x30 min. daily postoperatively	32	Blank tape intraoperatively, standard care postoperatively	29	Postoperative opioid requirement ICU length of stay Hospital length of stay
Chen, 2015‡	Total knee replacement	*Not specified*	Chinese piano and violin music	Preoperatively Postoperatively	Total 120 min.	15	Standard care	15	Postoperative opioid requirement

Table 1. Continued.

Study ID	Surgical procedure	Anesthesia	Intervention	Moment	Duration	N	Control	N	Outcome parameters
Ciğerci and Özbayir, 2016‡	Coronary artery bypass surgery	General	Choice of Turkish classical and folk music	Preoperatively Postoperatively	90 min. before surgery, after surgery 30 min. in ICU and 30 min. each day	34	Standard care	34	Postoperative opioid requirement
Cutshall, 2011‡	Coronary artery bypass graft and / or cardiac valve surgery	General	Choice of 4 CD's	Postoperatively	2x20 min. on POD 2-4, 120 min. in total	49	Standard care with bed rest for 20 min.	51	Postoperative opioid requirement Hospital length of stay
Dabu-Bondoc, 2010‡	Outpatient surgery	General	Own favorite music	Preoperatively Intraoperatively	Preoperative 30 min., procedure duration	20	Intra-operatively headphones with white noise	20	Intraoperative propofol requirement Intraoperative opioid requirement Postoperative opioid requirement PACU length of stay
Easter, 2010	Elective outpatient surgery procedures	*Not specified*	Choice of easy-listening, country, gospel, rock	Postoperatively	During length of stay in PACU	111	No music	102	Postoperative opioid requirement PACU length of stay
Ebneshahidi and Mohseni, 2008‡	Elective cesarean section surgery	General	Own favorite music	Postoperatively	30 min. in the recovery room	38	Headphones without music	39	Postoperative opioid requirement
Finlay, 2016	Total knee arthroplasty	Spinal with nerve block	32 tracks with range of genres	Postoperatively	15 min.	72	Headphones without music	17	Postoperative opioid requirement

Table 1. Continued.

Study ID	Surgical procedure	Anesthesia	Intervention	Moment	Duration	N	Control	N	Outcome parameters
Good, 1995[‡]	Elective, open abdominal surgery	General	Choice of sedative non-lyrical piano, harp, synthesizer orchestral or slow jazz music	Postoperatively	60 min. during the first 2 days after surgery	21	Standard care	21	Postoperative opioid requirement
Good, 1999	Elective, open, major abdominal surgery	General	Choice of taped soothing music	Preoperatively Postoperatively	First 2 days after surgery	151	Standard care	152	Postoperative opioid requirement
Graversen and Sommer, 2013[‡]	Laparoscopic cholecystectomy	General	Musicure using music pillow	Preoperatively Intraoperatively Postoperatively	Before surgery start until day care discharge	40	Standard care	35	Intraoperative propofol requirement Intraoperative opioid requirement Postoperative opioid requirement Day care unit length of stay
Heitz, 1992[‡]	(Para) thyroidectomy or unilateral modified radical mastectomy	General	Choice of three instrumental classical tapes	Postoperatively	15 min. after PACU arrival until discharge	20	Headphones without music	20	Postoperative opioid requirement PACU length of stay
							Standard care	20	
Hook, 2008[‡]	Moderate or major elective surgery	General	Choice of Malay, Western, Chinese, soothing music	Preoperatively Postoperatively	60 min. before and 180 min. after surgery	51	Standard care	51	Postoperative opioid requirement

Table 1. Continued.

Study ID	Surgical procedure	Anesthesia	Intervention	Moment	Duration	N	Control	N	Outcome parameters
Iblher, 2011	Open heart surgery (coronary bypass, valvular transplant, or both combined)	General	Baroque organ, flute, string orchestra music with 60-80 bpm	Postoperatively	60 min. after ICU admission	25	Standard care	25	Postoperative opioid requirement Postoperative catecholamine requirement
					60 min. after sedation stop	24			
Ignacio, 2012	Elective spine, hip or knee surgery	General	*Not specified*	Postoperatively	2x30 minutes	12	No music	9	Postoperative opioid requirement
Ikono -modou, 2004‡	Laparoscopic sterilization or tubal dyeing	General	Peaceful pan flute music	Preoperatively Postoperatively	30 minutes before and after surgery	29	Blank compact disk	26	Postoperative opioid requirement
Johnson, 2012	Gynaecological outpatient surgery	*Not specified*	Choice of soft country, new age / classical and inspirational music	Preoperatively Intraoperatively Postoperatively	On average 212 minutes	43	Headphones without music	35	Postoperative opioid requirement PACU length of stay
							Standard care	41	
Kar, 2015‡	Elective cardiac surgery under cardiopulmonary bypass	General	Raga therapy (Indian classical music)	Preoperatively Intraoperatively	30 min. before surgery and procedure duration	17	Headphones without music	17	Intraoperative sedative requirement Intraoperative opioid requirement
Kliempt, 1999	Diverse range of surgical procedures	General	Classical music Adagio Karajan	Intraoperatively	Procedure duration	25	Headphones without music	26	Intraoperative opioid requirement

Table 1. Continued.

Study ID	Surgical procedure	Anesthesia	Intervention	Moment	Duration	N	Control	N	Outcome parameters
Koch, 1998[‡]	Outpatient urological procedures	Spinal	Own favorite music	Intraoperatively	Procedure duration	19	Standard care	15	Intraoperative propofol requirement PACU length of stay
Koelsch, 2011[‡]	Total hip arthroplasty	Spinal	Joyful instrumental music	Preoperatively Intraoperatively	120 min before surgery and procedure duration	20	Headphones with breaking sea waves noise	20	Intraoperative propofol requirement
Kumar, 2014	Hernia, breast, appendix and thyroid surgery	*Not specified*	Raga Ananda Bairavi (Indian classical music)	Preoperatively Postoperatively	At admission and POD 1-3	30	Standard care	30	Postoperative opioid requirement
Laurion and Fetzer, 2003	Gynecological, laparoscopic outpatient day surgery	General	Piano music	Preoperatively Intraoperatively Postoperatively	2 times a day before surgery, procedure duration, PACU stay	28	Standard care	28	Postoperative opioid requirement PACU length of stay
Lepage, 2001[‡]	Non-oncologic, outpatient or short-stay surgery	Spinal	Choice of pop, jazz, classical, new age	Preoperatively Intraoperatively Postoperatively	Anesthesia induction until recovery	25	Standard care	25	Perioperative midazolam requirement
Liu and Petrini, 2015	Thoracic surgery	General	Soft, melodious music 60-80 bpm	Postoperatively	30 min. daily on POD 1-3	56	Standard care	56	Postoperative patient controlled analgesia requirement
Macdonald, 2003	Total abdominal hysterectomy	*Not specified*	Own favorite music	Postoperatively	2-6 hours on day of surgery	30	Standard care	28	Postoperative patient controlled analgesia requirement

Table 1. Continued.

Study ID	Surgical procedure	Anesthesia	Intervention	Moment	Duration	N	Control	N	Outcome parameters
Masuda, 2005‡	Orthopedic surgery	General and spinal	Choice of Noh, Gagaku, classical or Enka music	Postoperatively	20 minutes	22	Standard care	22	Hospital length of stay
McCaffrey and Loscin, 2006	Elective hip or knee surgery	*Not specified*	Choice of CD's	Postoperatively	60 min. 4 times a day	62	Standard care	62	Postoperative patient controlled analgesia requirement
McRee, 2003	'Low risk' surgery	General, spinal, local and regional	Soft piano music	Preoperatively	30 min.	13	Standard care	13	Postoperative opioid requirement
Migneault, 2004‡	Gynaecological surgery	General	Choice of jazz, classical, popular new-age or piano music	Intraoperatively	Procedure duration	15	Headphones without music	15	Intraoperative end-tidal isoflurane Intraoperative fentanyl requirement Postoperative opioid requirement
Miladinia, 2017‡	Abdominal surgery	General	Relaxing non-lyrical music with a bpm of 60-80	Postoperatively	3x 10 min. sessions on day of surgery	30	Standard care	30	Postoperative opioid requirement
Nielsen, 2018‡	Unspecified orthopedic, urological, gynaecological and general surgery	Epidural, spinal and local	Musicure	Intraoperatively	Procedure duration	58	Standard care	44	Intraoperative fentanyl requirement Intraoperative propofol requirement

3

Table 1. Continued.

Study ID	Surgical procedure	Anesthesia	Intervention	Moment	Duration	N	Control	N	Outcome parameters
Nilsson, 2001[‡]	Elective abdominal hysterectomy	General	Relaxing, calming music with sea waves sound	Intraoperatively	Procedure duration	30	Headphones with operation noise recording	28	Postoperative opioid requirement Hospital length of stay
Nilsson, 2003a[‡]	Daycare surgery: varicose veins, open inguinal hernia repair	General	Soft, relaxing and calming classical music	Postoperatively	PACU arrival until patient choose to stop	62	Headphones without music	63	Postoperative opioid requirement
Nilsson, 2003b[‡]	Daycare surgery: varicose veins, open inguinal hernia repair	General	Soft instrumental new-age synthesizer music	Intraoperatively	Procedure duration	51	Headphones without music	49	Postoperative opioid requirement
				Postoperatively	1 hour after PACU arrival	51			
Nilsson, 2005[‡]	Open hernia repair (Lichtenstein)	General	Soft, new-age synthesizer	Intraoperatively	Procedure duration	25	Headphones without music	25	Postoperative opioid requirement
				Postoperatively	1 hour after PACU arrival	25			
Nilsson, 2009a	Coronary artery bypass graft and/or aortic valve replacement	General	MusiCure using music pillow	Postoperatively	30 min. on POD1	20	Standard care	20	Postoperative opioid requirement
Nilsson, 2009b[‡]	Coronary artery bypass graft or aortic valve replacement	General	Soft, relaxing, new age style music using music pillow	Postoperatively	30 min. on POD1	28	Standard care	30	Postoperative opioid requirement

Table 1. Continued.

Study ID	Surgical procedure	Anesthesia	Intervention	Moment	Duration	N	Control	N	Outcome parameters
Reza, 2007[‡]	Elective caesean section	General	Soft, instrumental, Spanish style guitar music	Intraoperatively	Procedure duration	50	White music	50	Postoperative opioid requirement
Santhna, 2015	Total knee replacement surgery	*Not specified*	Choice of soothing and relaxing non-lyrical piano or violin music	Postoperatively	60 min., 4 times a day	20	Standard care	20	Postoperative opioid requirement
Schwartz, 2009[‡]	Coronary artery bypass graft surgery	General	Light piano music	Postoperatively	Patient's choice in ICU	35	Standard care	32	ICU length of stay Hospital costs
Sen, 2009a[‡]	Local urological procedures	Propofol PCS with local infiltration	Own favorite music	Intraoperatively	Procedure duration	30	Earphones without music	30	Intraoperative propofol requirement
Sen, 2009b[‡]	Elective caesarian section	General	Own favorite music	Preoperatively	60 min.	50	Headphones without music	50	Postoperative opioid requirement
Sen, 2010[‡]	Elective caesarian section	General	Own favorite music	Postoperatively	60 min.	35	No music	35	Postoperative opioid requirement
Szmuk, 2008	Laparoscopic hernia or cholecystectomy	General	Choice of pop-rock, classical or Israeli music	Intraoperatively	Procedure duration	20	Headphones without music	20	Intraoperative end-tidal sevoflurane Postoperative opioid requirement

3

Table 1. Continued.

Study ID	Surgical procedure	Anesthesia	Intervention	Moment	Duration	N	Control	N	Outcome parameters
Tse, 2005	Endoscopic sinus surgery or tubinectomy	*Not specified*	Choice of Chinese, Western or own favorite music	Postoperatively	2x30 min. after surgery and on POD1	27	Standard care	30	Postoperative analgesic medication requirement
Vaajoki, 2012	Elective major abdominal midline incision surgery	General	Choice of 2000 popular music songs	Postoperatively	Total of 7x30 min.	83	Standard care	85	Postoperative opioid requirement Hospital length of stay
Zhang, 2005‡	Total abdominal hysterectomy	General with spinal or epidural	Own favorite music	Intraoperatively	Procedure duration	55	Headphones without music	55	Intraoperative propofol requirement
Zhou, 2011‡	Radical mastectomy	General	Choice of 202 songs	Postoperatively	2x30 min. daily	60	Standard care	60	Hospital length of stay
Zimmer-man, 1996	Coronary artery bypass graft surgery	General	Choice of 5 soothing music tapes	Postoperatively	30 min. daily during POD1-3	32	Scheduled rest of 30 minutes	32	Postoperative opioid requirement Hospital length of stay

Table 1. Legend

CD = Compact disk
ICU = Intensive Care Unit
Min. = Minutes
N = Number of patients
PACU = Post-anesthesia care unit
PCS = Patient-controlled sedation
POD = Postoperative day
‡ = denotes study included in meta-analysis

The music intervention was commonly described as soothing, relaxing, non-lyrical, instrumental music and was preselected by the research team in most studies (45 studies, 82%): patients could select music from a preselected list in 21 studies (38%), while no choice was offered in 24 studies (44%). The preferred music of the patient was used in 9 studies (16%), while one study (1.8%) did not elaborate on the exact music intervention. In a majority of studies, music delivery was achieved using a music player and headphones (41 studies, 75%). Other reported music delivery methods were a music pillow (3 studies, 5.5%), CD-player (3 studies, 5.5%), personal stereo (1 study, 1.8%), an integrated music system in the patient room (1 study, 1.8%) or not specified (6 studies, 11%). The control group consisted of standard care (26 studies, 47%), headphones without music (16 studies, 29%), headphones with white noise or recorded OR noise intraoperatively (5 studies, 9.1%), no music without further specification (3 studies, 5.5%), or an unspecified rest period (3 studies, 5.5%). Two studies (3.6%) had both a standard care and headphones without music group acting as control.

Risk of bias assessment

An overview of the risk of bias assessment is presented in Figure 2 and a more detailed description in Appendix B. A potentially high risk of selection bias was present in several studies (8 studies, 15%)[24,54,29,55,56,47,57,58], as sequence generation was done using odd and even numbers, days of the week or hospital record number. Several studies provided insufficient details to assess selection bias (14 studies, 25%)[20,22,26-28,30,32,59-61,36,62,38,40]. A moderate to high risk of performance bias was present, as blinding of patients for the music intervention is only possible when the intervention is performed solely intraoperatively during general anesthesia. Blinding of personnel can theoretically be achieved by using headphones for all patients, but is more difficult in practice when patients are free to change music tracks or adjust the volume. Five studies (9.3%) employed a study design in which patients, surgical personnel and outcome assessors were all blinded adequately[63,38,41,46,64]. The 'other risk of bias' category was reported as unclear in more than half of the studies (36 studies, 65%), because one of the baseline characteristics age, gender, weight or the duration of surgery, can influence intraoperative and postoperative medication requirement, which was not reported. There was a high risk of other bias because of significant difference in either surgery duration or age between the music and control group in three studies[25,36,45]. A funnel plot to investigate publication bias of studies assessing the effect of perioperative music on postoperative opioid requirement showed a near funnel-shaped plot, lacking a small number of studies in the lower left corner which could be indicative of studies with relatively small samples sizes and small effect sizes being potentially absent (Appendix C).

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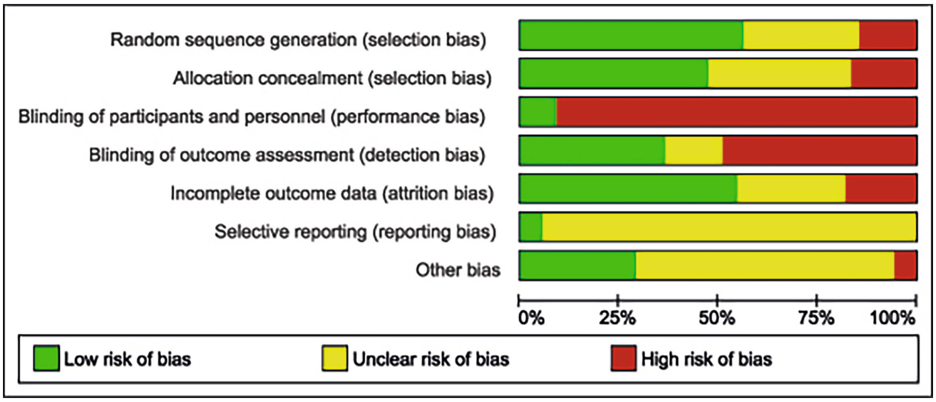
Figure 2. Risk of Bias Graph



Opioid requirement

The effect of perioperative music on postoperative opioid requirement was assessed in 42 studies, of which 20[22-24,26-32,38,39,42,41,43,45,46,49,50] could be included in the meta-analysis. Thirteen studies presented the postoperative opioid dose requirement as morphine equivalents (ME) or parenteral morphine. In three studies, postoperative ketobemidone requirement was evaluated, which are equipotent to parenteral morphine (1 mg parenteral ketobemidone = 1 mg ME[65]). Postoperative parenteral tramadol requirement (10 mg parenteral tramadol = 1 mg ME[66]) was assessed in three studies and pethidine requirement in one study (10 mg pethidine = 1 mg ME[67]). Length of follow-up differed, as five studies assessed opioid requirement during stay in the post-anesthesia care unit[26,29,30,32,43], three within the first two postoperative hours[27,42,44] and two within the first 12 postoperative hours[39,46]. Ten studies (50%) assessed opioid requirement for minimally 24 hours after surgery or longer[22-24,28,31,38,45,41,49,50]. General anesthesia was used during surgery in all of these 20 studies.

Perioperative music significantly reduced postoperative opioid requirement (pooled SMD -0.31 [95% CI -0.45 to -0.16], $p < 0.001$, $I^2 = 44.3$, N = 1398 patients) (Figure 3). The mean overall absolute reduction in postoperative opioid requirement of the 8 studies which measured postoperative opioid requirement during PACU stay or within the first two postoperative hours was -1.0 mg ME (95% CI -1.6 to -0.49, $p < 0.001$, $I^2 = 10.5$, N = 698 patients). The mean absolute reduction in postoperative opioid requirement of the 10 studies which measured postoperative opioid requirement for at least 24 hours or more after surgery was -4.4 mg ME (95% CI -8.2 to -0.65, $p = 0.022$, $I^2 = 69.6$, N = 598 patients). The mean absolute reduction in five of these studies which measured opioid requirement for at least three postoperative days and involved major surgical procedures was -9.82 mg ME (95% CI -17.9 to -1.70, $p = 0.018$, $I^2 = 48.8$, N = 298 patients)[22-24,31,41]. Intraoperative music during general anesthesia in three of the 20 studies in which the patients, surgical staff and outcome assessors were all blinded did not significantly reduce postoperative opioid requirement (pooled SMD -0.16 [95% CI -0.63 to 0.31], $p = 0.49$, $I^2 = 57.1$, N = 188 patients)[38,41,46].

The effect of preoperative and / or intraoperative music on intraoperative opioid requirement was assessed in 7 studies[23,26,29,33,63,38,40]. Meta-analysis was not performed because of insufficient data presented, the broad variation in the types of surgery performed and difference in surgery duration.

Intraoperative sedative requirement

The effect of perioperative music on intraoperative sedative medication requirement was assessed in 13 studies (846 patients). Propofol requirement was assessed in nine[20,26,29,33-35,40,48,51], midazolam requirement in three[21,33,36] and end-tidal inhalation anesthetics concentration in two studies[38,64]. In one of these aforementioned studies, both propofol and midazolam were administered intraoperatively for sedation[33]. Incremental intraoperative sedative medication doses were administered based on sedation depth, which was either assessed using a bispectral index monitor or a validated sedation scale. The infusion rate was patient-controlled in four studies[20,34,36,48]. The manner of sedation depth assessment and whether or not infusion rate was patient-controlled is specified in Figure 4.

Perioperative music significantly reduced intraoperative propofol requirement (pooled SMD -0.72 [95% CI -1.01 to -0.43], $p < 0.00001$, $I^2 = 61.1$, N = 554 patients, 9 studies) (Figure 4). All included studies evaluating the effect of music on propofol requirement, except two[29,40] that did not specify the manner of sedation depth assessment, reported that the level of sedation did not differ between the music and control group. This reduction in intraoperative propofol requirement remained present when these two studies[29,40] were excluded from the analysis (pooled SMD -0.86, [95% CI -1.18 to -0.53], $p < 0.00001$, $I^2 = 54.9$, N = 377 patients, 7 studies), and when the three studies with patient-controlled propofol infusion rate were analyzed as a separate subgroup (pooled SMD -0.82 [95% CI -1.25 to -0.38], $p = 0.00025$, $I^2 = 40.1$, N = 153 patients). Perioperative music also significantly reduced intraoperative midazolam requirement (pooled SMD -1.07 [95% CI -1.70 to -0.44], $p < 0.001$, $I^2 = 73.1$, N = 184 patients) (Figure 4), while achieving the same sedation depth.

Figure 3. Effect of perioperative music on postoperative opioid requirement

Study	N	Music Mean	Music SD	N_M	Control Mean	Control SD	N_C	Measurement duration
Blankfield 1995	61	20.3	16.6	32	26.4	34.5	29	Hospital length of stay
Chen 2015	30	12.04	14.43	15	12.90	8.05	15	Hospital length of stay
Cigerci and Özbayir 2016	47	16	9	20	33	23	27	Intensive Care Unit
Dabu-Bondoc 2010	40	14.4	13.2	20	16.9	12.8	20	PACU
Ebneshahidi and Mohseni 2008	77	1.6	1.7	38	2.5	1.9	39	First postoperative hour
Good 1995	42	4.73	5.02	21	4.83	5.57	21	First 24 postoperative hours
Graversen and Sommer 2013	75	10.0	7.19	40	8.0	4.81	35	Day care surgery
Heitz 1992	40	60	480.8	20	69	494.2	20	PACU
Hook 2008	102	24.38	36.68	51	35.50	69.24	51	First 72 postoperative hours
Ikonomidou 2004	55	2.2	2.9	29	4.3	2.4	26	PACU
Migneault 2004	30	85.8	40.0	15	69.4	30.9	15	First 24 postoperative hours
Miladinia 2017	60	1.680	1.611	30	2.517	2.107	30	First 12 postoperative hours
Nilsson 2001	58	61.7	31.9	30	81.5	40.5	28	First 72 postoperative hours
Nilsson 2003a	125	2.6	3.2	62	3.4	3.9	63	First 2 postoperative hours
Nilsson 2003b	153	1.95	2.65	102	3.1	3.6	51	PACU
Nilsson 2005	75	1.4	2.12	50	2.9	3.1	25	First postoperative hour
Nilsson 2009b	58	12.6	6.5	28	11.8	6.6	30	First 24 postoperative hours
Reza 2007	100	17.92	4.932	50	19.18	6.474	50	Until 6 hours after PACU discharge
Sen 2009b	100	28.9	6.4	50	36.4	10.7	50	First 24 postoperative hours
Sen 2010	70	30.743	6.251	35	35.257	10.902	35	First 24 postoperative hours
Total	**1398**			**738**			**660**	

Pooled SMD -0.31 [95% CI -0.45 to -0.16], *p* <0.001, I² = 44.3

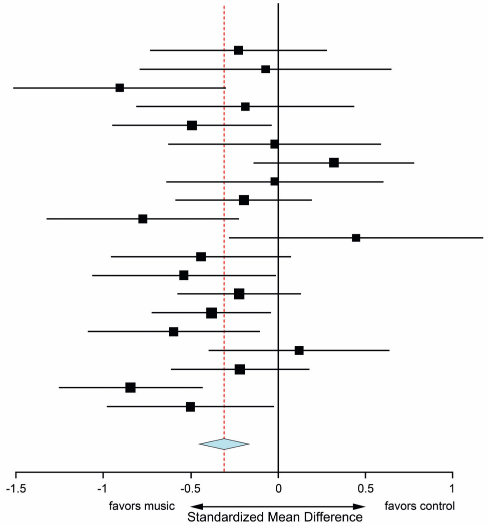


Figure 3 legend. Forest plot presenting the effect of perioperative music on postoperative opioid requirement (milligrams of morphine equianalgesics). CI = confidence interval; Mean = mean milligrams of morphine equianalgesics; N = total number of patients in study; N_C = number of patients in the control group; N_M = number of patients in the music group; PACU = Post Anesthesia Care Unit; SD = standard deviation in milligrams of morphine equianalgesics; SMD = standardized mean difference

Figure 4. Effect of perioperative music on intraoperative sedative medication requirement

Study	N	Music Mean	SD	N_M	Control Mean	SD	N_C	Sedation depth assessment
Ayoub 2005	59	19.4	37	31	51	52	28	OAA/S (PCS)
Dabu-Bondoc 2010	40	1.38	0.325	20	1.60	1.04	20	Bispectral index
Graversen and Sommer 2013	75	670.50	232.96	40	706.50	221.67	35	*Not specified*
Kar 2015	34	229.4	25.3	17	317.6	58.47	17	Bispectral index
Koch 1998	34	17	36	19	94	70	15	Cork sedation scale (PCS)
Koelsch 2011	40	253	107	20	322	71.7	20	Bispectral index
Nielsen 2018	102	90	84	58	137	101	44	*Not specified*
Sen 2009a	60	127.06	53.30	30	162.43	68.06	30	OAA/S (PCS)
Zhang 2005	110	171	98	55	251	92	55	Bispectral index and OAA/S
Total	**554**			**290**			**264**	
Propofol pooled SMD -0.72 [95% CI -1.01 to -0.43], p <0.00001, I^2 = 61.1								
Bansal 2010	100	2.17	0.53	50	3.25	0.77	50	Ramsay sedation score
Kar 2015	34	5.23	0.43	17	5.58	0.50	17	Bispectral index
Lepage 2001	50	0.6	0.7	25	1.3	1.1	25	*Not specified* (PCS)
Total	**184**			**92**			**92**	
Midazolam pooled SMD -1.07 [95% CI -1.70 to -0.44], *p* <0.001, I^2 = 73.1								

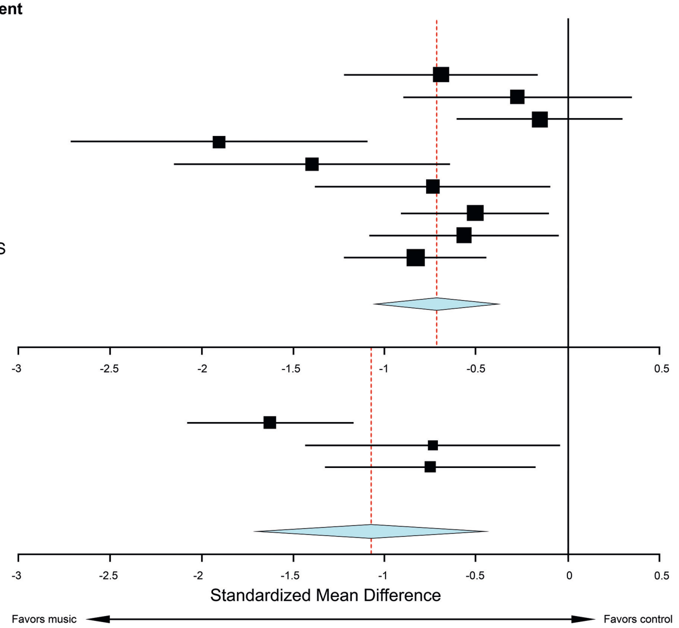


Figure 4 legend. Forest plot presenting the effect of perioperative music on intraoperative propofol (above) and midazolam (below) medication requirement.

CI = confidence interval; Mean = mean milligrams of propofol or midazolam; N = total number of patients in study; N_C = number of patients in the control group; N_M = number of patients in the music group; OAA/S = Observer Assessment of Alertness/Sedation Scale; PACU = Post Anesthesia Care Unit; PCS = Patient-controlled sedation; SD = standard deviation in milligrams of propofol or midazolam; SMD = standardized mean difference

Figure 5. Effect of perioperative music on length of stay

Study	N	Music Mean	Music SD	N_M	Control Mean	Control SD	N_C	Length of stay assessed
Ayoub 2005	59	98	45	31	119	64	28	PACU
Blankfield 1995	61	6.5	1.5	32	6.5	2.3	29	Hospital
Cutshall 2011	100	5.9	3.6	49	7.9	12.8	51	Hospital
Dabu-Bondoc 2010	40	156.9	65.6	20	162.8	68.2	20	PACU
Graversen and Sommer 2013	75	255	70.4	40	237	63.0	35	Day care
Koch 1998	34	105	47	19	111	55	15	PACU
Masuda 2005	44	3.8	1.6	22	3.3	1.6	22	Hospital
Schwartz 2009	67	1357	435	35	1657	950	32	Intensive Care Unit
Zhou 2011	120	13.62	2.04	60	15.53	2.75	60	Hospital
Total	**600**			**232**			**220**	

Pooled SMD -0.18 [95% CI -0.43 to 0.067], *p* = 0.15 I^2 = 56.0

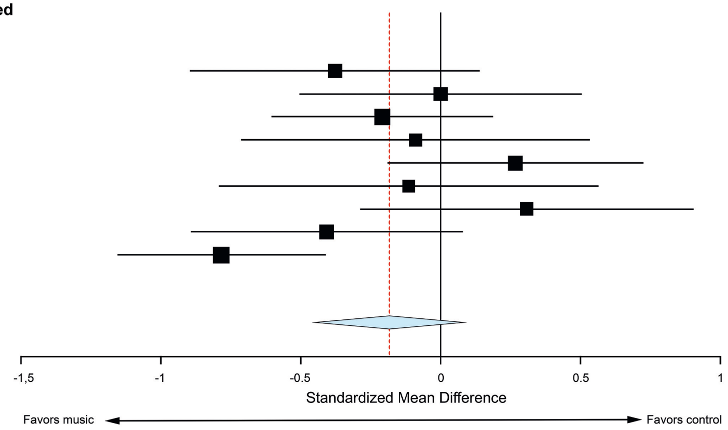


Figure 5 legend. Forest plot presenting the effect of perioperative music on length of stay
CI = confidence interval; Mean = mean length of stay; N = total number of patients in study; N_C = number of patients in the control group; N_M = number of patients in the music group; PACU = Post Anesthesia Care Unit; SD = standard deviation; SMD = standardized mean difference

Length of stay and medical costs

The effect of perioperative music on length of stay was assessed in 17 studies, of which nine studies could be included in the meta-analysis. Total length of hospital stay of surgical inpatients was assessed in four studies[22,25,37,52], length of stay in the post-anesthesia or day care unit of patients undergoing outpatient surgery in four other studies[20,26,29,34] and intensive care unit length of stay in one study[47]. Perioperative music did not significantly reduce length of stay (pooled SMD -0.18 [95% CI -0.43 to 0.067], $p = 0.15$, $I^2 = 56.0$, N = 600 patients) (Figure 5). When analyzing the studies with outpatient surgical patients (pooled SMD -0.053 [95% CI -0.35 to 0.24], $p = 0.73$, $I^2 = 13.1$, N = 208 patients) and inpatient operations (pooled SMD -0.21 [95% CI -0.66 to 0.25], $p = 0.37$, $I^2 = 75.2$, N = 325 patients) separately, length of stay was also not reduced. 3

Intensive care unit costs tended to be lower in one pilot study (3911 (SD 1566) versus 4365 dollars (SD 2632), $p = 0.09$), as time spent in the intensive care unit was significantly reduced in the music group compared to the control group[47]. However, this did not reach statistical significance and overall direct medical costs during hospital length of stay did not differ significantly.

Discussion

This systematic review and meta-analysis of 55 randomized controlled trials evaluates the effect of perioperative music on intraoperative and postoperative medication requirement and length of stay. Because of the current opioid epidemic, which has increased opioid-related deaths and led to a substantial financial burden[6,68], there is an increased interest in non-pharmacological interventions that can reduce both postoperative pain and opioid consumption. Perioperative music reduced opioid consumption by 4.4 mg ME in studies measuring opioid requirement for at least 24 hours or more after surgery. In studies measuring at least 72 hours or more after major surgical procedures, a reduction of 9.82 mg ME was observed. Opioid-related adverse effects have been observed to be dose-dependent and an increased requirement of three to four mg ME after surgery has been related to the occurrence of one additional, clinically meaningful, adverse event[69]. A maximum daily dose exceeding 2 mg of parenteral hydromorphone, equivalent to 10 to 14 mg ME[70], was significantly associated with the development of postoperative ileus after colorectal surgery, increasing morbidity, length of hospital stay and direct medical costs[71]. Both a higher daily opioid dose and a prolonged use in opioid-naïve patients also increase the risk of chronic opioid use[6]. As more elderly patients are nowadays undergoing surgery, this group would be of particular interest to the use of perioperative music, as they have an increased risk of opioid-related adverse effects and chronic abuse because of polypharmacy and comorbidity[72,73].

Perioperative music also significantly reduced both intraoperative propofol and midazolam requirement, whilst achieving the same sedation level. Midazolam is often used during locoregional anesthesia or as a preoperative anxiolytic, but is a risk factor for the occurrence of postoperative delirium[74]. A higher level of preoperative anxiety has been associated with a higher amount of intravenous sedation requirement to induce and maintain adequate sedation level during surgery[75]. Previous studies have reported a beneficial effect of perioperative music on anxiety levels[14-16], which could theoretically explain the reduced sedation dosage needed. While a dose-dependent relation of sedative medication and intraoperative hemodynamic changes has been observed[76], the predictive outcome capabilities of intraoperative hemodynamics have only been investigated sparingly[77].

No effect of perioperative music on length of stay was demonstrated. However, only four studies assessed total length of stay and organisational rather than patient factors are the most important predictors of delayed discharge[78]. Moreover, almost half of the studies (44%) that assessed length of stay did so in patients undergoing minor surgery in the outpatient setting, making it unlikely to find a clinically relevant difference. Even though opioids are relatively cheap, opioids accounted for 1% of total hospital costs in an observational study of patients undergoing joint replacement surgery[79]. As one of the most commonly performed procedures in the developed world, yearly costs in the United States alone amount to more than $20 billion[80]. It is therefore likely that the beneficial effects of perioperative music on mediation requirement will also be observed financially, especially when taking into account the costs that come with opioid-related adverse effects[10].

This meta-analysis has several strong points. A comprehensive literature search was performed with a dedicated biomedical information specialist. A predefined definition of music was used and studies with live music, a music therapist and concomitant interventions were excluded. In comparison to earlier performed meta-analyses investigating the effects of perioperative music, our focus was solely on medication requirement and length of stay in adult surgical patients. Vetter *et al.* (2015) did observe a significant reduction in pain medication requirement by perioperative music in fourteen studies, but this was not significant for the subgroup of patients who received general anesthesia in nine studies[15]. The meta-analysis by Hole *et al.* (2015) contained studies with both surgical as well as non-surgical, diagnostic procedures leading to clinical heterogeneity, and did not differentiate between opioid, benzodiazepines and sedative medication requirement[14]. Nevertheless, this meta-analysis has limitations as well. The included studies contained different surgical patients, surgical procedures and follow-up duration of the outcome assessment. This was reflected in the moderate to high level of heterogeneity observed. Medication requirement can be influenced by factors such as age, body weight and the duration of surgery. Some of these baseline characteristics were not reported in the included studies, potentially increasing the risk of bias in interpreting results. Therefore, it is not entirely clear whether perioperative music can have the same beneficial effect size on medication requirement for all surgical procedures. Measurement duration of postoperative opioid requirement in

15 of the 20 studies was 24 hours after surgery or less. Consequently, the mean absolute reduction in mg ME in the music group was relatively low and perhaps does not reflect the full beneficial effect of perioperative music on medication requirement. Although a meta-regression analysis could be performed with covariates such as music intervention duration, music exposure moment relative to the surgical procedure (i.e. preoperatively, intraoperatively, postoperatively or multiple moments), operative severity (i.e. minor, moderate or major surgery) and measurement duration, this was not deemed appropriate as at least ten studies for each co-variate are recommended[18]. Only postoperative opioids were assessed, as other analgesic medications were often not reported. Some included studies did report that perioperative music also reduced non-opioid analgesic requirement postoperatively[24,49].

Our literature search did not include patient-reported outcome measures. However, it should be noted that patients in the included studies were extremely positive towards the use of perioperative music. Almost all patients (88% or higher) found perioperative music to be an enjoyable experience[81,23,82,35,55,56,83]. Likewise, a majority would opt for music again in the future[25,21,28], even pro-actively asking for music in subsequent surgical procedures[21]. Patient satisfaction was also markedly increased in the music group[56,48-51], with the only negative comments observed being from those who did not get music or related to the type of available music[25,84]. While side-effects of perioperative music could theoretically occur, none of the included studies reported any adverse effects. Specifically, no cardiorespiratory depressions were observed[34,51], while McCaffrey *et al.* reported that perioperative music had a significant beneficial effect on delirium and confusion[85,56]. In some studies, care was taken to restrict music volume and adhere to the noise and hearing loss guidelines to prevent hearing damage[86], while others allowed patients the option to adjust the music volume to their liking. The most well-known implemented non-pharmacological, multimodal interventions in surgical patient care are part of the guidelines collectively known as the Enhanced Recovery After Surgery protocols, which focus on reducing the physiological stress response to surgery by optimizing nutritional state, reducing opioid use and early mobilization[87]. Originally introduced in colorectal surgical patient care, it has subsequently been implemented in a wide range of different surgical specialties with surgery-specific variations. Likewise, the use of perioperative music should be adapted to fit into the operative procedure, individual clinical setting, and wishes and requirements of the medical team. While it is difficult to draw a firm clinical recommendation based on the data in our meta-analysis, 75% of studies assessing opioid requirement exposed patients to a total of 120 minutes perioperative music on average or less, delivered either before, during and / or on the first two days after surgery. Therefore, it seems that a relatively short exposure to music can already be beneficial, with a majority of the studies using a music player and headphones in order to avoid disrupting communication of the medical staff. Further research could focus on the effect of perioperative music on postoperative complications, clinical recovery, costs and implementation.

Conclusion

Perioperative music can reduce postoperative opioid and intraoperative sedative medication requirement. Therefore, perioperative music may potentially improve patient outcome and reduce medical costs, as a higher opioid dosage is associated with an increased risk of adverse events and chronic opioid use. The use of perioperative music seems to be safe and patient-friendly, given the high patients satisfaction reported whilst no adverse effects were observed.

Author Disclosure Statement

No external funding was received for this study. The authors declare no conflicts of interest.

Acknowledgements

The authors would like to thank W. Bramer, biomedical information specialist of the Medical Library, Erasmus MC University Medical Centre, Rotterdam, for his assistance with the literature search. The authors would like to thank V.P.B. Elbers, BsC, medical student, for assistance in the literature screening. The authors would like to thank A. Tomer, MsC, statistician, for assistance in the statistical analysis.

Appendix A. Literature search

Database	Years of Coverage	Before deduplication	After deduplication
Embase.com	1971 – January 7, 2019	1066	1052
Medline Ovid	1946 – January 7, 2019	336	84
Web of Science	1900 – January 7, 2019	152	40
Cochrane Central	1992 – January 7, 2019	155	31
Scopus	2004 – January 7, 2019	224	25
PsycINFO	1887 – January 7, 2019	136	74
Cinahl	1937 – January 7, 2019	245	145
Google Scholar	Not applicable	100	69
Total		**2414**	**1520**

Embase.com
(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) AND ('economic evaluation'/exp OR 'economic aspect'/exp OR economics/exp OR 'length of stay'/de OR 'drug use'/de OR 'drug therapy'/exp OR 'drug therapy':lnk OR deprescription/de OR prescription/de OR 'analgesic agent'/exp OR 'anxiolytic agent'/exp OR 'sedative agent'/exp OR 'narcotic agent'/exp OR (econom* OR cost OR costs OR ((length OR duration*) NEAR/3 (stay OR hospital*)) OR ((drug OR drugs OR medication OR paracetamol OR acetaminophen* OR opiate* OR opioid* OR morphine OR morfine OR concentrat* OR pharmacologic* OR agent*) NEAR/10 (reduc* OR use OR usage OR used OR user OR users OR consum* OR therap* OR dose OR dosage OR intake OR demand* OR require*)) OR prescri* OR deprescri* OR analgesic* OR anxiolytic* OR sedative* OR narcotic*):ab,ti)

Medline Ovid
(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.) AND (exp "Economics"/ OR "Length of Stay"/ OR "drug therapy"/ OR "drug therapy".xs. OR Drug Prescriptions/ OR Deprescriptions/ OR exp "Analgesics"/ OR exp "Anti-Anxiety Agents"/ OR exp "Hypnotics and Sedatives"/ OR exp "Narcotics"/ OR (econom* OR cost OR costs OR ((length OR duration*) ADJ3 (stay OR hospital*)) OR ((drug OR drugs OR medication OR paracetamol OR acetaminophen* OR opiate* OR opioid* OR morphine OR morfine OR concentrat* OR pharmacologic* OR agent*) ADJ10 (reduc* OR "use" OR usage OR used OR user OR users OR consum* OR therap* OR dose OR dosage OR intake OR demand* OR require*)) OR prescri* OR deprescri* OR analgesic* OR anxiolytic* OR sedative* OR narcotic*).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*)) AND ((econom* OR cost OR costs OR ((length OR duration*) NEAR/3 (stay OR hospital*)) OR ((drug OR drugs OR medication OR paracetamol OR acetaminophen* OR opiate* OR opioid* OR morphine OR morfine OR concentrat* OR pharmacologic* OR agent*) NEAR/10 (reduc* OR use OR usage OR used OR user OR users OR consum* OR therap* OR dose OR dosage OR intake OR demand* OR require*)) OR prescri* OR deprescri* OR analgesic* OR anxiolytic* OR sedative* OR narcotic*)))

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) AND ((econom* OR cost OR costs OR ((length OR duration*) NEAR/3 (stay OR hospital*)) OR ((drug OR drugs OR medication OR paracetamol OR acetaminophen* OR opiate* OR opioid* OR morphine OR morfine OR concentrat* OR pharmacologic* OR agent*) NEAR/10 (reduc* OR use OR usage OR used OR user OR users OR consum* OR therap* OR dose OR dosage OR intake OR demand* OR require*)) OR prescri* OR deprescri* OR analgesic* OR anxiolytic* OR sedative* OR narcotic*):ab,ti)

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*) AND ((econom* OR cost OR costs OR ((length OR duration*) W/3 (stay OR hospital*)) OR ((drug OR drugs OR medication OR paracetamol OR acetaminophen* OR opiate* OR opioid* OR morphine OR morfine OR concentrat* OR pharmacologic* OR agent*) W/10 (reduc* OR use OR usage OR used OR user OR users OR consum* OR therap* OR dose OR dosage OR intake OR demand* OR require*)) OR prescri* OR deprescri* OR analgesic* OR anxiolytic* OR sedative* OR narcotic*)))

PsycINFO
(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.) AND (exp "Economics"/ OR "Treatment Duration"/ OR "drug therapy"/ OR exp "Analgesic Drugs"/ OR exp "Tranquilizing Drugs"/ OR exp "Sedatives"/ OR exp "Narcotic Drugs"/ OR (econom* OR cost OR costs OR ((length OR duration*) ADJ3 (stay OR hospital*)) OR ((drug OR drugs OR medication OR paracetamol OR acetaminophen* OR opiate* OR opioid* OR morphine OR morfine OR concentrat* OR pharmacologic* OR agent*) ADJ10 (reduc* OR "use" OR usage OR used OR user OR users OR consum* OR therap* OR dose OR dosage OR intake OR demand* OR require*)) OR prescri* OR deprescri* OR analgesic* OR anxiolytic* OR sedative* OR narcotic*).ab,ti.)

Cinahl
(MH music+ OR MH "music therapy+" OR TI (music OR musical OR musicotherap*) OR AB (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 TI (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*) OR AB (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*)) AND (MH "Economics+" OR MH "Length of Stay" OR MH "drug therapy" OR MW "drug therapy" OR MH "Prescriptions, Drug" OR MH "Analgesics+" OR MH "Antianxiety Agents+" OR MH "Hypnotics and Sedatives+" OR MH "Narcotics+" OR TI (econom*

OR cost OR costs OR ((length OR duration*) N2 (stay OR hospital*)) OR ((drug OR drugs OR medication OR paracetamol OR acetaminophen* OR opiate* OR opioid* OR morphine OR morfine OR concentrat* OR pharmacologic* OR agent*) N9 (reduc* OR “use” OR usage OR used OR user OR users OR consum* OR therap* OR dose OR dosage OR intake OR demand* OR require*)) OR prescri* OR deprescri* OR analgesic* OR anxiolytic* OR sedative* OR narcotic*) OR AB (econom* OR cost OR costs OR ((length OR duration*) N2 (stay OR hospital*)) OR ((drug OR drugs OR medication OR paracetamol OR acetaminophen* OR opiate* OR opioid* OR morphine OR morfine OR concentrat* OR pharmacologic* OR agent*) N9 (reduc* OR “use” OR usage OR used OR user OR users OR consum* OR therap* OR dose OR dosage OR intake OR demand* OR require*)) OR prescri* OR deprescri* OR analgesic* OR anxiolytic* OR sedative* OR narcotic*))

Google Scholar
music surgery|operative|operation|perioperative|postoperative|intraoperative|”operating theater”|”recovery
Room”|anesthesia|anesthesiological|anaesthesia|preanesthetic|postanesthetic
economics|cost|”length*stay|hospitalization”|”drug use|usage”

Appendix B. Bias assessment

Study ID	Method of randomization	Allocation concealment	Blinding participants	Blinding surgical staff	Blinding assessors	Incomplete outcome adequately addressed	Selective reporting	Other bias adequately addressed
Allred, 2007	Sealed envelope system	Yes	No	No	Unclear	Yes. Same number discontinued intervention	Unclear	Unclear, surgery duration not reported
Ames, 2017	Opaque, sealed envelope	Yes	No	No	No	Yes, exclusions unrelated to intervention	Low risk	Unclear, surgery duration and weight not reported
Ayoub, 2005	'Randomized' (unclear)	No, randomization and music by non-blinded member	No	Yes	Yes	Yes	Unclear	Yes
Bansal, 2010	Lottery method	Unclear	No	No	Unclear	Yes	Unclear	Yes
Binns-Turner, 2011	Drawing numbers from reclosable plastic bag	Yes	No	Yes	Yes	Yes, all enrolled completed the study	Unclear	Unclear, surgery duration and weight not reported
Blankfield, 1995	'Randomized' (unclear)	Unclear	No	No	Unclear	Yes	Unclear	Unclear, surgery duration and weight not reported
Chen, 2015	Sealed envelopes stratified by sex	Yes	No	No	Unclear	No, 16 / 56 excluded and only 30 completed study	Unclear	Unclear, weight not reported

Study ID	Method of randomization	Allocation concealment	Blinding participants	Blinding surgical staff	Blinding assessors	Incomplete outcome adequately addressed	Selective reporting	Other bias adequately addressed
Ciğerci and Özbayir, 2016	Randomization by odd and even numbers	No	No	No	Unclear	Unclear	Unclear	Unclear, surgery duration and weight not reported
Cutshall, 2011	Sealed envelopes	Yes	No	No	No	Unclear	Unclear	No, patients music group significantly older
Dabu-Bondoc, 2010	'Randomized' (unclear)	Unclear	No	Yes	Yes	Unclear	Unclear	Yes
Easter, 2010	Hospital visit number	No	No	No	Unclear	No	Unclear	Unclear, surgery duration and weight not reported
Ebneshahidi and Mohseni, 2010	'Randomly assigned' (unclear)	Unclear	No	No	Yes	No	Unclear	Yes
Finlay, 2016	Computer-generated pseudo-random numerical stratified schedule	Unclear	No	Yes	No	No	Unclear	Unclear, surgery duration, age and weight not reported
Good, 1995	Not specified (unclear)	Unclear	No	No	Unclear	Unclear, 18/102 excluded	Unclear	Unclear, surgery duration, age and weight not reported
Good, 1999	Computerized minimization program	Yes	No	No	No	No, 117/617 (19%) excluded, 44% missed at least 1 test	Unclear	Unclear, surgery duration, age and weight not reported

Study ID	Method of randomization	Allocation concealment	Blinding participants	Blinding surgical staff	Blinding assessors	Incomplete outcome adequately addressed	Selective reporting	Other bias adequately addressed
Graversen and Sommer, 2013	Randomization by day by picking an envelope	No	No	No	Unclear	No, 18/93 excluded	Low risk	Yes
Heitz, 1992	'Randomly assigned' (unclear)	Unclear	No	No	No	Yes	Unclear	Yes
Hook, 2008	Envelope method	Unclear, as safeguards not specified	No	No	No	Yes, equal number and reason for exclusion in both groups	Unclear	Unclear, surgery duration, age and weight not reported
Iblher, 2011	By lot	Unclear	No	No	No	Unclear, 34/160 excluded	Unclear	Unclear, surgery duration not reported
Ignacio, 2012	Computer-generated randomization list	Yes	No	No	No	Unclear, not specified	Unclear	Unclear, surgery duration not reported
Ikonomodou, 2004	'Randomly assigned' (unclear)	Unclear	No	Yes	Yes	Yes	Unclear	Yes
Johnson, 2012	'Randomized' (unclear)	Unclear	No	No	No	Yes	Unclear	Unclear, weight not reported
Kar, 2015	Computer-generated randomization	Yes	No	Yes	Yes	Yes	Unclear	Yes

Study ID	Method of randomization	Allocation concealment	Blinding participants	Blinding surgical staff	Blinding assessors	Incomplete outcome adequately addressed	Selective reporting	Other bias adequately addressed
Kliempt, 1999	Computer-generated random number table	Yes	Yes	Yes	Yes	Yes, exclusion before intervention and therefore unrelated	Unclear	Yes
Koch, 1998	Table of random numbers	Unclear whether open allocation	No	No	No	Unclear, 2 excluded, group unclear	Unclear	Unclear, weight not reported
Koelsch, 2011	Randomly chosen, identical looking mp3 player	Yes	No	Yes	Yes	No, 10 / 50 (20%) excluded because of study protocol deviation	Unclear	Unclear, surgery duration not reported
Kumar, 2014	Not specified (unclear)	Unclear	No	No	No	Unclear	Unclear	Unclear, surgery duration, age and weight not reported
Laurion and Fetzer, 2003	'Randomly assigned' (unclear)	Unclear	No	No	No	Unclear	Unclear	Unclear, surgery duration, age and weight not reported
Lepage, 2001	'Randomly assigned' (unclear)	Unclear	No	No	No	Yes	Unclear	No, surgery duration music group longer
Liu and Petrini, 2015	Odd and even day numbers	No	No	No	No	No, exclusions not evenly divided over groups	Unclear	Unclear, surgery duration and weight not reported

3

Study ID	Method of randomization	Allocation concealment	Blinding participants	Blinding surgical staff	Blinding assessors	Incomplete outcome adequately addressed	Selective reporting	Other bias adequately addressed
MacDonald, 2003	'Randomly assigned' (unclear)	Unclear	No	No	No	Unclear	Unclear	Unclear, surgery duration and weight not reported
Masuda, 2005	Table of random numbers	Unclear whether open allocation	No	No	No	Yes	Unclear	Unclear, surgery duration and weight not reported
McCaffrey and Loscin, 2006	Room number	No	No	No	No	Yes	Unclear	Unclear, surgery duration and weight not reported
McRee, 2003	Drawing lots	Unclear	No	No	No	Unclear	Unclear	Unclear, surgery duration not reported
Migneault, 2004	'Randomly assigned' (unclear)	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes
Miladinia, 2017	Block randomization	Yes	No	No	No	Yes	Low risk	Unclear, surgery duration and weight not reported
Nielsen, 2018	'Randomized' (unclear)	Yes	No	No	No	Unclear	Unclear	Unclear, surgery duration and weight not reported
Nilsson, 2001	Computer-generated randomization list	Yes	Yes	Yes	Yes	Yes	Unclear	Yes

Study ID	Method of randomization	Allocation concealment	Blinding participants	Blinding surgical staff	Blinding assessors	Incomplete outcome adequately addressed	Selective reporting	Other bias adequately addressed
Nilsson, 2003a	Computer-generated randomization list	Yes	No	Yes	Yes	Yes	Unclear	Unclear, weight not reported
Nilsson, 2003b	Computer-generated randomization list	Yes	No	Yes	Yes	Yes	Unclear	Unclear, weight not reported
Nilsson, 2005	Computer-generated randomization list	Yes	No	Yes	Yes	Yes	Unclear	Unclear, weight not reported
Nilsson, 2009a	Computer-generated randomization list	Yes	No	No	Yes	Yes	Unclear	No, surgery duration in music group significantly longer
Nilsson, 2009b	Computer-generated randomization list	Yes	No	No	Yes	Yes	Unclear	Unclear, weight not reported
Reza, 2007	Computer-generated random numbers	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear, weight not reported
Santhna, 2015	Sealed envelopes	Yes	No	No	No	No	Unclear	Unclear, surgery duration and weight not reported
Schwartz, 2009	Hospital bed	No	No	No	Yes	Unclear, 5 outliers removed but group not specified	Unclear	Unclear, surgery duration not reported
Sen, 2009a	Computer-generated	Yes	No	Yes	Yes	Yes	Unclear	Yes

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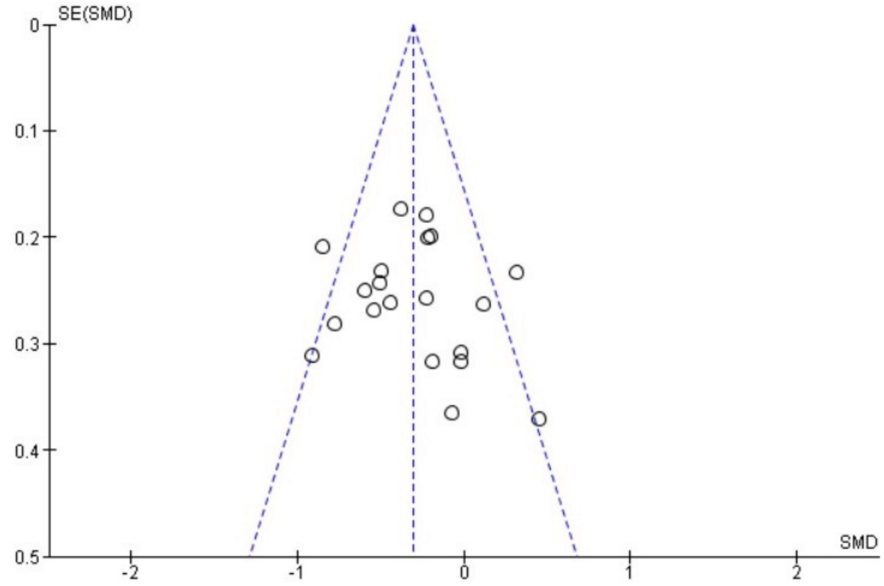
Study ID	Method of randomization	Allocation concealment	Blinding participants	Blinding surgical staff	Blinding assessors	Incomplete outcome adequately addressed	Selective reporting	Other bias adequately addressed
Sen, 2009b	Computer-generated	Yes	No	Yes	Yes	Yes	Unclear	Yes
Sen, 2010	Computer-generated	Yes	No	Unclear	Yes	Yes	Unclear	Yes
Szmuk, 2008	Computer-generated numbers in sequentially numbered opaque envelopes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Tse, 2005	Day of the week	No	No	No	No	Yes	Unclear	Unclear, surgery duration not reported
Vaajoki, 2012	Odd and even week	No	No	No	No	No, 17% patients excluded during study	Unclear	Unclear, weight not reported
Zhang, 2005	Computer-generated randomization list	Yes	No	Yes	Yes	Yes	Unclear	Yes
Zhou, 2011	Computer-generated random numbers	Yes	No	No	No	Yes	Unclear	Unclear, surgery duration and weight not reported
Zimmerman, 1996	Not specified (unclear)	Unclear	No	No	No	Unclear	Unclear	Unclear, surgery duration and weight not reported

Appendix B legend.
Yes = low risk of bias; No = high risk of bias; Unclear = unclear risk of bias

Appendix C. Funnel plot assessing publication bias



Appendix C legend. Funnel plot assessing publication bias of studies reporting the effect of perioperative music on postoperative opioid requirement.

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Chapter 4

Perception of Auditory Stimuli during General Anesthesia and its Effect on Patient Outcome: A Meta-Analysis

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Canadian Journal of Anaesthesia, 68(8):1231 – 1253, 2021

"Intraoperative auditory stimuli can be processed and perceived during general anesthesia, but only music can have beneficial effects on postoperative pain and opioid requirement depending on perioperative factors"

Abstract

Purpose: Interest in implicit memory formation and unconscious auditory stimulus perception during general anesthesia has resurfaced as perioperative music has been reported to produce beneficial effects. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating explicit and implicit memory formation during general anesthesia and its effects on postoperative patient outcomes and recovery.

Source: We performed a systematic literature search of Embase, Medline Ovid and Cochrane Central from inception date until October 15, 2020. Eligible for inclusion were RCTs investigating intraoperative auditory stimulation in adult surgical patients under general anesthesia in which patients, healthcare staff, and outcome assessors were all blinded. We used random effects models for meta-analyses. This study adhered to the PRISMA guidelines and was registered in PROSPERO (CRD42020178087).

Principal Findings: Fifty-three (4.200 patients) of 5.859 identified articles were included. Implicit memory formation evidence was present in 7 out of 17 studies (41%) when assessed using perceptual priming tasks. Mixed results were observed on postoperative behavioral and motor response after intraoperative suggestions. Intraoperative music significantly reduced postoperative pain (standardized mean difference [SMD] -0.84 [95% confidence interval [CI] -1.1 to -0.57], $p < 0.001$, $I^2 = 0$, N = 226) and opioid requirements (SMD -0.29 [95%CI -0.57 to -0.015], $p = 0.039$, $I^2 = 36$, N = 336), whilst positive therapeutic suggestions did not.

Conclusion: The results of this systematic review and meta-analysis show that intraoperative auditory stimuli can be perceived and processed during clinically adequate, general anesthesia irrespective of surgical procedure severity, leading to implicit memory formation without explicit awareness. Intraoperative music can exert significant beneficial effects on postoperative pain and opioid requirements. Whether the employed intraoperative anesthesia regimen is of influence is not yet clear.

Authorship

All authors made substantial contributions to this work. Victor X. Fu and Markus Klimek designed the study. Victor X. Fu, Karel J. Sleurink, and Joséphine C. Jansen performed literature screening and data extraction. Victor X. Fu performed the data analysis. Victor X. Fu, Bas P.L. Wijnhoven, Johannes Jeekel, and Markus Klimek interpreted the data. Victor X. Fu primarily drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version for publication.

Abbreviation list

95% CI	95% confidence interval
ANA	Anesthesia regimen
ASA	American Society of Anesthesiologists
Balanced anesthesia	Anesthesia induction with intravenous drugs, maintenance with inhalational drugs
BIS	Bispectral index
BP	Blood pressure
CO_2	Carbon dioxide
dBA	Decibels adjusted
ETAG	End-tidal anesthesia gas concentration
FiO_2	Fraction of inspired oxygen
fMRI	Functional magnetic resonance imaging
h	Hour
HR	Heart rate
HP	Hemodynamic parameter
IIM	Inhalational induction and maintenance anesthesia
kg	Kilogram
kPa	Kilopascal
MAC	Minimum alveolar concentration
MAP	Mean arterial pressure
mcg	Microgram
mg	Milligram
min	Minute
ml	Millilitre
MLAER	Mid-latency auditory evoked response
N	Number of patients
N_2O	Nitrous oxide

O_2	Oxygen
OAA/S	Observer Assessment of Alertness/Sedation Scale
OR	Operating room
PACU	Post Anesthesia Care Unit
PCA	Patient-controlled analgesia
POD	Postoperative day
PONV	Postoperative nausea and vomiting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
s	Second
SD	Standard deviation
SMD	Standardized Mean Difference
TIVA	Total intravenous anesthesia

Introduction

Explicit memory formation, defined as unwanted conscious awareness of intraoperative sensory stimuli, is normally abolished during adequate general anesthesia for elective surgical procedures. Reported incidences of explicit memory formation are estimated to be between 0.2 and 0.01 percent, but have been observed to be as high as 2% in selected populations [1-3]. However, some sensory cortex functioning seems to be preserved during general anesthesia, as the primary auditory cortex remains receptive and reactive to auditory stimuli even during deep sedation[4,5]. This would allow for implicit awareness, defined as intraoperative unconscious perception without explicit recall.

Especially in the early 1990s and 2000s, there was a strong interest to see whether this phenomenon was present using priming and learning tests. Priming consists of exposure to stimuli leading to a response, with the stimuli and response being associated with each other. Examples include completing a word stem of three letters after previously being exposed to that word, or assessment using semantically-related words like 'fish and 'salmon'[6]. Evidence for the presence of implicit memory formation can also be assessed by evaluating whether intraoperative auditory stimuli influence postoperative outcome when comparing an auditory intervention group and a control group in a well-designed randomized controlled trial. However, no definitive conclusions were drawn at that time[7,8].

Recently, a new interest in auditory perception has arisen as perioperative music has been reported to have beneficial effects[9-11]. Two recent meta-analyses evaluated the effects of perioperative music before, during and after surgery. The effects of intraoperative music – applied only whilst the patients were under general anesthesia – were only briefly assessed in passing in a subanalysis[9,10]. Although intraoperative music can seemingly reduce postoperative pain, this conclusion was based on a limited number of studies with high heterogeneity which was not further addressed[9]. Therefore, it is unsurprising that no definitive effect of sole intraoperative music on postoperative opioid requirements has been observed in an even lower number of studies[10]. Whether other auditory stimuli can achieve the same effects and to which extent different perioperative factors are of influence were also not evaluated. Consequently, by focusing solely on intraoperatively presented auditory stimuli during general anesthesia alone and not limiting assessment to music only, the mechanism of intraoperative auditory processing and perception can be evaluated. Moreover, a renewed systematic search and analysis with a larger number of studies had to address the issues of these previous studies in order to achieve a more definitive conclusion.

The aim of this systematic review and meta-analysis was to assess the perception and its effects of intraoperative auditory stimuli in adult patients undergoing surgery with general anesthesia by evaluating postoperative patient outcome, explicit memory formation, and implicit memory formation. Furthermore, we sought to explore the influence of perioperative factors on the effects of auditory stimuli on memory formation and patient outcome.

Methods

No Institutional Review Board approval or informed consent was deemed necessary for this systematic review and meta-analysis. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and was prospectively registered with the PROSPERO database (CRD42020178087)[12].

Literature search, eligibility criteria, and study selection

We performed a systematic literature search of the databases Embase, Medline Ovid, and Cochrane Central, from database inception date until 15 October, 2020. The exhaustive literature search method, which yields 44% more references and 20% more included studies compared to traditional literature search methods, was used[13], assisted by a biomedical information specialist (full search syntax available in Appendix A). Peer-reviewed, published, full-text-available, randomized controlled trials in the English language with patients, staff and outcome assessors all blinded and investigating the effect of intraoperative auditory stimulation and perception in adult surgical patients during general anesthesia were eligible for inclusion. Outcome measures of interest consisted of patient outcome and recovery, explicit memory formation, and implicit memory formation.

Eligibility criteria were thus as follows:

- Type of patients: Adult patients undergoing surgery with general anesthesia
- Type of studies: Peer-reviewed, published, full-text-available randomized controlled trials in the English language in which patients, perioperative staff, outcome assessors all are blinded
- Type of intervention and control: intraoperative auditory stimuli (for example: music, positive suggestions, stories) compared to a control group not receiving intraoperative auditory stimuli or a different intraoperative auditory stimulus
- Main outcome measure: postoperative patient outcomes and recovery, assessed through postoperative pain
- Secondary outcome measures: postoperative patient outcomes and recovery assessed through postoperative nausea and vomiting (PONV), postoperative antiemetic requirements, postoperative opioid requirements, length of stay and patient satisfaction, explicit memory formation, implicit memory formation
- Additional outcomes assessed: perioperative factors of potential influence on perception and processing of intraoperative auditory stimuli during general anesthesia

All studies were screened independently by three reviewers (VF, KS, JCJ) and assessed full-text when the aforementioned eligibility criteria were met. This was followed by mutual discussion to assess final inclusion of the screened studies in this study. Manual cross-referencing of included and relevant studies was performed as well by screening the references of all included studies using aforementioned eligibility criteria, whilst also screening the included studies of previously conducted systematic reviews and meta-analyses as well.

Data extraction

Study data were independently extracted by three reviewers (VF, KS, JCJ) using a custom made Microsoft Excel 2010 (Redmont, WA, USA) form. Baseline patient characteristics and perioperative anesthesia regimen details of the included studies were extracted, which are commonly reported in studies involving surgical procedures or have previously been of interest in regard to intraoperative auditory perception. These included the surgical procedure, the use of premedication, the method of anesthesia monitoring, the perioperative anesthesia drug regimen, and the postoperative analgesia regimen[7,14]. Data on factors potentially influencing the physiological stress response to surgery, which has been implicated in implicit memory formation, were extracted as well[15]. These included surgical severity classified according to the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) surgical scoring system[16], and the baseline characteristics age, sex, body-mass index or weight, and surgery duration were extracted as well. These factors can either influence the amount of perioperative medication administered or the duration of exposure to the intraoperative stimuli, and were prespecified in the previously performed meta-analysis as well[10]. We assessed the risk of bias using the Cochrane Collaboration's tool of assessing the risk of bias in randomized controlled trials[17]. If aforementioned baseline characteristics were not detailed per study group, the other risk of bias was considered unclear. A statistical significant difference in baseline characteristics between study groups was scored as a high in the other risk of bias category. Study authors were contacted by mail to provide additional information or data if deemed necessary.

Statistical analysis

Included studies evaluating the effect of intraoperative auditory stimuli were eligible for quantitative meta-analysis, if study data were presented as means and standard deviations. Medians were used as an approximation of means, if means were not reported. An approximation of the standard deviation (SD) was calculated using universally known formulas described in the Cochrane Handbook when interquartile ranges, ranges, or standard error of means were reported[18]. Meta-analysis was performed only when at least three studies with a comparable auditory intervention (i.e., all studies had music as an intervention, or positive therapeutic suggestions) assessed the same outcome parameter (i.e., postoperative pain). When multiple control groups were present, the group most resembling current standard patient care was included for meta-analysis. Random effect models with the DerSimonian and Laird method were used and standardized mean differences (SMDs) with 95% confidence intervals (95% CIs) were calculated. An SMD of -0.2 or less can be considered a small beneficial effect, -0.5 a moderate, and -0.8 or higher a large beneficial effect[18]. We assessed heterogeneity with the I^2 test. Data analysis was performed with OpenMeta-Analyst open source software, which uses R as underlying basis and Python for graphical user interface implementation[19]. The statistical significance threshold was set at $P < 0.05$. Publication bias was assessed if at least ten studies were included in the meta-analysis.

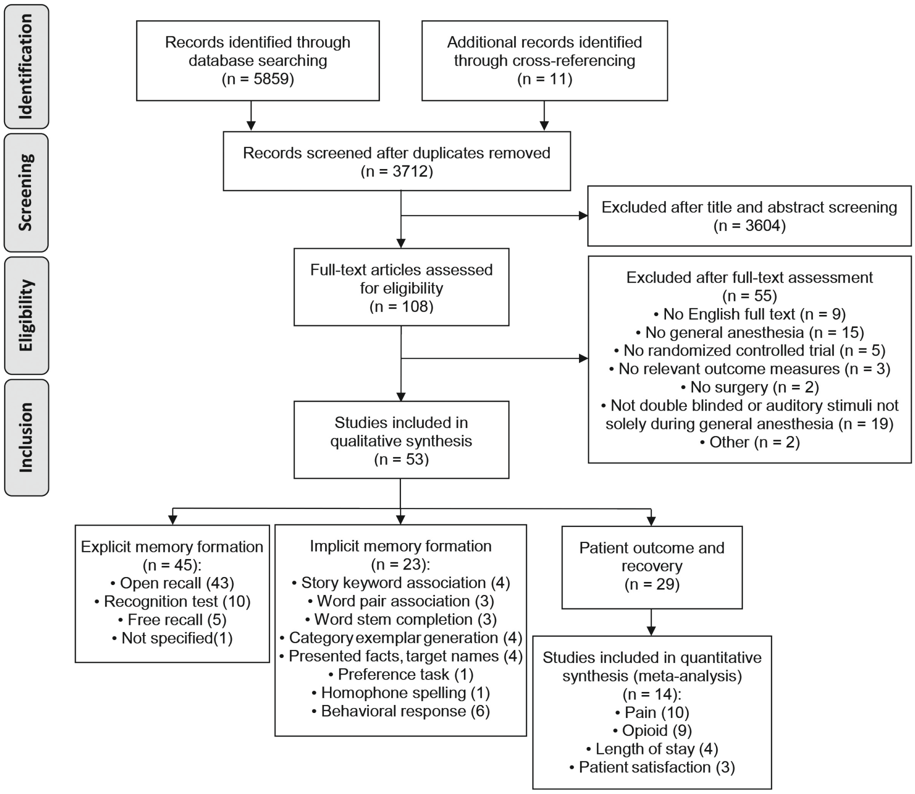
Deviations from the registered PROSPERO study protocol

The aim was to perform meta-analysis of all outcomes, but this was not possible for implicit and explicit memory due to the way of data presentation, as well as the lack of proper control factor in several studies. Although the type of patients, studies, intervention and control were specified for the PICO, the main and secondary outcome measures were registered twice as an entire list. Potential prespecified subgroup analysis intentions were the type of intraoperative auditory stimulation (i.e., music versus positive therapeutic suggestions), type of anesthesia (i.e., intravenous versus inhalational), and additional influencing factors like surgical severity. Only the first analysis was possible, due to the limited number of studies included in the quantitative synthesis. Likewise, meta-regression or publication bias assessment was not possible. Finally, some factors like perioperative data extracted and the other risk of bias category were not registered in the protocol, but followed our previously conducted meta-analysis[10].

Results

The literature search yielded 5.859 articles with 3.701 remaining after deduplication. Additionally, 11 articles were retrieved through cross-referencing. Full-text assessment was performed for 108 studies. A total of 53 randomized controlled trials (4.200 patients) assessing the effect of intraoperative auditory stimuli during general anesthesia were included, with 45 studies evaluating explicit memory formation (3.528 patients), 23 implicit memory formation (1.864 patients), and 29 postoperative patient outcome and recovery (2.249 patients) (Figure 1). There was a high inter-reviewer agreeability throughout the screening and data-extraction process of 92 percent, with all differences solved through mutual discussion.

Figure 1. PRISMA flow diagram



Two studies evaluated both patient outcome and recovery, as well as memory formation and behavioral change.
n = number of studies

Study characteristics

An overview of the included studies is presented in Table 1. Baseline study characteristics are presented in Table 2. Several studies employed multiple study groups with different intraoperative auditory interventions or a combined auditory intervention (i.e. positive therapeutic suggestions followed by a word list). Therefore, the intraoperative auditory intervention consisted of positive therapeutic suggestions in 22 studies; a words, facts or names list in 17 studies; music in 12 studies; and a story in seven studies. A prespecified auditory intervention duration was present in 13 studies whilst it played continuously throughout the surgical procedure in 38 studies. Two studies did not state the exact auditory intervention duration. The mean patient age was 21 to 40 years old in 15 studies (28%), 41 to 60 years old in 29 studies (55%), and 61 years old or higher in six studies (11%).

Table 1. Overview included studies

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Aceto 2003	Elective laparoscopic cholecystectomy	Repetitive story-keywords using familiar Christian religious stories	Sevoflurane and air (FiO_2 40%)	10	Sevoflurane and 60%N_2O in 40%O_2	10	Explicit memory (open-recall) Implicit memory (story-related free association) Mid-latency auditory evoked potential relationship with memory formation
			Isoflurane and air FiO_2 40%)	10	Isoflurane and 60%N_2O in 40%O_2	10	
Aceto 2013	Elective laparoscopic cholecystectomy	Repetitive story-keywords thrice lasting 9 min	Fairy story Pinocchio or puss in boots with four keywords	54	Over-ear, isolating headphones	52	Explicit memory (open-recall) Implicit memory (story-related free association) Stress response effect on memory formation
Aceto 2015	Elective thyroidectomy	Repetitive story-keywords thrice lasting 27 min	BIS-guided sevoflurane anesthesia	63	HP-guided sevoflurane anesthesia	64	Explicit memory (open-recall) Implicit memory (story-related free association) BIS-guided vs. HP-guided anesthesia
Adams 1998	Elective open cardiopulmonary bypass surgery	Two 15 word pair list 1 min tapes played continuously	Word list A	13	Word list B	12	Explicit memory (open-recall, recognition test) Implicit memory (word pair free association)
Bejjani 2009	Elective cardiopulmonary bypass surgery	Two 20 word pair list tapes played continuously	Word list A	19	Word list B	19	Explicit memory (open-recall, free recall) Implicit memory (word-stem completion test)
Bennett 1985	Inguinal hernia, cholecystectomy orthopedic surgery	Positive therapeutic and postoperative motor suggestions played continuously	Personalized tape interspersed with music	11	Operating room sounds through earphone stereo microphone	22	Explicit memory (open-recall) Implicit memory (postoperative non-verbal motor response)

Table 1. Continued.

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Block 1991	Elective gastroplasty, cholecystectomy or gynecological surgery	Positive therapeutic suggestions 6 min tape, continuously played except for the first 59 patients	Positive therapeutic suggestions	109	Headphones with blank tape	100	Patient outcome (pain, opioids, PONV, anti-emetics, length of stay)
Boeke 1988	Elective open cholecystectomy	Positive therapeutic suggestions and seaside sounds 30 min tape played continuously	Positive therapeutic suggestions with seaside sounds	24	Nonsense suggestions interspersed with seaside sounds	26	Explicit memory (open-recall) Patient outcome (pain, opioids, PONV, length of stay, subjective well-being)
			Seaside sounds	27	Earphones with operation room sound	29	
Bonebakker 1993	Elective surgery	Category word pair tape 30 min, followed by bird sounds continuously	30 word pair presentation tape	23	5 word pair presentation tape	18	Explicit memory (open-recall) Implicit memory (category exemplar generation task)
					Headphones without words	15	
Bonke 1986[†]	Elective cholecystectomy with or without choledochotomy	Positive therapeutic suggestions 3 min tape played continuously	Positive therapeutic suggestions	31	Continuous monotone noise	30	Explicit memory (open-recall) Patient outcome (pain, opioids, PONV, length of stay)
					Earphones with operation room sound	30	
Caseley-Rondi 1994	Total abdominal hysterectomy with or without salpingo-oophorectomy	Positive therapeutic suggestions with 24 Japanese melodies 60 min tape played continuously	Positive therapeutic suggestions	38	Headphones with blank tape	36	Explicit memory (open-recall, recognition test) Implicit memory (preference task) Patient outcome (opioids, PONV, length of stay)

Table 1. Continued.

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Dawson 2001†	Total abdominal hysterectomy	Three positive suggestions tapes played continuously	Positive therapeutic suggestions	103	White noise	35	Explicit memory (open-recall) Patient outcome (pain, opioids, PONV, anti-emetics, length of stay)
De Roode 1995	Strabismus surgery	Ten facts or names 15 min tape, with natural seaside sounds continuously	Presented facts (ten previously learned, largely forgotten historical facts)	43	Target names (ten fictitious non-famous people)	40	Explicit memory (open-recall) Implicit memory (presented facts and target names) Midazolam effect on memory formation
Deeprose 2005	Day care orthopedic surgery	Four 28 word list 14 min tapes played continuously	Propofol and N2O anesthesia with 1.5mg/kg fentanyl induction	32	Propofol and N2O anesthesia, no fentanyl	30	Explicit memory (open-recall, recognition test) Implicit memory (word-stem completion test) Fentanyl effect on memory formation
Donker 1996	Arthroscopy day care surgery	Eight ten facts or names tapes with filler sound continuously	Presented facts	29	Target names	29	Explicit memory (open-recall) Implicit memory (presented facts and target names)
Eberhart 1998†	Thyroidectomy	Positive therapeutic suggestion tape played continuously	Positive therapeutic suggestions	36	Headphones with blank tape	35	Explicit memory (open-recall) Patient outcome (pain, opioids, PONV, anti-emetics, length of stay)
Evans and Richardson 1988†	Total abdominal hysterectomy	Positive therapeutic suggestion 12 min tape repeated thrice	Positive therapeutic suggestions	19	Headphones with blank tape	20	Explicit memory (open-recall) Patient outcome (pain, PONV, length of stay)

Table 1. Continued.

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Ghoneim 2000	Elective general, gynecological, orthopedic and plastic surgery	Repetitive story-keyword 30 min tape repeated four times	Opioid 7.5 mcg/kg fentanyl bolus	100	N_2O-opioid infusion 1.5 mcg/kg/min alfentanil	40	Explicit memory (open-recall, recognition test) Implicit memory (story-related free association) Mid-latency auditory evoked potential relationship with memory formation
			Isoflurane 0.3% - fentanyl 1mcg/kg	16	Isoflurane 0.7% - fentanyl 1mcg/kg	24	
Hughes 1994	Elective ear-nose-throat, urological, gynecological, orthopedic surgery	Behavioral suggestion tape on smoking cessation played continuously	Smoking cessation message	50	Control tape with counted numbers	50	Explicit memory (open-recall) Implicit memory (postoperative behavioral response)
Ikedo 2007	Coronary artery bypass graft and/or open valve heart surgery	Prayer or hemisync played continuously	Generic prayer	24	Headphones with blank compact disc	27	Patient outcome (opioids, postoperative complications, length of stay)
			Hemisync	27			
Jansen 1991	Elective surgery lasting 45 to 240 min	Positive therapeutic suggestions and motor instructions 10 times during 15 min	Seaside sounds with motor suggestions	38	Seaside sounds	42	Explicit memory (open-recall) Implicit memory (postoperative motor response)
Jayaraman 2006	Laparoscopic cholecystectomy	Positive therapeutic suggestions and calming music played continuously	Music	24	Routine operating room sounds	34	Explicit memory (open-recall) Patient outcome (pain, PONV, subjective well-being)
			Music with positive therapeutic suggestions	27			
Jelicic 1992	Strabismus surgery	Ten facts or names 15 min tape, with filler seaside sounds continuously	Presented facts	21	Target names	22	Explicit memory (open-recall) Implicit memory (presented facts and target names)

Table 1. Continued.

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Jelicic 1993	Body surface surgery (majority breast surgery)	Ten facts or names 15 min tape, with filler seaside sounds continuously	Presented facts	20	Target names	21	Explicit memory (open-recall) Implicit memory (presented facts and target names)
Kahloul 2017[†]	Elective liver cyst, abdominal cancer biliary, proctologic surgery	Tunisian, Eastern, instrumental or Western music played continuously	Music	70	Headphones with no music	70	Explicit memory (unspecified test) Patient outcome (pain, patient satisfaction, Riker recovery scale)
Kerssens 2001	Elective general, orthopedic, urological outpatient surgery	Four common exemplars repeated 15 min followed by filler bird singing sounds continuously	Category exemplar list	41	Filler bird singing	41	Explicit memory (open-recall, recognition test) Implicit memory (category exemplar generation task)
Kerssens 2009	Elective hip or knee replacement surgery	Three 15 word lists with one played continuously	BIS-guided sevoflurane anesthesia	62	HP-guided sevoflurane anesthesia	47	Explicit memory (open-recall, recognition test) Preoperative fentanyl and BIS-guiding effect on recall
Kliempt 1999	General, non-cancer surgery	Classical music or hemisync played continuously	Adagio Karajan	25	Headphones with blank tape	16	Patient outcome (intraoperative fentanyl requirement)
			Hemisync	25			
Lebovits 1999	Elective day care hernia repair	Positive therapeutic suggestions or 7 min hospital story tape played continuously	Positive therapeutic suggestions	34	Hospital history story	36	Explicit memory (open-recall) Patient outcome (pain, PONV)

Table 1. Continued.

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Lequeux 2014	Unspecified ASA I-II surgery patients	Two 20 word lists with one played continuously	High-opioid remifentanil	39	No auditory stimuli control group for baseline	40	Explicit memory (open-recall, free recall, recognition test) Implicit memory (word-stem completion test) Noxious stimuli and opioid effect on memory
			Low-opioid remifentanil	39			
Lewis 2004	Laparoscopic bariatric or lumbar disk surgery	Hemisync played continuously	Hemisync	30	Headphones with blank tape	30	Patient outcome (intraoperative fentanyl requirement)
Liu 1992†	Total abdominal hysterectomy	Positive therapeutic suggestions 10 min tape or hospital story played continuously	Positive therapeutic suggestions	24	Hospital history story	25	Explicit memory (open-recall) Patient outcome (pain, analgesic requirement, PONV, length of stay)
					Headphones with blank tape	24	
Maroof 1997	Elective abdominal hysterectomy	Positive therapeutic suggestions 15 min tape played continuously	Positive therapeutic suggestions	25	Headphones with blank tape	25	Explicit memory (open-recall) Patient outcome (PONV, anti-emetics)
McLintock 1990†	Elective open abdominal hysterectomy	Positive therapeutic suggestions 15 min tape played continuously	Positive therapeutic suggestions	25	Headphones with blank tape	25	Explicit memory (open-recall) Patient outcome (pain, opioids, PONV)
Melzack 1996	Elective cholecystectomy or hysterectomy	Positive therapeutic suggestions and motor instructions 4 min tape	Positive therapeutic and postoperative motor response suggestions	10	Story-keywords on sensory perception and pain	10	Explicit memory (recognition test) Implicit memory (postoperative behavioral response) Patient outcome (pain, length of stay)

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Table 1. Continued.

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Migneault 2004†	Abdominal hysterectomy with (hystero)salpingo-oophorectomy	Classical, jazz, new-age or popular piano music compact disc	Music	15	Headphones without music	15	Explicit memory (open-recall) Patient outcome (opioids, intraoperative fentanyl requirement)
Millar and Watkinson 1983	Upper-abdominal, gynecological surgery	Four ten word lists 14 min tape	Word list	27	Headphone with static radio noise	26	Explicit memory (open-recall, free recall, recognition test)
Myles 1996	Elective or semi-elective surgery	Behavioral 3 min suggestion tape on smoking cessation played continuously	Positive suggestion for smoking cessation	185	Headphones with blank tape	178	Explicit memory (open-recall) Implicit memory (postoperative behavioral response)
Nilsson 2001†	Elective open abdominal hysterectomy	Positive therapeutic suggestions with or without music played continuously	Relaxing and calming music	30	Headphones with OR noise	28	Explicit memory (open-recall) Patient outcome (pain, opioids, PONV, length of stay, subjective well-being)
			Positive therapeutic suggestions with music	31			
Nilsson 2003†	Day case inguinal hernia repair or varicose vein surgery	Slow, flowing, new age 43 min music tape played continuously	Instrumental music	51	Headphones with blank CD	49	Explicit memory (open-recall) Patient outcome (pain, opioids, patient satisfaction)
Nilsson 2005†	Open inguinal Lichtenstein hernia repair	Slow, flowing, new age 43 min music tape played continuously	Instrumental music	25	Headphones with blank CD	25	Patient outcome (pain, opioids)
Oddby-Muhrbeck 1995†	Elective breast surgery	Positive therapeutic suggestions with soft music 32 min tape played continuously	Positive therapeutic suggestions with music	35	Headphones with blank tape containing low background sound	35	Explicit memory (open-recall) Patient outcome (pain, analgesic requirement, PONV, anti-emetics, length of stay)

Table 1. Continued.

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Parker 1994	Minor or moderate surgery	Four 20 min, 10 word lists with music played continuously	Word list	24	Headphones with blank tape	24	Explicit memory (free recall, recognition test)
Patil 2015	Elective laparoscopic cholecystectomy	Classical instrumental music played continuously	Music	30	Headphones without music	30	Explicit memory (open-recall) Patient outcome (intraoperative opioid and sedative requirement)
Renna 2000	Gynecological minor surgery	Positive suggestions and 8 word list played once before surgical stimuli start	Sevoflurane 1.2%	15	Sevoflurane 2.0%	16	Explicit memory (open-recall, recognition test) Implicit memory (postoperative behavioral response)
			Sevoflurane 1.5%	16			
Reza 2007†	Elective caesarean section	Soft instrumental Spanish guitar music played continuously	Music	50	White noise	50	Patient outcome (pain, opioids, PONV, anti-emetics)
Russel and Wang 2001	Gynecological major surgery	Motor instructions with vegetable or fruit word list played continuously	Fruit word list	20	Vegetable word list	20	Explicit memory (open-recall) Implicit memory (word pair free association, category exemplar generation task)
Simcock 2008†	Primary total knee arthroplasty	Music played continuously	Music	15	White noise	15	Explicit memory (open-recall) Patient outcome (pain, patient satisfaction)
Szmuk 2008†	Laparoscopic hernia repair or cholecystectomy	Classical, pop-rock or Israeli music played continuously	Music	15	Headphones without music	20	Patient outcome (pain, analgesic requirement)

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Table 1. Continued.

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Tsuchiya 2003	Elective laparoscopic cholecystectomy	Sounds of a ripple, small stream, soft wind and twitter played continuously	Natural environmental sounds	29	Undistinguishable dummy headphones and OR noise	30	Explicit memory (open-recall) Patient outcome (intraoperative hemodynamic parameters)
West-moreland 1993	Elective surgery	Two 20 word pair 50 min tapes, 2 four-exemplar categories and 10 homophones	Premedication midazolam 2 mg intravenous	24	No premedication midazolam 2 mg, but 2 ml saline intravenous	24	Implicit memory (category exemplar generation task, word pair free association, homophone spelling) Midazolam effect on memory formation
Williams 1994	Major gynecological surgery	Positive therapeutic suggestions 15 min tape played continuously	Positive therapeutic suggestions	22	Headphones with blank tape	29	Explicit memory (open-recall) Patient outcome (analgesic requirement, PONV, anti-emetics)
Zhang 2005†	Elective total abdominal hysterectomy	Participant-selected music played continuously	Music	55	Headphones without music	55	Explicit memory (open-recall) Patient outcome (patient satisfaction)

Table 1 legend. Overview of the included studies evaluating intraoperative auditory stimulation and perception, † indicates studies included in quantitative analysis (meta-analysis).
ASA = American Society of Anesthesiologists physical status; BIS = Bispectral index; BP = Blood pressure; FiO2 = Fraction of inspired oxygen; HP = Hemodynamic parameter; kg = Kilogram; MAC = Minimum alveolar concentration; mcg = Microgram; mg = Milligram; min = Minutes; ml = Milliliter; N1 = Number of patients in group 1; N2 = Number of patients in group 2; N2O = Nitrous oxide; O2 = Oxygen; OR = Operation room; PACU = Postoperative anesthesia care unit; PONV = Postoperative nausea and vomiting

Table 2. Baseline study characteristics

Baseline study characteristics		Overall	Explicit memory	Implicit memory	Patient outcome
Number of studies (patients)		53 (4200)	45 (3528)	23 (1864)	29 (2249)
Auditory intervention	Positive therapeutic suggestions	22	21	8	16
	Words, facts or names list	17	15	13	0
	Music	12	8	0	12
	Stories	7	7	5	4
	Other	3	1	0	2
ASA physical status	I	4	3	2	2
	I-II	27	24	13	15
	I-III	7	5	2	4
	Not specified	15	13	6	8
Surgical severity classification	Minor	7	6	5	2
	Moderate	11	8	3	8
	Major	19	18	5	15
	Multiple severity classes	7	6	4	0
	Not specified	9	7	6	4
Surgery duration	0 – 60 minutes	9	6	4	4
	60 – 120 minutes	18	17	5	14
	> 120 minutes	8	5	2	5
	Not specified	18	17	12	6
Auditory intervention duration	Continuously throughout surgery	38	31	12	27
	Prespecified tape duration	13	12	10	1
	Not specified	2	2	1	1
General anesthesia regimen	Premedication (opioid/ benzodiazepines)	31 (9/17)	28 (7/17)	13 (2/7)	16 (6/10)
	Balanced anesthesia	40	33	16	23
	Total intravenous propofol anesthesia	10	10	6	4
	Inhalational induction and maintenance	2	2	1	1
	Unspecified intraoperative anesthesia	1	0	0	1
	Patient controlled analgesia or spinal/epidural	9	9	2	7
	Bispectral index monitor	14	12	7	6

Table 2 legend. Overview of baseline study characteristics of the included studies. Jayaraman (2006), Lebovits (1999), Liu (1992), Melzack (1996), Nilsson (2001) employed multiple auditory intervention groups, whilst Renna (2000), Russel and Wang (2001) employed an auditory intervention consisting of both suggestions with a word list. Not all studies specified the administered premedication.

Three studies did not specify the age of the participants (5.7%). In 18 studies (34%), the entire study population was female.

Perioperative anesthesia regimens employed in the included studies are specified in Appendix B. In thirty-one studies, premedication was administered before general anesthesia induction, with opioids in nine and benzodiazepines in 17 (Table 2). Anesthesia consisted in the majority of studies of balanced anesthesia (40 studies, 75%), with thiopental or propofol induction in 90% of studies and inhalational drug maintenance. Ten studies employed total intravenous anesthesia (TIVA) with propofol. In 14 studies (26%), a bispectral (BIS) index monitor was employed. Nine studies (17%) used patient-controlled or spinal-epidural analgesia postoperatively.

Several studies assessed different outcome measures together. Twenty studies assessed both implicit and explicit memory formation; 20 studies assessed both explicit memory formation and patient outcome; and two studies assessed explicit memory formation, implicit memory formation and patient outcome altogether. In seven studies, only patient outcome measures were assessed, whereas three studies only assessed explicit memory formation and one study only implicit memory formation.

Explicit memory formation

Explicit memory formation or conscious recollection of auditory stimuli was assessed in 45 studies (3.528 patients) through three different assessment methods (Figure 1, Table 3). Assessment was performed immediately postoperatively in four studies, within the first 24 hours postoperatively in 30 studies, and within the first and seventh postoperative day during hospital stay in ten studies. One study assessed explicit memory formation four weeks after discharge.

The open-recall test consists of three open-ended questions on the last thing the patient remembered before going to sleep, the first thing they remembered after waking up, and anything happening in between. These questions are also part of the Brice questionnaire[20]. Among 43 studies (3.320 patients) which used the open-recall test, positive tests indicative of explicit memory formation were observed in three (7.0%; 0.54% of patients). Two studies reported positive open-recall tests in respectively six (3.4%) and three patients (2.3%), though none remembered hearing any auditory stimuli[21,22]. Nine of the 15 patients (60%) reported being aware of intraoperatively played music during total knee arthroplasty[23].

The recognition test, in which patients are asked whether or not they recognized the auditory stimuli which was played intraoperatively[24], was used in ten studies (798 patients). In four studies[25,26,22,27], an above chance probability was observed in regards to correctly recognizing the auditory stimuli when compared to the control group, indicating potential explicit memory formation. Except for one patient who correctly remembered a single test word[22], no explicit memory formation through the open-recall test was found, and patients undergoing the recognition test generally were unsure about their yes or no choice.

The free recall test, during which patients are asked to write down words they remember hearing after being exposed to a word list during surgery, was assessed in five studies (277 patients), with no evidence for explicit memory formation[28-32].

Implicit memory formation

Implicit memory formation was assessed in 23 studies (1.864 patients) (Figure 1, Table 3), with 17 using perceptual learning or priming test and six assessing change in postoperative behavioral patient response. In total, nine studies (39%) reported evidence for implicit memory formation. Two studies used multiple tests[33,34].

Seven out of the 17 studies (41%) reported evidence for implicit memory formation using perceptual learning or priming tests. All but one of these studies assessed memory formation within the first 24 hours postoperatively[35]. Patients were exposed to one word list or story at random intraoperatively. A list or story that was not played intraoperatively or a patient group wearing headphones without any auditory stimuli acted as a control. Implicit memory formation was considered potentially present when a higher percentage of positive tests during the postoperative interview occurred when compared to the control group, whilst no explicit recall is present. The story-related free association test was used in four studies, with all employing a balanced anesthesia regimen without premedication[36-38,21]. All four studies observed evidence for implicit memory formation, as patients postoperatively stated matter associated with the intraoperatively presented story after being exposed to the related keyword. The word pair association test, relating postoperatively presented stimuli cue words to words that were presented intraoperatively as a correlated word pair, was used in three studies[35,33,34]. A high rate of correct word pair associations was observed in 25 elective cardiopulmonary bypass surgery patients undergoing isoflurane-fentanyl anesthesia. Two studies – Westmoreland *et al.* (1993), who used a comparable anesthesia maintenance regimen in elective surgical patients, and Russel and Wang (2001), who evaluated major gynecological surgery patients undergoing TIVA propofol-alfentanil anesthesia – did not observe evidence of implicit memory formation. In both of these studies, premedication with benzodiazepines was administered to at least half of the patients. The word stem completion test, correctly completing a list of three-letter stems to words that have been presented intraoperatively, was used in three studies with BIS-guided anesthesia[28,26,29]. Only Deeprose *et al.* (2005) reported implicit memory formation in propofol-nitrous oxide (N_2O) day care orthopedic surgery patients[26], but the two TIVA propofol studies with benzodiazepine premedication did not. The presented facts and target names test was used in four studies (15%)[39-42], which consisted of asking patients questions relating intraoperatively presented statements and fictitious names[43].

Table 3. Explicit and implicit memory assessment

Study	Intervention	ANA	Explicit recall	Implicit memory formation	Time	Comments
Aceto 2003[††]	Repetitive Christian story-keyword sequence	Balanced	Open-recall test (0%)	Story-related free association test (1/40, 2.5%)	24h	MLAER Pa latency increase related to implicit memory formation
Aceto 2013[††]	Repetitive fairy story-keyword sequence	Balanced	Open-recall test (0%)	Story-related free association test (3/54, 5.5%)	End, 24h	Auditory stimulation associated with lower prolactin concentrations
Aceto 2015[††]	Repetitive fairy story-keyword sequence	Balanced	Open-recall test (0%)	Story-related free association test (8/127, 6.3%)	End, 24h	BIS or HP-guided anesthesia no difference in implicit memory formation, cut-off value mean age-adjusted MAC of 0.9 for implicit memory formation
Adams 1998[††]	Repetitive word list	Balanced	Open-recall test (0%) Recognition test (NS)	Word pair free association test (evidence of preserved implicit memory)	POD3-6	23 of 25 patients showed higher rate of correct word pair associations of intraoperatively presented word list
Bejjani 2009	Repetitive word list	TIVA	Open-recall test (0%) Free recall test (0%)	Word-stem completion test (no evidence of implicit memory formation)	POD1	Correct answer rate between word list that was played and was not played not different
Bennett 1985[††]	Positive suggestions with postoperative motor suggestions and music	Balanced	Open-recall test (0%)	Postoperative non-verbal motor response (significant higher motor response in suggestions group)	After POD 2	Although twice more patient allocated to control, postoperative motor response still higher in suggestions group
Boeke 1988	Positive therapeutic and nonsense suggestions, seaside sounds	Balanced	Open-recall test (0%)	Not assessed	POD 6 or 7	No explicit memory formation

Table 3. Continued.

Study	Intervention	ANA	Explicit recall	Implicit memory formation	Time	Comments
Bonebakker 1993	Unfamiliar word categories with bird sound filler	Balanced	Open-recall test (0%)	Category exemplar generation task (no evidence of implicit memory formation)	115 min (mean)	Unfamiliar target words exemplars of common categories were tested, with a high number of possible exemplars
Bonke 1986	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	POD 6 or 7	No explicit memory formation
Caseley-Rondi 1994[†]	Personalized positive suggestions with music	Balanced	Open-recall test (0%) Recognition test (above chance recognition)	Preference task (no evidence of implicit memory formation)	24h, POD3	Above chance accuracy on patient's guesses who correctly assessed that suggestions were played
Dawson 2001	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	POD 5	No explicit memory formation
De Roode 1995	Presented facts and target names with seaside sounds	Balanced	Open-recall test (0%)	Presented facts and target names (no evidence of implicit memory formation)	End	No implicit memory in contrast to earlier study with same anesthesia regimen but no midazolam premedication
Deeprose 2005[† ††]	Repetitive word list	Balanced	Open-recall test (0%) Recognition test (above chance recognition)	Word-stem completion test (implicit memory formation present both in fentanyl and no fentanyl group)	1.5h	Slightly higher mean implicit memory formation score for no fentanyl group, but not statistically significant
Donker 1996	Presented facts and target names	TIVA	Open-recall test (0%)	Presented facts and target names (no evidence of implicit memory formation)	30-60 min	Overall higher mean score in more familiar target name list than in unfamiliar list
Eberhart 1998	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	24h	No explicit memory formation

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Table 3. Continued.

Study	Intervention	ANA	Explicit recall	Implicit memory formation	Time	Comments
Evans and Richardson 1988	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	POD 5	No explicit memory formation, all but one in the intervention group correctly guessed the suggestion tape played
Ghoneim 2000[† ††]	Repetitive story-keyword sequence	Balanced	Open-recall test (6/179 (3.4%)) Recognition test (NS)	Story-related free association test (implicit memory formation present in opioid bolus-70% N_2O group)	POD1 or POD3-4	Significant explicit and implicit memory formation in opioid bolus-70%N_2O MLAER Nb amplitude increase related to explicit, while Na, Pa and Nb latency decrease related to implicit recall
Hughes 1994[††]	Behavioral change message	Balanced	Open-recall test (0%)	Postoperative behavioral response (significantly changed)	4 weeks	Significant more stopped or reduced smoking in intervention group
Jansen 1991	Postoperative motor suggestion	Balanced	Open-recall test (0%)	Postoperative motor response (no difference between groups)	POD 1 or 2	Relatively low number overall of motor response
Jayaraman 2006	Music and positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	End	No explicit memory formation
Jelicic 1992[††]	Presented facts; target names with natural seaside filler sounds	Balanced	Open-recall test (0%)	Presented facts and target names (evidence present of implicit memory formation)	End	Implicit memory present in contrast to later 1993 study, during which enflurane was added as maintenance anesthetic
Jelicic 1993	Presented facts; target names with natural seaside filler sounds	Balanced	Open-recall test (0%)	Presented facts and target names (no evidence of implicit memory formation)	POD1	No implicit memory in spontaneously breathing patients, in contrast to N_2O-opioid anesthesia in 1992 study

Table 3. Continued.

Study	Intervention	ANA	Explicit recall	Implicit memory formation	Time	Comments
Kahloul 2017	Tunisian, Eastern, Western or instrumental music	Balanced	Not specified	Not assessed	24h	No significant difference in awareness between intervention and control group
Kerssens 2001	Familiar word category exemplars with filler birds singing sound	TIVA	Open-recall test (0%) Recognition test (NS)	Category exemplar generation task (no evidence of implicit memory formation)	113 min (mean)	Indication that words presented at BIS levels of 45 are not processed to the extent of memory formation
Kerssens 2009[†]	15 word list	Balanced	Open-recall test (3/109 (2.3%)) Recognition test (above chance recognition in BIS-guided group)	Not assessed	6h	BIS-guided group higher mean BIS and above chance recognition, no higher recognition rate in HP-guided group. Preoperative fentanyl reduces change of memory formation.
Lebovits 1999	Positive therapeutic suggestions, story	TIVA	Open-recall test (0%)	Not assessed	End, 6h, 24h	No explicit memory formation
Lequeux 2014	20 word list	TIVA	Open-recall test (0%) Free recall test (NS) Recognition test (NS)	Word-stem completion test (no evidence of implicit memory formation)	2-3h	No implicit memory formation during BIS-guided propofol-remifentanil anesthesia with low remifentanil doses
Liu 1992	Positive therapeutic suggestions, story	Balanced	Open-recall test (0%)	Not assessed	POD 1	No explicit memory formation
Maroof 1997	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	24h	No explicit memory formation
McLintock 1990	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	24h	No explicit memory formation

Table 3. Continued.

Study	Intervention	ANA	Explicit recall	Implicit memory formation	Time	Comments
Melzack 1996	Personalized positive therapeutic and motor suggestions versus repetitive story-keyword	Balanced	Free recall (NS)	Postoperative behavioral response (no difference between groups, no trend in keywords chosen postoperatively)	POD1-4	Also did not observe a significant beneficial effect on postoperative pain levels and hospital length of stay
Migneault 2004	Classical, jazz, new-age or popular piano music	Balanced	Open-recall test (0%)	Not assessed	24h	No explicit memory formation
Millar and Watkinson 1983	10 word list	Balanced	Open-recall test (0%) Free recall test (NS) Recognition test (higher recognition rate, but NS)	Not assessed	24h	Although higher word recognition rate indicating explicit recall, no significant difference in hand movements for isolated forearm technique
Myles 1996	Behavioral change message	Balanced	Open-recall test (0%)	VAS motivation to stop smoking Postoperative behavioral response (no difference between groups)	End (explicit); 2 and 6 months	Only 29 patients (8%) had stopped smoking at 6 months, which is similar to spontaneous smoking cessation rates
Nilsson 2001	Music with either sea wave sounds or positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	24h	No explicit memory formation
Nilsson 2003	Instrumental new-age synthesizer music	Balanced	Open-recall test (0%)	Not assessed	PACU release	No explicit memory formation

Table 3. Continued.

Study	Intervention	ANA	Explicit recall	Implicit memory formation	Time	Comments
Oddby-Muhrbeck 1995	Positive therapeutic suggestions interspersed with soft music	Balanced	Open-recall test (0%)	Not assessed	24h	No explicit memory formation
Parker 1994	10 word list	Balanced	Free recall test (0%) Recognition test (NS)	Not assessed	POD1	Almost all patients attributed the recognition test as guesswork
Patil 2015	Classical instrumental music	Balanced	Open-recall test (0%)	Not assessed	24h	No explicit memory formation
Renna 2000†	Positive suggestions and 8 word list played once before surgical stimuli	IMM	Open-recall test (0%) Recognition test (higher recognition rate, only present in 1.2% group)	Postoperative behavioral response (no difference in subjective assessment postoperatively)	2-3h	Recognition test was classified as an implicit memory formation assessment instead of an explicit recall test
Russel and Wang 2001	Personalized motor command followed by either fruit or vegetable category word list	TIVA	Open-recall test (0%)	Category exemplar generation task and word pair free association test (no evidence of implicit memory formation)	Within 2h	Only one word pair was correctly chosen repeatedly during the word pair association test, but not significantly different in both groups
Simcock 2008	Choice of 3 music compact discs	TIVA	Open-recall test (60%)	Not assessed	24h	60% patients reported correctly that they were exposed to music
Tsuchiya 2003	Natural environmental sounds (ripple, stream, wind and twitter)	TIVA	Open-recall test (0%)	Not assessed	24h	No explicit memory formation

Table 3. Continued.

Study	Intervention	ANA	Explicit recall	Implicit memory formation	Time	Comments
Westmoreland 1993	10 homophones, 10 word pairs and 2 categories	Balanced	Not tested	Category exemplar generation task, word pair free association test, homophone spelling (no implicit memory formation)	2h and 48h	No implicit memory formation, therefore unclear whether premedication midazolam influences memory formation
Williams 1994	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	24h	No explicit memory formation
Zhang 2005	Participant-selected music	Balanced	Open-recall test (0%)	Not assessed	24h	No explicit memory formation

Table 3 legend. Overview of explicit and implicit memory formation after intraoperative auditory stimuli during general anesthesia.
† denotes evidence for explicit memory formation
†† denotes evidence for implicit awareness through memory formation or postoperative behavioral response.
ANA = Anesthesia regimen; Balanced = Balanced anesthesia using intravenous anesthesia induction and inhalational anesthesia maintenance; BIS = Bispectral index; End = Assessment upon awakening from anesthesia at end of operation; h = hours; HP = Hemodynamic parameters; IMM = Inhalational induction and maintenance anesthesia; min = minutes; MLAER = Mid-latency auditory evoked response; N_2O = nitrous oxide; NS = No significant difference among groups in correct recognition or free recall test rate; POD = Postoperative day; Time = Moment of assessment of explicit / implicit memory; TIVA = Total intravenous anesthesia

Jelicic *et al*. (1992) observed implicit memory formation in strabismus surgery patients undergoing opioid-N_2O anesthesia, but did not find this in body surface surgery patients one year later when enflurane was added to the anesthesia regimen. Additional factors that could influence the contradictory findings were the time to testing being later in Jelicic *et al*. (1993), as well as the administration of morphine before and after surgery. No evidence was observed through the category exemplar generation task, during which target words belonging to a certain category were presented intraoperatively [44,45,33,34], nor using the preference task[25], evaluating preference of intraoperatively presented melodies[24].

Six studies (643 patients) assessed implicit memory formation through change in postoperative behavioral patient response after intraoperatively played taped suggestions, with two (33%) showing evidence for implicit memory formation. Two studies that assessed motor response during the postoperative interview reported conflicting results[46,47], as did two studies that evaluated smoking cessation after intraoperatively played taped instructions[48,49]. Finally, two studies did not find different answering or higher use of keywords postoperatively whilst filling out a questionnaire, indicating no implicit memory formation[32,27].

Postoperative patient outcomes

Postoperative patient outcomes and recovery were assessed in 29 studies (2.249 patients). Postoperative pain was assessed in 19 studies, with ten included in the meta-analysis[50-57,23,58]. Intraoperative music significantly reduced postoperative pain when assessed within the first three hours after surgery (pooled SMD -0.51 (95% CI -0.81 to -0.22), $p < 0.001$, $I^2 = 38$, N = 320 patients in 5 studies) and after 24 hours (pooled SMD, -0.84 [95% CI, -1.1 to -0.57]; $P < 0.001$; $I^2 = 0$; $n = 226$ patients in 3 studies). Intraoperative positive therapeutic suggestions did not reduce postoperative pain (pooled SMD 0.033 (95% CI -0.34 to 0.40), $p = 0.861$, $I^2 = 43$, N = 202 patients in 4 studies) (Figure 2). Postoperative opioid requirements were assessed in 12 studies, with nine included in the meta-analysis[59,60,52,53,61,54-57]. Intraoperative music significantly reduced postoperative opioid requirements (pooled SMD -0.29 (95% CI -0.57 to -0.015), $p = 0.039$, $I^2 = 36$, N = 336 patients in 5 studies), whereas positive therapeutic suggestions did not (pooled SMD -0.12 (95% CI -0.40 to 0.16), $p = 0.413$, $I^2 = 39$, N = 372 patients in 5 studies) (Figure 3).

PONV was assessed in 16 studies, but no meta-analysis could be performed due to the methods of PONV assessment and reporting. Two reported short-lasting PONV relief directly after surgery but not when evaluated later that day[62,63], whilst three studies found PONV to be reduced when patients had been exposed to positive therapeutic suggestions[64,60,65]. Postoperative antiemetic requirement was assessed in seven studies, but given the different auditory interventions and result presentation, no meta-analysis was performed.

Figure 2. Effect of music and positive therapeutic suggestions on pain

Music < 3 hours

Study	N	Music Mean	SD	N_M	Control Mean	SD	N_C	Moment
Nilsson 2003	100	1.8	1.1	51	2.6	1.6	49	2 hours
Nilsson 2005	50	2.4	1.8	25	3.8	1.9	25	1 hours
Reza 2007	100	7.06	2.55	50	7.26	2.75	50	PACU
Simcock 2008	30	1.47	1.39	15	3.87	3.44	15	3 hours
Szmuk 2008	40	3.3	2.7	20	5.0	2.7	20	15 minutes
Total	**320**			**161**			**159**	

Pooled SMD -0.51 [95%CI -0.81 to -0.22], $p < 0.001$, $I^2 = 38$

Music 24 hours

Study	N	Music Mean	SD	N_M	Control Mean	SD	N_C	Moment
Kahloul 2017	140	3.38	1.36	70	4.51	1.62	70	24 hours
Nilsson 2001	56	1.8	0.70	29	2.7	0.80	27	24 hours
Simcock 2008	30	2.41	1.67	15	4.03	2.89	15	24 hours
Total	**226**			**114**			**112**	

Pooled SMD -0.84 [95%CI -1.1 to -0.57], $p < 0.001$, $I^2 = 0$

Positive therapeutic suggestions

Study	N	PTS Mean	SD	N_{PTS}	Control Mean	SD	N_C	Moment
Evans & Richardson 1988	39	2.39	2.00	19	2.65	2.54	20	Day 5
Liu 1992	48	3.97	2.06	24	3.00	1.77	24	12 hours
McLintock 1990	60	2.0	2.03	30	1.7	2.28	30	24 hours
Nilsson 2001	55	2.3	1.2	28	2.7	0.8	27	24 hours
Total	**202**			**101**			**101**	

Pooled SMD 0.033 [95%CI -0.34 to 0.40], $p = 0.861$, $I^2 = 43$

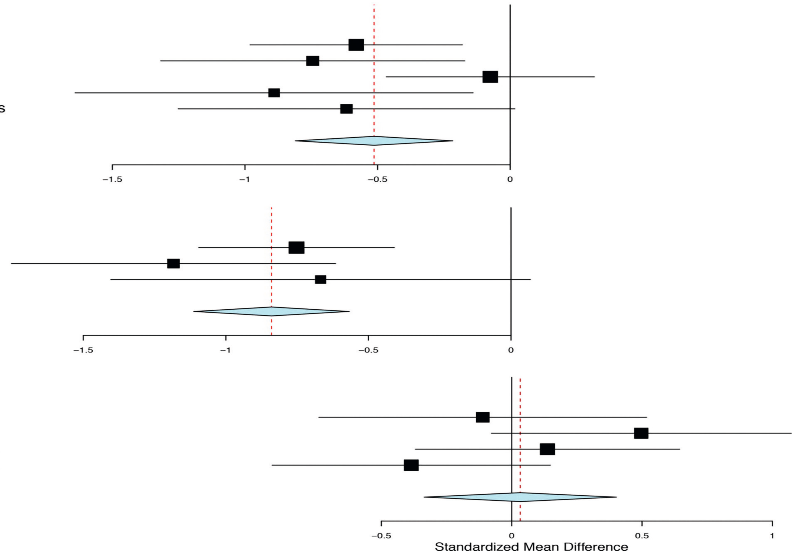


Figure 2 legend. Forest plot presenting the effect of intraoperative music and positive therapeutic suggestions on postoperative pain.
CI = confidence interval; Moment = moment of measurement; N = total number of patients per study; N_C = number of patients in control group; N_M = number of patients in music group; N_{PTS} = number of patients in positive therapeutic suggestions group; PACU = post-anesthesia care unit; PTS = positive therapeutic suggestions; SD = standard deviation; SMD = standardized mean difference

Figure 3. Effect of music and positive therapeutic suggestions on opioid requirement

Music

Study	N	Music Mean	SD	N_M	Control Mean	SD	N_C	Moment	Opioid
Migneault 2004	30	85.8	40.0	15	69.4	30.9	15	24 hours	Morphine equivalent
Nilsson 2001	56	22.2	13.5	29	32.8	17.1	27	24 hours	Ketobemidone i.v.
Nilsson 2003	100	2.0	2.5	51	3.1	3.6	49	2 hours	Morphine equivalent
Nilsson 2005	50	1.8	2.4	25	2.9	3.1	25	1 hours	Morphine equivalent
Reza 2007	100	4.52	2.74	50	5.3	3.7	50	PACU	Morphine equivalent
Total	**336**			**170**			**166**		

Pooled SMD -0.29 [95%CI -0.57 to -0.015], $p = 0.039$, $I^2 = 36$

Positive therapeutic suggestions

Study	N	PTS Mean	SD	N_{PTS}	Control Mean	SD	N_C	Moment	Opioid
Dawson 2001	138	44.2	25.4	103	41.5	24.0	35	24 hours	Morphine equivalent
Eberhart 1998	71	12.6	13.0	36	13.6	12.9	35	48 hours	Piritramide i.v.
Liu 1992	48	94.0	32.5	24	85.7	32.9	24	48 hours	Papaveretum i.m.
McLintock 1990	60	51.0	24.5	30	65.7	26.9	30	24 hours	Morphine equivalent
Nilsson 2001	55	26.5	17.7	28	32.8	17.1	27	24 hours	Ketobemidone i.v.
Total	**372**			**221**			**151**		

Pooled SMD -0.12 [95%CI -0.40 to 0.16], $p = 0.413$, $I^2 = 39$

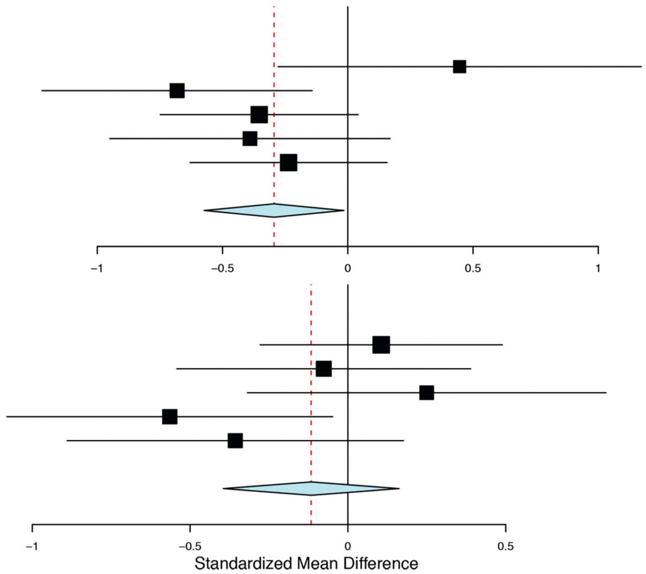


Figure 3 legend. Forest plot presenting the effect of intraoperative music and positive therapeutic suggestions on postoperative opioid requirement (milligrams of morphine equivalents).
CI = confidence interval; i.m. = intramuscular; i.v. = intravenous; Moment = moment of measurement; N = total number of patients per study; N_C = number of patients in control group; N_M = number of patients in music group; N_{PTS} = number of patients in positive therapeutic suggestions group; Opioid = opioid drug used in study, dosage converted to milligrams of morphine equivalents; PACU = post-anesthesia care unit; PTS = positive therapeutic suggestions; SD = standard deviation; SMD = standardized mean difference

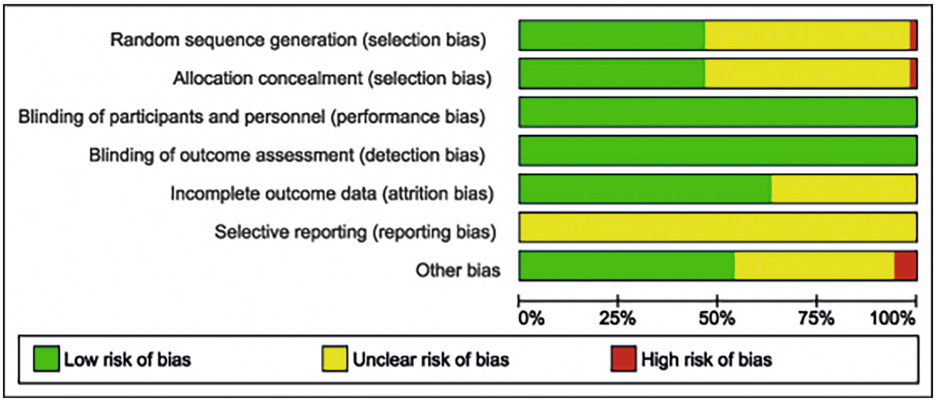
4

Length of stay was assessed in 12 studies, of which six qualified for inclusion into the meta-analysis[66,59,60,50,52,67]. All evaluated positive therapeutic suggestions, but no significant differences in length of hospital stay (pooled SMD -0.17 (95% CI -0.67 to 0.33), $p = 0.517$, $I^2 = 73$, N = 286 patients in 4 studies) or postoperative anesthesia care unit stay pooled SMD -0.093 (95% CI -0.42 to 0.24), $p = 0.580$, $I^2 = 0$, N = 141 patients in 2 studies) were observed. Patient satisfaction or subjective well-being was assessed in seven studies, of which three assessing intraoperative music qualified for inclusion into the meta-analysis[54,23,68]. No significant difference was observed (pooled SMD 0.63 (95% CI -0.98 to 2.2), $p = 0.441$, $I^2 = 96$, N = 198 patients in 3 studies).

Risk of Bias Assessment

A Risk of Bias summary figure is presented in Figure 4, with a detailed individual study level bias risk description in Appendix C and D. Selection bias was considered to be low in 25 studies (47%). In 27 studies (51%), the randomization and allocation methods were not specified and therefore considered as unclear. One study (1.9%) had a potentially high risk of selection bias, as randomization was performed depending on the odds and even days of the week[51]. All patients were considered to be blinded as the auditory intervention was played intraoperatively during general anesthesia. In several studies, study groups received different anesthesia regimens in order to assess its effects on memory formation. Therefore, the anesthesiologist was not blinded to group allocation. However, as different tapes (i.e., several composed word lists or stories) were used at random intraoperatively, the anesthesiologist and personnel were blinded to the specific intraoperative auditory intervention used and could therefore not influence the postoperative memory assessment. Given that outcome assessors were all blinded as well, the risk of performance and detection bias in all included studies was considered to be low. Attrition bias was considered to be low in 33 studies (62%), and unclear due to lack of specification of details on excluded patients in 20 studies (38%). The other risk of bias category was considered adequately addressed and therefore a low bias risk if specific baseline characteristics did not differ significantly between study groups in included studies. Surgery duration, age, sex, weight or body mass index and intraoperative medication dose requirements did not differ significantly in 28 studies (53%). Due to insufficient specification, the other risk of bias category was considered unclear in 22 studies (42%). In three studies (5.7%), the other risk of bias category was considered to be potentially high[25,69,33]. Publication bias was not assessed due to the limited number of studies included in quantitative synthesis, following the recommendations of the Cochrane Handbook[18].

Figure 4. Risk of bias graph



Discussion

This systematic review and meta-analysis of 53 randomized controlled trials with 4.200 patients evaluated the perception and effect of intraoperative auditory stimulation during general anesthesia. Approximately 0.5% of patients explicitly recalled auditory stimuli. Implicit recall, awareness without conscious recall, was observed in nine studies. Implicit memory formation is more difficult to evaluate than explicit recall; while different perceptual learning or priming tests have been developed to assess this, some likely are more sensitive than others[7]. Given the varying tests employed, the occurrence, consequences, and possible therapeutic applications of implicit memory formation are therefore not entirely clear[70].

A secondary aim was to assess which factors could potentially influence implicit memory formation. The physiological stress response to surgery has previously been implicated in implicit memory formation by impairing memory-relevant brain structures [15]. A more vigorous response could impair memory due to higher cortisol levels influencing memory-relevant brain structures[71]. No specific perioperative factors seem to play a defining role in the occurrence of implicit memory formation. Our findings imply that implicit memory formation can occur in a range of procedures irrespective of surgical severity. Although the role of perioperative opioids has been investigated, this seems less clinically relevant because adequate analgesia should be provided to all patients. Explicit awareness has been theorized to occur more often when TIVA is administered instead of inhalational anesthesia, due to the drug mechanism and lack of end-tidal anesthesia gas (ETAG) values to guide drug administration[72]. This was not apparent for implicit memory formation, although the use of premedication could have been of influence. Anterograde amnesic effects of benzodiazepines have clearly been established, but their role in preventing processing during general anesthesia and formation of implicit memory is unclear[73-75]. In all included studies with evidence of implicit memory formation and the music intervention studies in the present meta-analysis, no benzodiazepine premedication was used. Studies using similar memory tests and with comparable anesthesia regimens that included preoperative benzodiazepine administration did not observe implicit memory formation. Therefore, benzodiazepines may possibly affect implicit memory formation, warranting further research. Due to the manner of data reporting, it was not possible to perform analyses to test this hypothesis. Some might argue that no implicit memory formation occurs, but that it is merely a degree of explicit memory formation during periods of lighter anesthesia depths with no conscious recollection due to drug-induced amnesia. Whilst sedation depth level plays a clear role in explicit recall, implicit memory formation was also observed in several studies which appeared to employ clinically adequate, ETAG- or BIS-guided anesthesia[36,37,26]. Although this does not exclude periods of lighter anesthesia depth, this is currently the accepted clinical practice during surgery. As it could be argued that even more attention is given to the maintenance of adequate anesthesia depth by following trial protocols in a 'controlled setting', true implicit awareness rates might be even higher in routine surgical patient care.

Effect of intraoperative auditory stimuli on clinical outcome and recovery

Whether implicit memory formation can and should be prevented is debatable, as it can improve immediate postoperative patient outcomes and recovery. We observed a significant moderate-to-large beneficial effect of intraoperative music during general anesthesia on postoperative pain and opioid requirements within the first 24 hours after surgery during which pain levels are generally the highest[76,77]. The underlying mechanism could involve an attenuating effect on the physiological stress response to surgery and stress hormone levels[11]. In the present meta-analysis, all but one of the included studies also used preselected music. Interestingly enough, no such effects were observed with positive therapeutic suggestions, which consisted of personalized speech tapes with specific suggestions or instructions. These differences might relate to the fact that different brain regions are active during music versus speech [78,79]. The variation in several potential implicit memory formation factors such as premedication use and longer measurement duration of patient outcome parameters compared to the 'music medicine' studies should also be noted[7]. Whether long-term negative effects of implicit memory formation exist is not yet clear. Given the relatively high rate of implicit memory formation observed, this would be expected to lead to many distressed patients after surgery in clinical practice.

Strengths and limitations

To date, we believe this to be the most comprehensive and detailed systematic literature review on the perception of different intraoperative auditory stimuli and its effect on surgical patients. The strengths of this study include the exhaustive literature search with a dedicated biomedical information specialist, extensive cross-referencing, and thorough extraction of perioperative factors. Moreover, a low bias risk was deemed present in all included studies due to the blinding of patients, staff and outcome assessors. Only adult patients undergoing surgery were included and no sedated volunteers without surgery, as mediation by the physiological stress response to surgery has been implicated in implicit memory formation[80,15,36]. In contrast to previous meta-analyses[9,10], we focused solely on the mechanism and effect of auditory processing and perception during general anesthesia. We also included more studies which were previously not examined. This allowed us to deal with the issue of high heterogeneity levels, whilst also taking into account the follow-up measurement moment and different type of auditory stimuli, strengthening our results. Whilst clinical heterogeneity is still assumed to be present, we observed acceptable levels of heterogeneity ($I^2 < 40\%$)[18]. In contradiction to our previous meta-analysis, we also observed a significant beneficial effect of intraoperative music on postoperative opioid requirements. Due to the manner of reporting, different memory formation tests employed, and varying control groups in the included studies, it was not possible to evaluate or analyze the incidence and potential influencing perioperative factors of implicit memory formation. Due to the limited number of included studies in the meta-analysis, additional subgroup analyses and assessment of publication bias were also not possible. A significant proportion of the included studies used N_2O, but its use is declining worldwide[81]. Nevertheless, the more recent studies which employed volatile inhalational anesthesia such as isoflurane or sevoflurane, as well as those using total intravenous propofol anesthesia, also observed effects of intraoperative auditory stimuli.

Although the variations in the included aforementioned studies in patient population, surgical procedures, perioperative anesthesia regimens, and outcome must be acknowledged, our results indicate that intraoperative auditory stimuli can be unconsciously perceived and positively affect patient outcomes during the immediate postoperative period. No definitive conclusions on the influence of perioperative factors could be established, although benzodiazepine premedication may possibly affect implicit memory formation. Further studies are needed to evaluate these factors and further define the effects on postoperative patient outcomes.

Conclusion

The present systematic review and meta-analysis show that intraoperative auditory stimuli can be perceived and processed during clinically adequate, general anesthesia, leading to implicit memory formation without explicit awareness. Intraoperative music can exert beneficial effects on postoperative pain and opioid requirements, whilst positive therapeutic suggestions had no apparent effects on patient recovery.

Author Disclosure Statement

No external funding was received for this study. The authors declare no conflicts of interest.

Acknowledgments

The authors would like to thank W. Bramer, biomedical information specialist of the Medical Library, Erasmus MC University Medical Centre, Rotterdam, for his assistance with the literature search, and P. Oomens, MD, for his assistance with the figure illustrations.

Appendix A. Literature search

Database	Years of Coverage	Before deduplication	After deduplication
Embase.com	1971 – October 15, 2020	2306	2268
Medline Ovid	1946 – October 15, 2020	2342	839
Cochrane Central	1992 – October 15, 2020	1211	594
Total		**5859**	**3701**

Embase.com

(music/de OR 'music therapy'/de OR 'sensory evoked potential'/de OR 'auditory evoked potential'/exp OR 'tape recorder'/de OR 'auditory stimulation'/de OR 'voice recorder'/de OR (music OR musical OR musicotherap* OR ((auditor* OR vestibul* OR sensory) NEAR/3 (process* OR evoke* OR information*)) OR tape-record* OR (suggestion* NEAR/3 (positive OR negative OR therapeutic OR played OR auditory)) OR melod* OR headphone* OR (recording NEAR/3 (story OR stories OR auditory))):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 'surgical stress'/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) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim) AND [English]/lim

Medline Ovid

(music/ OR music therapy/ OR Evoked Potentials/ OR exp Evoked Potentials, Auditory/ OR Tape Recording / OR Acoustic Stimulation / OR (music OR musical OR musicotherap* OR ((auditor* OR vestibul* OR sensory) ADJ3 (process* OR evoke* OR information*)) OR tape-record* OR (suggestion* ADJ3 (positive OR negative OR therapeutic OR played OR auditory)) OR melod* OR headphone* OR (recording ADJ3 (story OR stories OR auditory))).ab,ti.) AND (General Surgery/ OR exp Surgical Procedures, Operative/ OR exp Postoperative Complications/ OR exp Anesthesiology/ OR exp Perioperative Care/ OR exp 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.fx.) AND (Controlled clinical trial/ OR Crossover procedure/ OR Double-blind procedure/ OR Single-blind procedure/ OR (random* OR factorial* OR crossover* OR (cross ADJ over*) OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti.) NOT (exp animals/ NOT humans/) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND english.la.

Cochrane Central
((music OR musical OR musicotherap* OR ((auditor* OR vestibul* OR sensory) NEAR/3 (process* OR evoke* OR information*)) OR tape NEXT record* OR (suggestion* NEAR/3 (positive OR negative OR therapeutic OR played OR auditory)) OR melod* OR headphone* OR (recording NEAR/3 (story OR stories OR auditory))):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)

Appendix B. General anesthesia regimen

Study	Premedication (time before surgery)	Anesthesia induction	Anesthesia maintenance	Postoperative analgesia	Anesthesia monitoring	Surgery duration
Aceto 2003	None	Thiopental 5 mg/kg Fentanyl 3 mcg/kg Vecuronium 0.08 mg/kg	One of four inhalational anesthesia regimens (MAC 1.0) with fentanyl 2 mcg/kg if needed	Not reported	MAC (Datex Capnomac Ultima)	91 (10.5) 90 (12.5) 107 (9.0) 97 (9.5)
Aceto 2013	None	Propofol 2mg/kg Remifentanil 0.25 mcg/kg/min Cisatracurium 0.15mg/kg	Sevoflurane ETAG 2.2% (MAC 1.0) Remifentanil 0.1-0.4 mcg/kg/min (MAP and HR within 20% baseline)	Morphine 0.06 mg/kg Paracetamol 1000 mg	BIS Vista (unspecified)	86.8 (28.8) 90.3 (25.7)
Aceto 2015	None	Propofol 2 mg/kg Fentanyl 3 mcg/kg Cisatracurium 0.15 mg/kg	MAC Sevoflurane BIS- or hemodynamic parameter (MAP and HR within 20% baseline) guided	Paracetamol 1000 mg Tramadol 1.2 mg/kg	BIS Vista (unspecified), MAP and HR	74.4 (15.2) 77.6 (13.6)
Adams 1998	None	Midazolam 0.05-0.15 mg/kg Etomidate 0.1 mg/kg if needed Fentanyl 10-20 mcg/kg	Midazolam with isoflurane in O_2 Fentanyl	Not reported	Not reported	300 (51)
Bejjani 2009	Alprazolam 0.5 mg p.o. (30 min)	Propofol Remifentanil Cisatracurium	Propofol (target controlled infusion) Remifentanil Cisatracurium Ventilation mix air/O_2	Not reported	BIS A-2000 (V3.21); Infusion Toolbox ITB	221 (45) 213 (52)
Bennett 1985	No protocol, meperidine, morphine, glycopyrrolate, hydroxyzine, droperidol, pentobarbitone all used	Thiopental	N_2O and either enflurane or halothane Neuromuscular blocking, unspecified	Not reported	Not reported	Not reported

Study	Premedication (time before surgery)	Anesthesia induction	Anesthesia maintenance	Postoperative analgesia	Anesthesia monitoring	Surgery duration
Block 1991	Morphine 9.6 mg with or without glycopyrrolate 0.2 mg i.m. (30-60 min)	Thiopental Non-depolarizing muscle relaxant	70%N_2O in O_2 with isoflurane ETAG 1.0, 1.3, 1.5MAC and fentanyl 0.75 mcg/kg; or 70% N_2O in O_2 with fentanyl 7.5 mcg/kg and 2.5 mcg/kg bolus (BP and HR within 15% baseline); or 70% N_2O in O_2 with alfentanil 50 mcg/kg and infusion 1-3 mcg/kg/min	Codeine, meperidine, morphine, paracetamol and/or ibuprofen	Clinical signs and ETAG	128 (61) 121.1 (47)
Boeke 1988	Lorazepam 2 mg p.o. (120 min) or thalamonal 1-2 ml i.m. (60 min)	Thiopental Suxamethonium Atropine 0.25-0.50 mg i.m.	67%N2O in O2, enflurane if needed Fentanyl Pancuronium	Not reported	Clinical signs	72.5 60.0
Bonebakker 1993	Diazepam 0.1 mg/kg, temazepam 10 mg or oxazepam 10 mg (night before)	Thiopental 4 mg/kg Sufentanil 0.5 mcg/kg Vecuronium 0.1 mg/kg Atropine 0.5 mg i.m.	N2O in O2 2:1 with isoflurane 0.25-0.5% ETAG 0.2-0.4 MAC Sufentanil if needed Vecuronium if needed	Not applicable	Not reported	Not reported
Bonke 1986	Dehydrobenz-peridol-fentanyl 1-2 ml Atropine 0.25-0.5 mg (60 min)	Thiopental Suxamethonium	N_2O in O_2 Fentanyl Dehydrobenzperidol (45%) Pancuronium	Not reported	Not reported	128 (42) 130 (45) 134 (42)
Caseley-Rondi 1994	Diazepam 0.1 mg/kg p.o. (90 min) if needed	Thiopental 2-5 mg/kg Sufentanil 0.5 mcg/kg Atracurium 0.5 mg/kg or vecuronium 0.1 mg/kg	70%N_2O in O_2, isoflurane 0.5% (ETAG CO_2 35-45 mm Hg) Sufentanil 1 mcg/kg/h Atracurium or vecuronium as needed	PCA morphine	Clinical signs and ETAG	Not specified, but differed significantly

Study	Premedication (time before surgery)	Anesthesia induction	Anesthesia maintenance	Postoperative analgesia	Anesthesia monitoring	Surgery duration
Dawson 2001	Morphine 10 mg i.m. Domperidone 30 mg rect. (90 min)	Thiopental 3-5 mg/kg Morphine 0.1-0.15 mg/kg Vecuronium 0.1 mg/kg Diclofenac 100 mg rect.	66%N_2O in O_2 (ETAG CO_2 4.7-5.3 kPa) and isoflurane ETAG 0.8-1.2% Morphine as needed Vecuronium as needed	Diclofenac 100 mg rect. PCA morphine	Clinical signs and ETAG	97 (27.9) 90 (18.8)
De Roode 1995	Midazolam 0.1 mg/kg i.m. (30 min)	Thiopental 4-5 mg/kg Alfentanil 30 mcg/kg Suxamethonium 1 mg/kg Atropine 0.5 mg	70%N_2O in O_2 (ETAG CO_2 3.5-4%) Alfentanil 0.5-1.0 mg if needed (HR and BP within 10% baseline) Vecuronium 4-6 mg	Not applicable	Clinical signs and ETAG	Not reported
Deeprose 2005	None	Propofol with or without fentanyl 1.5 mcg/kg	Propofol 3-9 mg/kg/h target controlled infusion with 66%N_2O in 33%O_2	Morphine 'as clinically appropriate'	BIS A1000 (V2.51)	34 (12) 41 (22)
Donker 1996	None	Induction dose of 0.2 ml/kg mixture sufentanil 5 mcg/ml and propofol 10 mg/ml Atropine 0.5 mg Atracurium 15 mg	Maintenance dose of induction mixture of 15ml with 0.2 ml/kg Bolus 2ml of mixture if necessary (HR and BP within 10% baseline) ETAG CO_2 35 mm Hg)	Not applicable	Clinical signs and ETAG	27.6 (9.0) 28.6 (12.2)
Eberhart 1988	Midazolam 7.5 mg p.o. (at least 120 min)	Droperidol 100 mcg/kg Fentanyl 4 mcg/kg Methohexitone 1-1.5 mg/kg	N_2O in O_2 3:1.6 with ETAG CO_2 4.4-5.0 Fentanyl 2 mcg/kg after skin incision Fentanyl 2 mcg/kg bolus (BP and HR within 30% baseline), if insufficient additional droperidol 30 mcg/kg	Piritramide	Clinical signs and ETAG	69.9 (20.5) 64.9 (21.0)

Study	Premedication (time before surgery)	Anesthesia induction	Anesthesia maintenance	Postoperative analgesia	Anesthesia monitoring	Surgery duration
Evans and Richardson 1988	Not reported	Thiopental	N_2O, halothane (85% patients), enflurane (15% patients)	Not reported	Not reported	70.6 (23.9) 66.3 (16.8)
Ghoneim 2000	None	Thiopental with either: - Fentanyl 7.5 mcg/kg bolus - Alfentanil 50 mcg/kg - Fentanyl 1 mcg/kg	70%N_2O in 30%O_2 with either: - Fentanyl bolus 2.5 mcg/kg if needed (HR and BP within 15% baseline) - Alfentanil 1.5 mcg/kg/min infusion - Isoflurane ETAG 0.3%, fentanyl - Isoflurane ETAG 0.7%, fentanyl	Not reported	Clinical signs and ETAG	Not reported
Hughes 1994	Not specified, but received by majority	Propofol, thiopental or etomidate	Inhalational volatile drug with opioid and positive pressure ventilation	Not reported	Not reported	Not reported
Ikedo 2007	Not reported	Not reported	Not reported	Morphine	Not reported	228 (78) 210 (66) 222 (60)
Jansen 1991	Lorazepam 1.0 mg p.o. (night before) and/or midazolam 2.5 mg i.m. (30 min) if necessary	Thiopental 4 mg/kg Fentanyl 0.005 mg/kg Pancuronium 0.1 mg/kg or vecuronium 0.1 mg/kg	N_2O in O_2 2:1 with enflurane ETAG 0.2-0.4 MAC, ETAG CO_2 4.3-4.5% Incremental fentanyl (HR and BP) Pancuronium or vecuronium if needed	Not reported	Not reported	Not reported

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Study	Premedication (time before surgery)	Anesthesia induction	Anesthesia maintenance	Postoperative analgesia	Anesthesia monitoring	Surgery duration
Jayaraman 2006	Alprazolam 0.5 mg p.o. (night before) Metoclopramide 10 mg and ranitidine 150 mg (morning of surgery)	Propofol 1 mg/kg Fentanyl 1 mg/kg Vecuronium 0.1 mg/kg	70%N_2O in O_2 with sevoflurane ETAG 0.6-1.0%	Diclofenac	Clinical signs and ETAG	79.1 (43.6) 82.6 (36.6)
Jelicic 1992	None	Thiopental 4-5 mg/kg Alfentanil 20 mcg/kg Suxamethonium 1 mg/kg Atropine 0.5 mg	65%N_2O in O_2 (ETAG CO_2 3.5-4.0%) Alfentanil 0.5-1.0mg (HR and BP within 10% baseline) Vecuronium 4-6 mg, 1mg every 20 min	Not applicable	Clinical signs and ETAG	Not reported
Jelicic 1993	Morphine 10-15 mg and cyclizine 50 mg i.m. (45 min)	Thiopental	N_2O and enflurane in 34%O_2 with ETAG enflurane 1.1%	Morphine 10 mg and cyclizine 50 mg as needed	Clinical signs and ETAG	Not reported
Kahloul 2017	Not reported	Propofol Fentanyl 3mcg/kg Cisatracurium 0.15 mg/kg	Isoflurane with 50%O_2 / 50% air Fentanyl as needed Cisatracurium as needed	Nefopam	Clinical signs	79.1 (43.6) 82.6 (36.6)
Kerssens 2001	None	Propofol 6mcg/ml target controlled infusion Alfentanil 0.02mg/kg Vecuronium 0.1 mg/kg	BIS-guided propofol target controlled infusion Ventilation mixture 40%air / 60%O_2	Not applicable	BIS A1000 (V3.2)	38 (28) 34 (23)

Study	Premedication (time before surgery)	Anesthesia induction	Anesthesia maintenance	Postoperative analgesia	Anesthesia monitoring	Surgery duration
Kerssens 2009	Fentanyl 50-100 mcg if needed during epidural or PCA placement	Propofol 2 mg/kg Fentanyl 3 mcg/kg Vecuronium 0.1 mg/kg	Sevoflurane in O_2 Fentanyl 50-100 mcg Esmolol 0.5 mg/kg Phenylephrine 100 mcg if needed	Epidural (meperidine / bupivacaine or morphine) or PCA (hydromorphone or morphine	ETAG and/or BIS XP (V3.4)	126 (51) 112 (48)
Kliempt 1999	None	Propofol 2.5 mg/kg	66%N_2O in 33%O_2 with isoflurane ETAG MAC 1.2% Fentanyl (BP and HR within 20% baseline)	Not applicable	Clinical signs and ETAG	53 (42) 63 (41) 48 (28)
Lebovits 1999	None	Propofol 1-2 mg/kg Succinylcholine 1 mg/kg with tubocurarine 3 mg or vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg	Propofol 75-200 mcg/kg/min with 65%N_2O in 35%O_2 Isoflurane <0.6% if needed Fentanyl 5 mcg/kg Vecuronium 0.01 mg/kg	Fentanyl 1-2 mcg/kg Local infiltration with bupivacaine 0.25-0.5%	Not reported	77.6 75.5
Lequeux 2014	Midazolam 0.1 mg/kg p.o. (before arrival in operating room)	Propofol Remifentanil	BIS-guided propofol target controlled infusion with remifentanil effect-site either same or double	Not applicable	BIS XP (unspecified)	54 (36) 52 (48) 69 (40)
Lewis 2004	Midazolam 2 mg (entering operating room)	Propofol Fentanyl 100 mcg (lumbar) or 250 mcg (bariatric) Vecuronium 8-10 mg	Isoflurane with N_2O (lumbar) or without N_2O (bariatric), and O_2 Fentanyl 25 mcg (SBP within 20% and HR within 15% baseline)	Not applicable	BIS (unspecified)	150 (70) 156 (58)

4

Study	Premedication (time before surgery)	Anesthesia induction	Anesthesia maintenance	Postoperative analgesia	Anesthesia monitoring	Surgery duration
Liu 1992	Papaveretum 0.15 mg/kg and prochlorperazine 0.18 mg/kg i.m. (before surgery)	Thiopental 5 mg/kg Vecuronium 0.1 mg/kg	66%N_2O and 1-1.5% enflurane in O_2 Papaveretum 0.1 mg/kg if needed	Papaveretum i.m. Coproxamol p.o.	Not reported	81.4 (16.2) 75.6 (14.3)
Maroof 1997	Promethazine 0.5 mg/kg and buprenorphine 0.04mg/kg i.m. (before surgery)	Thiopental 5 mg/kg Vecuronium 0.1 mg/kg	Halothane 1-2% in 60%N_2O and 40%O_2	Diclofenac 75 mg i.m.	Clinical signs and ETAG	126 (13.7) 118 (15.3)
McLintock 1990	Midazolam (unspecified)	Thiopental 4 mg/kg Morphine 0.15mg/kg Vecuronium	66%N_2O with O_2, enflurane 0.8-1.5%	PCA morphine	Not reported	Not reported
Melzack 1996	None	Thiopental 5 mg/kg Fentanyl 100 mg Vecuronium 0.1 mg/kg	Isoflurane 1-2% with 100%O_2 Vecuronium as needed	Opioid as needed	Not reported	79.5 (21.1) 70.7 (20.4)
Migneault 2004	None	Propofol 1.5-2 mg/kg Fentanyl 3 mcg/kg Rocuronium 0.6 mg/kg	BIS-guided isoflurane ETAG 0.3-1.5% and 50%O_2 / 50%air Fentanyl 0.5-1 mcg/kg (BP and HR within 20% baseline) Rocuronium 10-20 mg	Morphine 3-5 mg bolus followed by PCA morphine	BIS (unspecified), clinical signs and ETAG	106 (18) 125 (45)
Millar and Watkinson 1983	Papaveretum or perphenazine with scopolamine, or pethidine and promethazine	Thiopental or althesin	N_2O 66% in O_2 with or without halothane 0.25-1.0%	Not reported	Isolated forearm technique	Not reported

Study	Premedication (time before surgery)	Anesthesia induction	Anesthesia maintenance	Postoperative analgesia	Anesthesia monitoring	Surgery duration
Myles 1996	Benzodiazepine, opioid or other unspecified (60%)	Thiopental or propofol	Isoflurane or enflurane Neuromuscular blocker (60%)	Not reported	Not reported	56 (46) 50 (41)
Nilsson 2001	Pethidine 50 mg and dixyrazine 10 mg i.m. (unspecified)	Propofol 1-2 mg/kg Fentanyl 2-3 mcg/kg Rocuronium 0.6 mg/kg	70%N_2O in O_2 and isoflurane ETAG ≥0.7	PCA ketobemidone	Clinical signs and ETAG	96 (31.7) 90 (29.1) 100 (31.7)
Nilsson 2003	None	Propofol 1-2 mg/kg Fentanyl 1-2 mcg/kg	70%N_2O in O_2 with sevoflurane ETAG ≥1.2 MAC	Diclofenac 100 mg rect. Morphine 1-3 mg	Clinical signs and ETAG	23 (8.4) 24 (7.2)
Nilsson 2005	None	Propofol 1-2 mg/kg Fentanyl 1-2 mcg/kg	70%N_2O in O_2 with sevoflurane ETAG ≥1.2 MAC	Diclofenac 100 mg rect. Morphine 1-3 mg	Clinical signs and ETAG	23 (8.8) 23 (4.9)
Oddby-Muhrbeck 1995	Midazolam 4-5 mg i.m. (30-45 min)	Thiopental Fentanyl 2 mcg/kg Suxamethonium	O_2 to N_2O 1:2 with isoflurane	Morphine or ketobemidone	Clinical signs	62 (16) 69 (22)
Parker 1994	Diazepam 10 mg p.o. (90-360 min)	Thiopental 5 mg/kg Fentanyl 3 mcg/kg Midazolam 0.07 mg/kg Atracurium 0.6 mg/kg	70%N_2O in O_2, ETAG CO_2 4-4.7 kPa Fentanyl 50 mcg if needed Atracurium if needed	Not reported	Clinical signs and ETAG	57.9 (32.1) 63.4 (30.5)
Patil 2015	Midazolam 0.03 mg/kg (unspecified)	Propofol (eyelash reflex loss) Fentanyl 1.5 mcg/kg Vecuronium 0.1 mg/kg	BIS-guided isoflurane ETAG 0.3-1.5% Mixture 50%O_2 in air Fentanyl 1 mcg/kg if needed	Diclofenac in 100 ml normal saline	BIS (unspecified)	125 (20) 130 (34)

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Study	Premedication (time before surgery)	Anesthesia induction	Anesthesia maintenance	Postoperative analgesia	Anesthesia monitoring	Surgery duration
Renna 2000	Ketorolac 10 mg (30 min)	Sevoflurane in O_2 (ETAG 1.2, 1.5 or 2.0% randomized)	Sevoflurane in O_2 (ETAG 1.2, 1.5 or 2.0% randomized) during auditory intervention followed by 'surgical anesthesia'	Not applicable	BIS A1000 (V2.51), ETAG	Not reported
Reza 2007	None	Thiopental 3-5 mg/kg Succinylcholine 1 mg/kg	50%N_2O in O_2 with halothane 0.8 MAC Midazolam 1-2 mg Morphine 5-7 mg	Morphine	Not reported	23.7 (6.4) 21.6 (5.2)
Russel and Wang 2001	Temazepam 20 mg p.o. (60-120 min) Epidural 0.5% bupivacaine L2-L3	Propofol 2-2.5 mg/kg target controlled infusion Alfentanil 10-12.5 mcg/kg Suxamethonium 1-1.5 mg/kg	Propofol 10-8-6-4 mg/kg/h stepdown with incremental alfentanil (1mg:5mcg) Atracurium 0.2-0.4 mg/kg Ventilation mixture air 35-40%O_2 (ETAG CO_2 4-5%)	Epidural topped up with 10cc of 0.125% bupivacaine with 3 mg diamorphine	Isolated forearm technique	78.9 (35.5) 109.3 (58.8)
Simcock 2008	Not reported	Spinal-epidural anesthesia with propofol sedation	Spinal-epidural anesthesia with propofol sedation	Spinal-epidural anesthesia with propofol sedation	Ketorolac, oxytocin, oxycodone	Not reported
Szmuk 2008	None	Sevoflurane ETAG6%, with 100%O_2 Fentanyl 2 mcg/kg Rocuronium 0.6 mg/kg	50%N_2O in O_2 with BIS-guided sevoflurane, ETAG CO_2 30-35 mm Hg Fentanyl 1 mcg/kg/h Rocuronium if needed	Meperidine 20 mg and dipyrone 2000 mg bolus if needed	BIS AS3 (unspecified)	83 (37) 74 (28)
Tsuchiya 2003	Midazolam 0.08 mg/kg i.m. (60 min) Epidural catheter T9-10	Propofol 3-4 mg/kg Fentanyl 4 mcg/kg Vecuronium 0.15 mg/kg Epidural 1.5% lidocaine 5ml, fentanyl 0.1mg loading dose	Propofol 5-8 mg/kg 100%O2 and ETAG CO_2 35-38 mm Hg Continuous epidural infusion of 1.5% lidocaine 5 ml/h	Epidural lidocaine infusion until leaving PACU after 20 min	BIS (unspecified)	Not specified, but same

Study	Premedication (time before surgery)	Anesthesia induction	Anesthesia maintenance	Postoperative analgesia	Anesthesia monitoring	Surgery duration
Westmore-land 1993	Ranitidine 150 mg and metoclopramide 10 mg p.o. (morning of surgery); Randomized to 2 mg midazolam or saline	Propofol 2.5 mg/kg Fentanyl 3 mcg/kg	Isoflurane 1.3 MAC until incision, then isoflurane 1.0 MAC in 70%N_2O Fentanyl 50-100 mcg increments	Not reported	Not reported	Not reported
Williams 1994	Papaveretum 10-20 mg and hyoscine 0.2-0.4 mg i.m. (unspecified)	Thiopental 4-6 mg/kg Suxamethonium 1 mg/kg Vecuronium 0.1 mg/kg	66%N_2O in 33%O_2 with isoflurane 1% (ETAG CO_2 4-4.7 kPa) Vecuronium as needed	Papaveretum 10-20 mg, diclofenac 100 mg rect.	Clinical signs and ETAG	Not specified, but same
Zhang 2005	Spinal epidural L2-3 tetracaine 0.55% 1.5-2.0cc followed by lidocaine 2% 4-6cc	Propofol 0.5 mg/kg Fentanyl 1 mcg/kg	Propofol 0.2-1.2 mcg/ml every 10 min target controlled infusion, OOA/S guided	Not reported	OAA/S BIS HXD-I (V3.31)	86 (28) 85 (28)

Appendix B legend. Perioperative anesthesia regimen of studies investigating intraoperative auditory interventions during general anesthesia on memory formation and patient outcome. All medication are either intravenously administered, except in the case of inhalational anesthesia administration or if otherwise stated (p.o. = per os, oral administration, i.m. = intramuscular administration).

BIS = Bispectral index; BP = Blood pressure; Clinical signs = Monitoring with standard equipment (electrocardiogram, non-invasive blood pressure, pulse oximetry); CO_2 = carbon dioxide; ETAG = End-tidal anesthesia gas concentration; HR = Heart rate; kg = kilogram; kPa = kilopascal; MAC = Minimum alveolar concentration; MAP = Mean arterial pressure; mcg = microgram; mg = milligram; ml = milliliter; mm = millimeter; Not applicable = No postoperative medication was given before memory formation testing; OAA/S = Observer Assessment of Alertness/Sedation Scale; O_2 = oxygen; PCA = patient-controlled analgesia; Surgery duration = Surgery duration in minutes, reported as mean (standard deviation) in minutes. Group 1 is noted first, followed by group 2 and other groups if applicable

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Appendix C. Risk of Bias Assessment

Study	Method of randomization	Allocation concealment	Blinding participants	Blinding personnel	Blinding assessors	Incomplete outcome	Selective reporting	Other bias addressed
Aceto 2003	Yes, premade randomization tables	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Aceto 2013	Yes, computerized randomization list	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Aceto 2015	Yes, computer generated randomization	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Adams 1998	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear (OR)
Bejjani 2009	Yes, random number generator	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
Bennett 1985	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear (OR)
Block 1991	Unclear, premade randomization tables	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes
Boeke 1988	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear (BMI)
Bonebakker 1993	Yes, premade randomization	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear (BMI)
Bonke 1986	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear (BMI)
Caseley-Rondi 1994	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	No (OR)
Dawson 2001	Yes, table of random numbers	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Deeprose 2005	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear (Age)
De Roode 1995	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear (OR)
Donker 1996	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear (BMI)
Eberhart 1998	Unclear, but stratified randomization	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes
Evans and Richardson 1988	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear (BMI)

Study	Method of randomization	Allocation concealment	Blinding participants	Blinding personnel	Blinding assessors	Incomplete outcome	Selective reporting	Other bias addressed
Ghoneim 2000	Yes, premade randomization tables	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear (OR)
Hughes 1994	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear (OR)
Ikedo 2007	Yes, computer-generated randomization	Yes	Yes	Yes	Yes	Unclear	Unclear	No (SS)
Jansen 1991	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear (BMI)
Jayaraman 2006	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear (age, BMI, OR)
Jelicic 1992	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear (BMI)
Jelicic 1993	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear (BMI)
Kahloul 2017	No, odds and even days	No	Yes	Yes	Yes	Yes	Unclear	Yes
Kerssens 2001	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes
Kerssens 2009	Yes, computer-generated list	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
Kliempt 1999	Yes, computer-generated randomization	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Lebovits 1999	Yes, random numbers table	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
Liu 1992	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes
Maroof 1997	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes
McLintock 1990	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes
Melzack 1996	Yes, random number list	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
Migneault 2004	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes

Study	Method of randomization	Allocation concealment	Blinding participants	Blinding personnel	Blinding assessors	Incomplete outcome	Selective reporting	Other bias addressed
Millar and Watkinson 1983	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear (OR)
Myles 1996	Yes, random number list	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear (BMI)
Nilsson 2001	Yes, computer-generated randomization	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Nilsson 2003	Yes, computer-generated randomization	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Nilsson 2005	Yes, computer-generated randomization	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Oddby-Muhrbeck 1995	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes
Parker 1994	Yes, sealed envelopes method	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Patil 2015	Yes, computer-generated randomization	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Renna 2000	Yes, drawing code from a hat	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear (OR)
Reza 2007	Yes, computer-generated randomization	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Russel and Wang 2001	Yes, sealed envelopes method	Yes	Yes	Yes	Yes	Yes	Unclear	No (age, OR)
Simcock 2008	Yes, sealed envelopes method	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Szmuk 2008	Yes, computer-generated randomization	Yes	Yes	Yes	Yes	Yes	Unclear	Yes

Study	Method of randomization	Allocation concealment	Blinding participants	Blinding personnel	Blinding assessors	Incomplete outcome	Selective reporting	Other bias addressed
Tsuchiya 2003	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear (age)
Westmoreland 1993	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear (age, BMI, OR)
Williams 1994	Unclear, randomly assigned	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear (age, BMI)
Zhang 2005	Yes, computer-generated randomization	Yes	Yes	Yes	Yes	Yes	Unclear	Yes

Appendix C legend. Detailed risk of bias summary.
Yes = Yes, low risk of bias; No = No, high risk of bias; Unclear = Unclear risk of bias; Other bias = Potential bias factors include group sex, age, BMI or weight, and duration of surgery; OR = Surgery duration not reported; BMI = BMI or weight not reported; Age = age not reported; SS = Sample size not reached

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Chapter 5

Intraoperative Music to PROMote PaTient oUtcome (IMPROMPTU): a double-blind, placebo-controlled, randomized multicenter trial

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Submitted

"Intraoperative auditory stimuli can be processed and perceived during general anesthesia, but only music can have beneficial effects on postoperative pain and opioid requirement depending on perioperative factors"

Abstract

Introduction: Perioperative music can have beneficial effects on postoperative pain, anxiety, opioid requirement, and the physiological stress response to surgery. The aim was to assess the effects of intraoperative music during general anesthesia in patients that underwent surgery for esophagogastric cancer.

Methods: The IMPROMPTU study was a double-blind, placebo-controlled, randomized multicenter trial. Adult patients undergoing surgery for stage II-III esophagogastric cancer were eligible. Exclusion criteria were a hearing impairment, insufficient Dutch language knowledge, corticosteroids use, or objection to hearing unknown music. Patients wore active noise-cancelling headphones intraoperatively with preselected instrumental classical music for the music group and no music for the control group. Computerized randomization with centralized allocation, stratified according to surgical procedure using variable block sizes, was employed. Primary endpoint was postoperative pain. Secondary endpoints were postoperative opioid requirement, intraoperative medication requirement, the stress response to surgery, postoperative complication rate, length of stay, and mortality, with follow-up lasting 30 days.

Results: From November 2018 to September 2020, 145 patients were assessed and 83 randomized. Seventy patients (music n=31, control n=39) were analyzed. Median age was 70 [IQR 63–70] and 48 patients (69%) were male. Music did not reduce postoperative pain (NRS 1.8 (SD0.94) versus 2.0 (1.0), mean difference -0.28 [95%CI -0.76–0.19], p=0.236). No statistically significant differences were seen in medication requirement, stress response, complication rate, and length of stay.

Conclusion: Intraoperative, preselected, classical music during esophagogastric cancer surgery did not significantly improve postoperative outcome and recovery when compared to no music using noise-cancelling headphones.

Trial Registry: Dutch Trial Registry (NTR7546).

Authorship

Each author certifies that he has made a direct and substantial contribution to the work reported in the manuscript. VF, SL, CF, SB, WD, JJ, and BW contributed to study concept and design. VF and KM collected the data. Data analysis was performed by EF and VF. Interpretation of data was performed by all authors. Drafting of the manuscript was primarily performed by VF and BW, with all authors providing critical revisions that were important for the intellectual content. All authors approved the final version of the manuscript.

Abbreviation List

95%CI	95% Confidence interval
BIS	Bispectral index
CRP	C-reactive protein
IL-6	Interleukin-6
IQR	Interquartile range
ME	Morphine equivalent, with 1 mg ME being equivalent to 1 mg of parenteral morphine
NRS	Numeric rating scale
NTR	Netherlands Trial Register
PCA	Patient-controlled analgesia
RCT	Randomized controlled trial
SD	Standard deviation
TNF-α	Tumor necrosis factor alpha

Introduction

Esophageal and gastric cancer are among the most common cancers worldwide and rank high among the top ten of cancer related-mortality causes[1]. Multimodal treatment including surgery is the treatment of choice for stage II and III disease. Despite advancements in perioperative patient care and surgical techniques, postoperative morbidity remains relatively high[2]. Suboptimal pain management leading to immobility and impairment of effective breathing can contribute to the development of pulmonary complications and might impair postoperative recovery[3]. Moreover, postoperative pain levels are the predominant predictor of quality of life in the early postoperative period[4, 5]. Whilst epidural analgesia is effective and seen as the current standard for postoperative pain management after esophagogastric cancer surgery[6, 7], its use is associated with side-effects and impairment of postoperative patient mobility[8, 9]. Furthermore, additional systemic opioid analgesics are required in almost half of cases due to misplacement or displacement[10], leading to potential opioid-related adverse effects[11-13]. Therefore, other ways for controlling postoperative pain have been evaluated as part of multimodal analgesia[14].

Perioperative music can have beneficial effects on postoperative pain[15], anxiety, intraoperative sedative medication requirement[16], and postoperative opioid medication requirement[16]. Intraoperative music can have significant beneficial effects on postoperative pain and opioid requirement within the first 24 hours after surgery as well[17]. Furthermore, intraoperative music might also attenuate the physiological stress response to surgery, with lower levels of cortisol and cytokines in studies employing locoregional anesthesia with sedation[18]. This could prove beneficial in major surgical procedures with a vigorous stress response like esophagogastric cancer surgery. To date, effects of music on clinical outcome has only been assessed sparingly[18]. Intraoperative music is relatively cheap, easily applicable, and can increase patient satisfaction[19]. Hence, it may be useful as part of multimodal analgesia. The aim of this double-blind, randomized multicenter trial is to investigate the effect of intraoperative music during general anesthesia on postoperative pain, medication requirement, the physiological stress response to surgery, and the postoperative clinical outcome and recovery in patients undergoing surgery for esophagogastric cancer.

Methods

Trial design

This two-arm parallel, double-blind, multicenter, randomized controlled trial was conducted at three Dutch hospitals (Erasmus University Medical Center, Rotterdam; Maasstad Hospital, Rotterdam; and Elisabeth-Tweesteden Hospital, Tilburg). Institutional medical research ethics committee approval was obtained (MEC-2018-127, NL64875.078.18). Two substantial study protocol amendments were approved in order to facilitate participation at the latter two hospital sites, without any change regarding trial design, eligibility criteria or outcome assessment. The study was registered with the Netherlands Trial Register (NTR 7546) and followed the CONSORT guidelines (Appendix A).

Participants

Eligible patients were informed by the surgeon about the study preoperatively. All adult patients ≥ 18 years old undergoing elective, curative esophageal or gastric cancer resection surgery were eligible for this study. All patients were discussed in a multidisciplinary session in order to assess the perioperative treatment strategy and received preoperative chemoradiation (esophageal cancer) or perioperative chemotherapy (gastric cancer) according to the Dutch national guidelines. Exclusion criteria were a known hearing impairment or usage of a hearing aid, insufficient knowledge of the Dutch language, or objection to hearing any unknown music. As systemic steroid, immunosuppressant and cytotoxic medication affect the physiological stress response to surgery, patients using these medications were also excluded[20]. In case of unresectable esophageal or gastric cancer during surgery or distant metastases found intraoperatively with no surgical resection performed, the participating patient and collected data were excluded from the final analysis and the patient was replaced.

Interventions

A custom four-item questionnaire on music preferences and the importance of music in daily life was filled out by all participating patients (Appendix B). The music intervention consisted of a five hours long playlist of popular instrumental, non-lyrical, classical music, selected by an expert panel of five research physicians (Appendix C). When the operation lasted more than five hours, the playlist was repeated automatically. Consent was obtained from the Buma Association (Dutch: Vereniging Buma) and Stemra Foundation (Dutch: Stichting Stemra), who manage music copyright in the Netherlands, to use music for research purposes in this study. The control group wore the same over-ear, active noise-cancelling headphones as the music intervention group, but a blank file without sounds was played continuously.

After induction of general anesthesia and before skin incision, active noise-cancelling, Bose QuietComfort 35 II over-ear headphones connected to a Sandisk Sansa Clip Sport MP3-player were applied to all patients from incision start until wound closure. Depending on the group allocation, the allocated playlist with either preselected music or silence was selected by a member of the research team. Whilst the research team was not blinded to the intervention, it was not possible for the perioperative care team to distinguish which auditory file was played. At the end of the surgical procedure, the elapsed playing time was noted to denote the duration of the intervention. Intraoperative opioid, sedative and catecholamine requirement were recorded, starting from placement of headphones until removing of the headphones at the moment of wound closure. Blood samples or physiological stress response to surgery assessment were drawn preoperatively before incision (baseline sample), with the second blood sample being drawn exactly eight hours later. Peak stress response levels in major surgical procedures are observed after 8 hours[20-22]. Blood samples were centrifuged with 2000g during 10 minutes within two hours after blood drawing and stored at -80 degrees Celsius.

Perioperative care

A standardized anesthesia protocol was used consisting of bispectral-index (BIS) guided, total intravenous propofol anesthesia. All patients undergoing esophagectomy received an epidural catheter, or a patient-controlled analgesia (PCA) pump, as well as a central venous line and arterial line. Patients undergoing gastrectomy received PCA and an arterial line if deemed necessary by the perioperative care team. Surgery was performed by dedicated upper-gastrointestinal surgeons who had performed more than one hundred procedures. Minimally invasive gastrectomy was performed as previously described[23]. The preferred surgical approach for the esophagus was left to the discretion of the surgeon and involved transthoracic and transhiatal totally minimally invasive esophagectomy with an anastomosis in the chest (Ivor lewis) or neck (Mc Keown). Also hybrid (laparoscopy and open chest) and totally open resections were allowed.

Postoperatively, the pain team of the anesthesiology department was responsible for the epidural or PCA pump and analgesic medication regimen during the first postoperative days until removal of the epidural and PCA pump. Pain scores were assessed daily by the nursing staff, with analgesic medication administered accordingly if needed. Mobilization was encouraged as early as possible directly after surgery, following the Enhanced Recovery After Surgery protocols. All patients that underwent esophagectomy were admitted to the intensive care unit postoperatively for at least 24 hours. Patients that underwent gastrectomy were only admitted to the intensive care unit if deemed necessary. Patients were kept on a nil-per-os regimen for the first postoperative days until the nasogastric tube was removed after esophagectomy, whilst the jejunostomy catheter was used for feeding during the first postoperative month. After gastrectomy, patients were allowed liquid oral feeding from the first postoperative day onwards.

Outcome measures

The primary outcome was postoperative pain on the first postoperative day. This was assessed using an 11-point numeric rating scale (NRS) during the first postoperative week. Postoperative pain was calculated by averaging the pain scores of the morning, afternoon and evening on each postoperative day, including the additional pain score by the pain team responsible for the epidural catheter and PCA pump during the first few postoperative days. Both the mean pain score of each postoperative day per group, as well as the average of the entire first postoperative week per group, were analyzed. Pain scores were assessed as part of standard care by patients and the nursing staff, who were blinded to the intervention.

Secondary outcome measures were postoperative pain during the first postoperative week, the physiological stress response to surgery, intraoperative medication requirement (opioid, sedatives, inotropes and vasopressors), postoperative opioid medication requirement, postoperative complication rate (classified according to the Clavien-Dindo classification), hospital and intensive care length of stay, and 30-day mortality. All outcome measures, except de physiological stress response to surgery, were part of standard patient care, assessed by health care providers blinded for the intervention and documented in the electronic patient database. The physiological stress response to surgery was assessed by measuring serum cortisol levels as a derivative for neurohormonal stress response activity using Siemens Immulite 2000XPi immunoassay. For the immunological stress response activity, measurement of interleukin-6 (IL-6) levels using Genprobe Diaclone ELISA immunoassay, tumor necrosis factor alpha (TNF-α) levels using R&D Systems ELISA immunoassay, and C-reactive protein (CRP) levels using Roche cobas assay were conducted. Opioid requirement was converted using universal formulas to calculate milligrams (mg) of morphine equivalent (ME) dosage, with 1 mg ME being the equivalent of 1 mg parenteral administered morphine[16]. Fentanyl 0.1 mg parenteral was considered to be equipotent to 10 mg ME[24], oxycodone 20 mg oral to be 10 mg ME[24], tramadol 100 mg oral to be 6.7 mg ME[25], fentanyl transdermal 12.5 mcg/h to be 8.3 mg ME[26], sufentanil 0.1 mg to be 100 mg ME[27], and piritramide 15 mg parenteral to be 10 mg ME[28]. As remifentanil does not have a reliable conversion factor, this was reported separately. Continuous opioid infusion through epidural catheters and PCA pumps combined with the amount of administered bolus injections were converted to mg ME as well.

Participants were followed during the first 30 days after surgery. Postoperative pain and opioid requirement were assessed during the first postoperative week. Postoperative complications and mortality were recorded during a 30 day follow-up period.

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Randomization and blinding

Patients fulfilling eligibility criteria and providing written informed consent were randomly allocated in a 1:1 ratio to either the intervention (intraoperative music) or control group. Centralized allocation concealment was present by using a computer-generated randomization sequence through the web-based software ALEA[29]. The randomization was stratified according to the surgical procedure (esophagectomy or gastrectomy) and planned surgical approach (esophagectomy: minimally invasive, hybrid or open;

gastrectomy: minimally invasive or open). Variable block sizes of 4 or 6 designed by a statistician not involved in study procedures or data analysis were used. Computerized randomization revealed the allocated intervention to the coordinating research physician, who implemented allocation with the research team during surgery by applying the noise-cancelling headphones and selecting the correct playlist (music or silence). These non-blinded research team members were not involved in patient care. As all participating patients received general anesthesia and wore active noise-cancelling headphones during the surgical procedure, the patients and perioperative care team were blinded to the intervention. All outcome measures were assessed by perioperative care team members blinded to the intervention. The laboratory technicians conducting the blood sample measurements for the stress response to surgery were blinded to the group allocation as well. Postoperative complications were assessed by physicians conducting the primary patient care and if needed discussed with the supervising surgeons by the coordinating research physician. Statistical analysis was encoded and performed by a member of the research team blinded to the group allocation. Data collection, recording of perioperative complications and additional quality measures followed the proposed system by the Esophagectomy Complications Consensus Group[2]. Deblinding was performed after finalization of the data analysis.

Sample size calculation

A retrospective analysis of 24 esophagogastric cancer patients who underwent surgery in the six months prior to study approval revealed a mean postoperative pain score of 2.6 and a standard deviation of 1.92. A reduction of 1.3 points on an 11 point scale were deemed clinically relevant. Comparable studies in regards to the surgical procedure severity with major abdominal surgery and intraoperative music were scarce, but in major visceral abdominal surgical procedures, a similar effect was observed[19]. Sample size calculation resulted in each study arm requiring 35 patients in order to obtain a power of 80% with alpha of 5% and planned two-sided testing.

Statistical analysis

Descriptive analysis was performed in order to report outcome measures for both the music and control group. The mean and standard deviation (SD), in case of parametric data, or the median and interquartile range [IQR], in case of non-parametric data, was reported. Statistical significance of difference was tested using a student's T-test or Mann-Whitney U-test, as appropriate. Mean differences with 95% confidence interval (95%CI) were presented. Percentile confidence intervals for differences in medians were obtained using 2000 bootstrap samples. Except for the percentile confidence intervals for differences in medians which were performed using R, all data analyses were performed using IBM SPSS version 20.0. Statistical significance was set at $p < 0.05$.

Results

Patients

From November 1, 2018 to September 16, 2020, 145 patients undergoing surgery for esophagogastric cancer were assessed for eligibility. Due to logistical reasons, 35 patients were not approached. Twenty-one patients were not eligible due to use of corticosteroids (n = 8), insufficient knowledge of the Dutch language (n = 5), hearing impairment (n = 2), or planned palliative surgery (n = 6). Six patients (6.7%) refused to participate. Eighty-three patients were randomized (41 patients in the music and 42 in the control group). Thirteen patients were excluded according to the protocol due to the administration of corticosteroids intraoperatively (n = 1), no resection performed (n = 9), or change in scheduling (n = 3). Of the remaining 70 patients (31 patients in the music and 39 in the control group), all completed follow-up and were included for data analysis (Figure 1).

Figure 1. CONSORT Flow Diagram

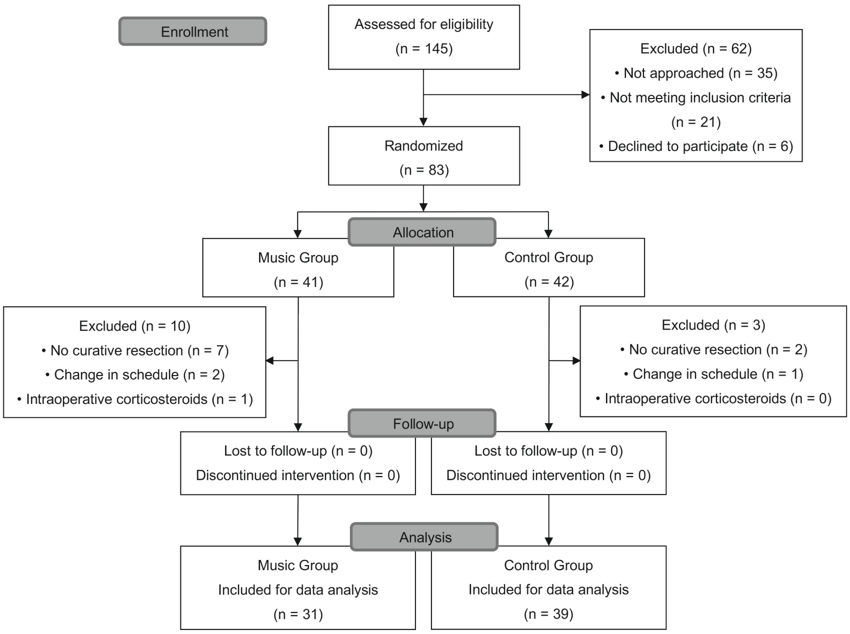

Figure 1 legend. n = number of patients

Table 1. Baseline and treatment characteristics of the study groups

Baseline and treatment characteristic		Music Group (n = 31)	Control Group (n = 39)
Age (years)		70 [63 – 73]	70 [62 – 75]
Sex (n)	Female	10	12
	Male	21	27
ASA classification (n)	1	2 (6.5%)	2 (5.1%)
	2	15 (48%)	24 (62%)
	3	14 (45%)	11 (28%)
	4	0 (0%)	2 (5.1%)
Body mass index		27 (4.5)	27 (6.2)
Charlson Comorbidity Index		5 [3 – 9]	5 [2 – 9]
WHO Performance Score (n)	0	9 (29%)	18 (46%)
	1	20 (65%)	16 (41%)
	2	1 (3.2%)	3 (7.7%)
	Missing	1 (3.2%)	2 (5.1%)
Neoadjuvant therapy (n)	Full course	26 (84%)	29 (74%)
	Incomplete (<100% of planned)	2 (6.5%)	3 (7.7%)
	No	3 (9.7%)	7 (18%)
Esophageal cancer resection (n)	Open	2 (6.5%)	1 (2.6%)
	Hybrid	6 (19%)	9 (23%)
	Minimally invasive	14 (45%)	16 (41%)
Stomach cancer resection (n)	Open	0 (0%)	0 (0%)
	Minimally invasive	9 (29%)	13 (33%)
Conversion (n)		3 (9.7%)	3 (7.7%)
Duration of surgery (minutes)		306 (122)	299 (102)
Duration of anesthesia (minutes)		373 (142)	364 (113)
Duration of intervention (minutes)		280 (117)	287 (95.0)

Table 1 legend. Baseline and perioperative treatment characteristics. For categorical variables, absolute numbers (percentage of allocated study group) are presented. For continuous variables, medians [interquartile ranges] or means (standard deviations) are presented, as appropriate. No statistical significant differences between groups were observed.
n = number of patients; WHO = World Health Organization

Table 2. Music preferences and importance of music in daily life

Outcome Measure		Music Group		Control Group	
How often do you listen to music in your daily life?	**Frequency**	**n**	**hours**	**n**	**hours**
	Almost the entire day	11 (36%)	-	12 (31%)	-
	A couple of hours every day	13 (42%)	3.0 (1.8)	19 (49%)	3.4 (1.6)
	A couple of hours every week	6 (19%)	5.2 (4.4)	8 (21%)	3.9 (2.0)
	Almost never	1 (3.2%)	-	0 (0.0%)	-
Importance of music in daily life (NRS)		8 [7-8]		7 [7-9]	
Top three preferred music genre		**Genre**	**n**	**Genre**	**n**
		Dutch	12 (18%)	Rock	14 (16%)
		Pop	10 (15%)	Classical	12 (14%)
		Country	9 (13%)	Country	11 (13%)
Plays a musical instrument	Yes	6 (19%)		3 (7.7%)	
	Used to	5 (16%)		12 (31%)	
	No	20 (65%)		24 (62%)	

Table 2 legend. Custom questionnaire on music preferences and importance of music in daily life. For categorical variables, absolute numbers (percentage of allocated study group) are presented. For continuous variables, medians [interquartile ranges] are presented.
n = Number of patients; NRS = Numeric Rating Scale

Patient characteristics are shown in Table 1 and Appendix D. Median age was 70 [IQR 63 – 70] and 48 of the 70 patients (69%) were male. Approximately 80 percent of participants listened to music every day, with the importance of music in daily life being rated as 8 and 7 out of 10 in the music and control group, respectively (Table 2). The majority of participants had never played a musical instrument.

Treatment characteristics

Perioperative treatment characteristics are shown in Table 1. Forty-eight patients (69%) underwent esophagectomy and 22 patients (31%) underwent laparoscopic gastrectomy. In six patients (8.6%), conversion to open resection was required for technical reasons. No statistically significant differences between groups were present regarding duration of surgery, duration of anesthesia, and total procedural time. All participating patients received BIS-guided, total propofol anesthesia. In 13 of the 70 patients (19%), ketamine was administered intraoperatively, which was in most cases due to lack of an epidural and equally divided among the music (n = 7) and control (n = 6) group.

Postoperative pain and perioperative medication requirement

The effects of intraoperative music on postoperative pain levels and perioperative medication requirement are presented in Table 3. Mean (SD) postoperative pain levels were not statistically significant different between the music and control group on the first postoperative day (NRS 1.8 (1.6) versus 2.2 (1.5), mean difference -0.44 (95%CI -1.2 to 0.31), $p = 0.249$), nor did it differ during the first week after surgery (NRS 1.8 (0.94) versus 2.0 (1.0), mean difference -0.28 (95%CI -0.76 to 0.19), $p = 0.236$). Postoperative opioid requirement was also not statistically significant different during the first week after surgery between the music and control group (median 379 mg ME [IQR 121 – 800] versus 407 [37.5 – 982], median difference -28 (95%CI -434 to 144), $p = 0.718$). There were also no statistically significant differences between both treatment arms for mean NRS and mg ME for each postoperative day.

Mean (SD) intraoperative propofol requirement did not differ significantly between the music and control group (2900 mg (1692) versus 2929 (1844), mean difference -28.75 (95%CI 882.6 to 825.1), $p = 0.874$). Post-hoc sensitivity analysis excluding the 13 patients that received ketamine, which can have contradictory effects on BIS values[30], did not change the results. Three patients, one in the music group and two in the control group, required additional intraoperative midazolam. Intraoperative opioid requirement was comparable for both groups (median 50 mg ME [IQR 25 – 87] versus 51 [35 – 93], median difference 1.0 (95%CI -25 to 26), $p = 0.901$), nor did remifentanil requirement (4.3 mg (SD 3.4) versus 3.6 (2.4), median difference 0.79 (95%CI -0.60 to 2.2) $p = 0.260$) differ. Mean (SD) intraoperative noradrenaline requirement did not differ significantly between the music and control group (59 mg (69) versus 70 mg (96), mean difference -11 (95%CI -52 to 30), $p = 0.590$). Twenty-one patients required additional intraoperative inotropes or vasopressors, of which ten had been allocated to the music group and 11 to the control group.

Physiological stress response to surgery

The effects of intraoperative music on the physiological stress response to surgery are presented in Table 4. All preoperative blood samples for stress response assessment were drawn before incision and all postoperative blood samples eight hours after the preoperative samples. All the second samples were drawn after wound closure. No statistically significant differences in preoperative levels of cortisol, IL-6, or TNF-α were observed between the groups. Mean (SD) postoperative levels of cortisol (880 nmol / L (445) versus 939 (365), mean difference -58.4 (95%CI -252 to 135), $p = 0.549$), IL-6 (median 277 pg/mL [IQR 135 – 427] versus 165 [94 – 440], median difference 110 (95%CI -33.0 to 206), $p = 0.221$], and TNF-α (median 10 pg/mL [IQR 10 – 21] versus 16 [10 – 27], median difference -4.8 (-15 to 4.5), $p = 0.178$] did not differ statistically significant between groups. Mean CRP levels were statistically significantly higher in the music group compared to the control group on the first (108 mg/L (27.3) versus 89.9 (31.1), mean difference 18.4 [95%CI 2.82 to 33.9], $p = 0.021$) and third postoperative day (231 (113) versus 127 (70.2), mean difference 104 [95%CI 7.71 to 200], $p = 0.036$).

Table 3. Postoperative pain and perioperative medication requirement

Outcome Measure		Music Group n	Music Group M (SD) or [IQR]	Control Group n	Control Group M (SD) or [IQR]	Mean or median difference (95%CI)	*p*-value
Postoperative pain (Numeric Rating Scale)	Postoperative day 1	30	1.8 (1.6)	38	2.2 (1.5)	-0.44 (-1.2 to 0.31)	0.249
	Postoperative day 2	31	1.7 (1.5)	39	1.9 (1.5)	-0.19 (-0.91 to 0.53)	0.608
	Postoperative day 3	29	1.4 (1.1)	38	1.8 (1.4)	-0.38 (-1.0 to 0.25)	0.231
	Postoperative day 4	28	1.7 (1.7)	35	1.6 (1.3)	0.069 (-0.67 to 0.80)	0.852
	Postoperative day 5	28	1.9 (1.4)	31	2.4 (1.9)	-0.48 (-1.4 to 0.40)	0.278
	Week 1 average	31	1.8 (0.94)	39	2.0 (1.0)	-0.28 (-0.76 to 0.19)	0.236
Postoperative opioid requirement (mg ME)	Postoperative day 1	31	90.0 [46.0 - 192]	39	96.0 [10.2 – 176]	-6.0 [-55 to 89]	0.331
	Postoperative day 2	31	86.5 [10.0 – 168]	39	96.0 [5.00 – 168]	-9.5 [-64 to 108]	0.590
	Postoperative day 3	29	66.0 [5.00 – 159]	38	74.3 [9.38 – 153]	-8.3 [-59 to 63]	0.970
	Postoperative day 4	28	25.3 [1.25 – 115]	37	63.0 [5.00 – 138]	-38 [-89 to 22]	0.209
	Postoperative day 5	27	80.1 [0.00 – 71.5]	33	26.0 [0.50 – 61.0]	54.1 [-41 to 14]	0.393
	Week 1 average	31	379 [121 – 800]	39	407 [37.5 – 982]	-28 [-434 to 144]	0.718
Intraoperative opioid requirement (mg ME)		31	50 [25 – 87]	39	51 [35 – 93]	1.0 [-25 to 26]	0.901
Intraoperative remifentanil requirement (mg)		31	4.3 (3.4)	39	3.6 (2.4)	0.79 (-0.60 to 2.2)	0.260
Intraoperative propofol requirement (mg)		31	2900 (1692)	39	2929 (1844)	-28.75 (-882.6 to 825.1)	0.947
Intraoperative noradrenaline requirement (mg)		31	59 (69)	39	70 (96)	-11 (-52 to 30)	0.590

Table 3 legend. Postoperative pain and perioperative medication requirement. Data presented as mean (standard deviation) or median [interquartile range], as appropriate. Opioids were converted to milligrams of parenteral Morphine Equivalent (mg ME). Median differences with 95% confidence interval were calculated using 2000 bootstrap samples for postoperative and intraoperative opioid requirement.
95% CI = 95% confidence interval; IQR = interquartile range; M = mean or median; mg = milligram; n = number of patients; SD = standard deviation.

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Table 4. Physiological stress response to surgery

Physiological stress response to surgery parameter		Music Group		Control Group		Mean or median difference (95%CI)	*p*-value
		n	M (SD) or [IQR]	n	M (SD) or [IQR]		
Cortisol	Preoperative	31	338 (126)	39	351 (139)	-13.0 (-77.1 to 51.1)	0.687
	Postoperative	31	880 (445)	39	939 (365)	-58.4 (-252 to 135)	0.549
Interleukin-6	Preoperative	31	9.00 [9.00 – 13.0]	39	9.00 [9.00 – 11.0]	0.00 (-1.00 to 1.00)	0.484
	Postoperative	31	277 [135 – 427]	39	165 [94.0 – 440]	110 (-33.0 to 206)	0.221
Tumor necrosis factor-alpha	Preoperative	31	10 [10 – 23]	39	10 [10 – 28]	0.0 (-10 to 0.0)	0.248
	Postoperative	31	10 [10 – 21]	39	16 [10 – 27]	-4.8 (-15 to 4.5)	0.178
C-reactive protein	CRP POD 1	24	108 (27.3)	37	89.9 (31.1)	18.4 (2.82 to 33.9)	0.021
	CRP POD 2	22	225 (86.8)	19	198 (75.3)	27.4 (-24.3 to 79.2)	0.290
	CRP POD 3	4	231 (113)	14	127 (70.2)	104 (7.71 to 200)	0.036

Table 4 legend. Effect of intraoperative music during esophageal and stomach cancer surgery on the physiological stress response to surgery. Data presented as mean (standard deviation) or median [interquartile range], as appropriate. Cortisol, interleukin-6, and tumour necrosis factor-alpha were assessed before incision (preoperative) and eight hours later (postoperative). C-reactive protein was assessed on the first three postoperative days in light of standard perioperative care. Median differences with 95% confidence interval were calculated using 2000 bootstrap samples.
95%CI = 95% Confidence interval; CRP = C-reactive protein; IQR = interquartile range; POD = postoperative day; SD = standard deviation

Postoperative complications and length of stay

The effects of intraoperative music on postoperative complications and length of stay are presented in Table 5. There was no statistically significant difference in the number of patients with postoperative complications, with 19 patients (61%) in the music group and 26 (67%) in the control group having at least one postoperative complication ($p = 0.641$). Also, no difference in complication severity according to the Clavien-Dindo classification was observed.

Mean (SD) hospital length of stay was comparable (15.5 days (11.7) versus 14.7 (10.7), mean difference 0.817 (95%CI -4.52 to 1.16), $p = 0.671$). Four patients were readmitted to the intensive care unit, two in each group (6.5% versus 5.1%, $p = 0.780$). None of the participating patients remembered hearing music during surgery when assessed postoperatively during drawing of the second blood sample, whilst no reported adverse side effects were observed due to the music intervention or headphones employed.

Table 5. Postoperative complications and length of stay

		Music Group (n = 31)	Control Group (n = 39)	*p*-value
Postoperative complications (n, %)		19 (61%)	26 (67%)	0.641
Clavien-Dindo classification (n)	Grade I	8	14	0.796
	Grade II	26	34	0.468
	Grade IIIa	9	16	0.740
	Grade IIIb	1	6	0.249
	Grade IVa	3	0	0.110
	Grade IVb	0	0	
Anastomotic leak (n, %)		5 (16%)	7 (18%)	0.841
Chyle leak (n, %)		2 (6.5%)	4 (10%)	0.572
Intensive care length of stay (days)		2.0 [1.0 – 3.0]	2.0 [1.0 – 3.0]	0.773
Hospital length of stay (days)		15.5 (11.7)	14.7 (10.7)	0.761
Readmission to intensive care (n, %)		2 (6.5%)	2 (5.1%)	0.780
Discharge to home (n, %)		28 (90%)	35 (90%)	0.936
30-day mortality (n, %)		0 (0%)	0 (0%)	

Table 5 legend. Effect of intraoperative music on postoperative complication rate and length of stay. For categorical variables, absolute numbers (percentage of allocated study group) are presented. For continuous variables, medians [interquartile ranges] or means (standard deviations) are presented, as appropriate.
n = number of patients.

Discussion

This double-blind, multicenter, randomized controlled trial investigated the effects of intraoperative, pre-selected, instrumental classical music compared to active noise cancelling headphones with silence on the postoperative outcome and recovery in r patients that underwent esophagogastric cancer surgery. We chose to study intraoperative application of music as it is easy to perform in all patients and can be well controlled. However, no statistically significant beneficial effects regarding postoperative pain, intraoperative medication requirement, postoperative opioid requirement, stress response to surgery, postoperative complication rate or length of stay were observed.

Recently, it has been observed that auditory sensory information including music can still be processed in propofol-sedated subjects[31]. Our results contradict other studies that reported less postoperative pain and opioid requirement in patients that were exposed to intraoperative music during general anesthesia[17]. Several reasons may explain this discrepancy. Only limited research on the music characteristics has been performed. A meta-analysis of 85 randomized controlled trials identified non-lyrical instrumental music as the only characteristic described sufficiently for analysis with a beneficial effect and acceptable heterogeneity[32]. Even less is known about intraoperative music during general anesthesia, with the majority using preselected, soft, instrumental music[17, 19, 33-36]. The employed soft classical instrumental music genre in our study did not rank among the top three favorite music genres of the music group as revealed in our questionnaire. In regards to perioperative music applied before, during and after the surgical procedure, a larger beneficial effect of preselected music offering a choice seemed present when compared to no choice[15]. It is unclear whether the favorite genre of the patient would yield different results, especially during general anesthesia with unconscious perception. Furthermore, the control group employed was not standard care, but consisted of patients wearing noise-cancelling headphones in order to assess the effect of music itself. Several previously conducted studies used recorded operation room noise or white noise as an auditory control factor[19, 33, 36, 37]. Noise is recognized universally as a stressor and seems to have negative effects on patient outcome[38]. Finally, it seems that the administration of benzodiazepines preoperatively may influence intraoperative auditory perception during general anesthesia[17]. This only became known to us recently after patient inclusion was completed, and at least 20 percent of patients in our study received benzodiazepines before surgery.

Perioperative music can reduce intraoperative medication requirement[16]. It is speculated that this is due to its anxiolytic effects, as higher anxiety levels can require an increased dosage to induce and maintain anesthesia[39]. The effect of music on anxiety was observed to be highest when played preoperatively[15]. To date, a beneficial effect on anxiety by solely intraoperative music has not been observed[15], which might account for the lack in effect on intraoperative medication requirement. No attenuating effect of intraoperative music was observed on the physiological stress response to surgery. The severity of the physiological stress response to surgery is partly dependent on tissue damage by the invasiveness of the surgical procedure. Given the major surgical procedures investigated in this study, it could well be possible that the influence of music on the stress response is too small to be measured. Whilst postoperative CRP levels were significantly higher in the music group on the first and third postoperative day, the clinical relevance is unclear as postoperative complication rate did not differ between groups.

Strengths of the present study were the prespecified, BIS-guided, total intravenous propofol anesthesia regimen, in order to ensure adequate sedation levels and reduce potential influence on implicit auditory perception by the employed drug regimen. The patients and entire perioperative care team were blinded to the intervention, with centralized allocation concealment and statistical analysis performed by a statistician unaware of patient allocation. Care was taken to ensure that the research team could not influence the study results, as outcomes were assessed by health care staff blinded to the intervention. No participant-preferred choice concerning the music intervention was taken into account, partly due to practical barriers and the effort it would have required by both patients and research team if the patient-preferred music would have been used. Sample size was relatively small and included different surgical approaches (hybrid and laparoscopic) and procedures (esophageal and gastric cancer surgery). This is reflected in the outcome measures, with fairly wide confidence intervals making definitive conclusion of study results difficult. Mean pain levels were generally low, with a mean NRS for pain under 2.0. This was approximately 25 percent lower than expected, based on which the sample size was calculated. In general, all patients who underwent esophagectomy with gastric tube reconstruction received an epidural or PCA pump, with continuous infusion often not lowered when analgesic results were adequate.

Based on the present study, it is not likely that intraoperative music can improve postoperative patient outcome and recovery in esophagogastric cancer patients. Future studies should consider focusing on one specific type of surgery with a large sample size, given the observed broad confidence intervals in this study. Furthermore, more attention should be diverted to assess whether music preference could make a difference.

Conclusion

Intraoperative, research-selected, classical instrumental music played during oesophageal and gastric cancer surgery did not reduce postoperative pain and perioperative medication requirement, attenuate the physiological stress response, or improve postoperative patient outcome.

Acknowledgements

The authors would like to thank A. Tomer, MSc, statistician Erasmus MC, for his assistance with the randomization procedure, Drs. W.J.B.M. Jansen, physician assistant Elisabeth-Tweesteden Hospital, and T. Rapmund-van Dijk, oncology nurse Maasstad Hospital, for their assistance with the recruitment of participants, Kwint T.R. Mackenbach, BSc, medical student Leiden University Medical Center, for his assistance in data collection, and E.L. Fu, BSc, PhD student at the department of Epidemiology, Leiden University Medical Center, for his assistance in performing the statistical analysis.

Funding

External funding was received from the Gravin van Bylandt Stichting (grant number 2018-5.BY.083), Stichting Elise Mathilde (2018.0797), Stichting Erasmus Heelkundig Kankeronderzoek (grant number unspecified), Stichting Thurkowfonds (grant number unspecified), G.Ph. VerhagenStichting (grant number RMG/V2020072), Stichting Futur 21 (grant number unspecified), and Erasmusstichting (grant number MJW/RMG/E20200065), amongst others. The funders had no role in trial design, data analysis, or interpretation of study results.

Appendix A. CONSORT Checklist for randomized controlled trials

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	5,6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7,11,12
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7-11
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10,11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7
Sample size	7a	How sample size was determined	12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			

Section/Topic	Item No	Checklist item	Reported on page No
Sequence generation	8a	Method used to generate the random allocation sequence	11,12
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	11,12
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	11,12
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7-12
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	11,12
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11,12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13
	13b	For each group, losses and exclusions after randomisation, together with reasons	13
Recruitment	14a	Dates defining the periods of recruitment and follow-up	13
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1,3
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1

5

Section/Topic	Item No	Checklist item	Reported on page No
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14-16
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	14-16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	16
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17-19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17-19
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17-19
Other information			
Registration	23	Registration number and name of trial registry	Abstract, 7
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

Appendix B. Music Questionnaire

1. How often do you listen to music in your daily life

☐ Almost the entire day
☐ A few hours a day, namely: ___
☐ A few hours a week, namely: ___
☐ Rarely / never

2. How important is music for you, with 0 indicating totally not important and 10 extremely important?

Totally not important									Extremely important
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
1	2	3	4	5	6	7	8	9	10

3. Which music genre do you prefer (choose up to 3 options)

☐ Blues
☐ Hip Hop
☐ Classical
☐ Dutch / folk music
☐ Rhythm and blues
☐ Don't know
☐ Country
☐ Jazz
☐ Metal
☐ Pop
☐ Rock
☐ Other, namely: __________

4. Do you play a music instrument or do you sing?

☐ Yes, I play __________
☐ In the past, I have played __________
☐ Yes, I sing
☐ In the past, I have sung
☐ No

Appendix C. Music Selection IMPROMPTU study

No.	Music piece	Composer	Instrument	Duration (minutes)
1.	Salut d'Amour Op. 12	E. Elgar	Violin, piano	2:30
2.	Violin Concerto Op. 61 - II 'Andante'	E. Elgar	Violin, orchestra	11:07
3.	Nocturne Op. 9 No. 1	F. Chopin	Piano	5:24
4.	Nocturne Op. 9 No. 2	F. Chopin	Piano	4:17
5.	Nocturne Op. 20	F. Chopin	Piano	4:06
6.	Sonate Pathétique Op. 13 - II 'Adagio cantabile'	L. van Beethoven	Piano	5:18
7.	Mondschein Sonate Op. 27 No. 2 - I 'Adagio'	L. van Beethoven	Piano	6:43
8.	Mondschein Sonate Op. 27 No. 2 - II 'Allegretto'	L. van Beethoven	Piano	2:27
9.	Humoresque Op. 101 No. 7	A. Dvorak	String, orchestra	3:29
10.	Symphony Op. 95 No. 9 ' From the New World'	A. Dvorak	Orchestra	15:26
11.	Lieder Ohne Worthe Op. 19 No. 1	F. Mendelssohn	Piano	3:53
12.	Lieder Ohne Worthe Op. 19 No. 3	F. Mendelssohn	Piano	2:35
13.	Venetianisches Gondellied Op. 19 No. 6	F. Mendelssohn	Piano	2:36
14.	Venetianisches Gondellied Op. 30 No. 6	F. Mendelssohn	Piano	2:48
15.	Lieder Ohne Worthe Op. 38 No. 6	F. Mendelssohn	Piano	2:51
16.	Médiation, from Thaïs	J. Massenet	Violin, orchestra	5:28
17.	Goldberg Variations BWV 988 Aria	J.S. Bach	Piano	3:45
18.	Goldberg Variations BWV 988 Variatio 1	J.S. Bach	Piano	2:00
19.	Ave Maria	J.S. Bach - Gounod	Violin, piano	3:10
20.	Air on the G string	J.S. Bach	Violin, orchestra	4:44
21.	Arabesque No. 1	C. Debussy	Piano	4:09
22.	Claire de Lune (Suite bergamasque)	C. Debussy	Piano	4:09
23.	Raindrop Prelude Op. 28 No. 15	F. Chopin	Piano	4:46
24.	Piano Concerto Op. 11 Romance	F. Chopin	Piano, orchestra	9:34
25.	Nocturne Op. 27 No. 2	F. Chopin	Piano	6:11
26.	Cello Concerto in G minor RV 417 'Adante'	A. Vivaldi	Cello, strings	4:59

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No.	Music piece	Composer	Instrument	Duration (minutes)
27.	Cello Concerto in A minor RV 420 'Adante'	A. Vivaldi	Cello, strings	4:58
28.	Piano Sonate No. 11 K331	W.A. Mozart	Piano	13:49
29.	Piano Sonate No. 16 K545 'Allegro'	W.A. Mozart	Piano	3:22
30.	Piano Sonate No. 16 K545 'Andante'	W.A. Mozart	Piano	7:05
31.	Piano Concert No. 21 K467 'Andante'	W.A. Mozart	Piano, orchestra	6:50
32.	Impromptu Op. 142 No. 2	F. Schubert	Piano	6:45
33.	Impromptu Op. 90 No. 3	F. Schubert	Piano	6:08
34.	The Swan (Le carnaval des animaux)	C. Saint-Saëns	Cello, piano	2:57
35.	Médiation, from Thaïs	J. Massenet	Cello, piano	5:49
36.	Ave Maria	J.S. Bach - Gounod	Cello, piano	3:05
37.	Traumerei Op. 15 No. 7	R. Schumann	Piano	3:11
38.	Des abends (Fantasiestücke) Op. 12 No. 1	R. Schumann	Piano	3:24
39.	Arabeske Op. 18	R. Schumann	Piano	6:19
40.	Von fremden ländern und menschen Op. 15 No. 1	R. Schumann	Piano	1:48
41.	Nocturnes	E. Satie	Piano	13:03
42.	3 Gymnopédies	E. Satie	Piano	7:42
43.	Consolation No. 3	F. Liszt	Piano	4:22
44.	Canon in D	J. Pachelbel	String	4:38
45.	Cello Suite No. 1 in G BWV 1007	J.S. Bach	Cello	3:12
46.	Intermezzo Op. 117 No.1	J. Brahms	Piano	5:20
47.	Intermezzo Op. 118 No. 2	J. Brahms	Piano	5:52
48.	Waltz Op. 39 No. 15	J. Brahms	Piano	1:38
49.	Waltz Op. 64 No. 2	F. Chopin	Piano	3:38
50.	Waltz Op. 69 No. 2	F. Chopin	Piano	4:24
51.	Moldau	B. Smetana	Orchestra	13:11
52.	Song without words Op. 2 No. 3	P. Tchaikovsky	Violin, piano	3:14
53.	Peer Gynt Suite Op. 46 Morning Mood	E. Grieg	Orchestra	4:20
54.	Peer Gynt Suite Op. 55 Solveig's Song	E. Grieg	Orchestra	5:22

No.	Music piece	Composer	Instrument	Duration (minutes)
55.	Op. 12 No. 1 Arietta	E. Grieg	Piano	1:30
56.	Prelude Op. 28 No. 4	F. Chopin	Piano	1:45
57.	Prelude Op. 64 No. 1	F. Chopin	Piano	0:39
58.	Piano Trio K 502 Larghetto	W.A. Mozart	Piano, violin	8:17
59.	Concerto K 622 Adagio	W.A. Mozart	Orchestra, clarinet	6:21
60.	Ave Maria	F. Schubert – A. Wilhelmj	Violin, piano	5:50
60.	Fantaisie Impromptu Op. 66	F. Chopin	Piano	5:11

Appendix D. Histopathology

Characteristic		Music Group (n = 31)	Control Group (n = 39)
Histopathology (n)	Adenocarcinoma	24	34
	Squamous cell carcinoma	3	1
	Other	4	4
Pathological T stage (n)	pT0	4 (13%)	4 (10%)
	pT1	4 (13%)	5 (13%)
	pT2	5 (16%)	8 (21%)
	pT3	15 (48%)	18 (46%)
	pT4	3 (9.7%)	4 (10%)
Pathological N stage (n)	pN0	17 (55%)	21 (54%)
	pN1	6 (20%)	7 (18%)
	pN2	4 (13%)	7 (18%)
	pN3	4 (13%)	4 (10%)
Pathological M stage (n)	pM0	30 (97%)	37 (95%)
	pM1	1 (3.2%)	2 (5.1%)

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Chapter 6

Effect of Music on Clinical outcome after Hip fracture OPeratIoNs (MCHOPIN): Study protocol of a Multicenter Randomized Controlled Trial.

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BMJ Open, 11:e049706, 2021.

"But why think, why not try the experiment?"

John Hunter, August 2, 1775, surgeon and scientific pioneer.

Abstract

Background: Patients undergoing proximal femur fracture surgery are at high risk for postoperative complications, with postoperative delirium occurring in 25-40% of patients. Delirium has profound effects on patient outcome and recovery, the patient's family, caregivers, and medical costs. Perioperative music has a beneficial effect on eliciting, modifiable risk factors of delirium. Therefore, the aim of this trial is to evaluate the effect of perioperative recorded music on postoperative delirium in proximal femur fracture patients undergoing surgery.

Methods and analysis: The MCHOPIN study is an investigator-initiated, multicentre, randomised controlled, open-label, clinical trial. Five hundred and eight proximal femur fracture patients meeting eligibility criteria will be randomised to the music intervention or control group with concealed allocation in a 1:1 ratio, stratified by hospital site. The perioperative music intervention consists of preselected lists totalling 30 hours of music, allowing participants to choose their preferred music from these lists (classical, jazz and blues, pop, Dutch). The primary outcome measure is postoperative delirium rate. Secondary outcome measures include pain, anxiety, medication requirement, postoperative complications, hospital length of stay, and 30-day mortality. A 90-day follow-up will be performed in order to assess nursing home length of stay, readmission rate and functional ability to perform daily living activities. Furthermore, the cost and cost-effectiveness of the music intervention will be assessed. Data will be analysed according to an intention-to-treat principle.

Ethics and dissemination: The study protocol has been approved by the Medical Research Ethics Committee Erasmus MC on October 8, 2018 (MEC-2018-110; NL64721.078.18). The trial will be carried out following the Declaration of Helsinki principles, Good Clinical Practice guidelines and Dutch Medical Research Involving Human Subjects Act. Research data will be reported following CONSORT guidelines and study results will be published in a peer-reviewed journal.

Registration details: Dutch Trial Register (NTR7036).

Authorship

VXF, EMMVL, MJP, JJ and MHJV developed the study concept and design, with critical evaluation by DVDV, LJPS, RH, and JH. All authors have read, critically revised and approved the final manuscript.

Abbreviation list

ASA	American Society of Anesthesiologists
AVG	Dutch Personal Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming)
DOS	Delirium Observation Screening
DSM-IV criteria	Diagnostic Statistical Manual-IV criteria
ERAS	Enhanced Recovery After Surgery
IGZ	Dutch Health Care Inspectorate (in Dutch: Inspectie voor de Gezondheidszorg)
Katz-ADL6	Katz Index of Activities of Daily Living
ME	Morphine Equivalent (1 mg ME = 1 mg of parenteral morphine)
mg	Milligram
MMSE	Mini-Mental State Examination
NRS	Numeric Rating Scale
STAI	State Trait Anxiety Inventory
STAI-6	State Trait Anxiety Inventory-6
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch wetenschappelijk Onderzoek met Mensen).

Introduction

Proximal femur fractures are common in the elderly and are primarily treated surgically[1]. These frail patients are at a high risk for the occurrence of postoperative complications, as they often have significant comorbidity with polypharmacy use[2]. A prevalent in-hospital complication of the elderly is delirium, an acute, fluctuating, cognitive and consciousness disorder[3]. Postoperative delirium rates in elderly Dutch proximal femur fracture surgery patients have been observed to vary between 25 to 40%[4,5]. It has been associated with an increased rate of additional postoperative complications[6], a prolonged length of hospital stay[6,7], and higher medical costs[7]. Moreover, it has a thorough impact on the patient's family[8,9], increasing the risk of poor long-term functional recovery and mortality rate[10-12].

As the consequences of experiencing an episode of delirium are profound, delirium is nowadays regarded as a state of acute brain dysfunction[13]. Therefore, there is an increasing interest in delirium prevention and reduction. The exact pathophysiological mechanism of delirium is multifactorial and complex. Primary prevention with non-pharmacological interventions is generally regarded as the most accepted and effective treatment strategy[3,14], especially since conflicting reports on the effectiveness of prophylactic drug use to prevent delirium have been reported[15-17]. Multiple modifiable precipitating risk factors have been identified[3,18]. These include increased postoperative pain levels[19-21], higher opioid, sedative and benzodiazepine medication dosages[22,23,21], as well as a more vigorous physiological stress response to surgery and elevated stress hormone cortisol level[3,24]. Current patient care aims to reduce these risk factors in order to prevent delirium.

Perioperative recorded music as a non-pharmacological intervention can reduce postoperative pain[25], intraoperative sedative and postoperative opioid medication requirement[26], and attenuate the physiological stress response to surgery[26]. Comparisons have been drawn with the most well-known non-pharmacological interventions for surgery, collectively known as the Enhanced Recovery After Surgery (ERAS) protocols, which have the same objectives[27]. Moreover, the music intervention seems to be well-liked by patients, with high patient satisfaction levels and willingness to listen to perioperative music again if they were to undergo surgery in the future[26]. The effects of perioperative music on postoperative complications, patient outcome, and recovery have only sparingly been investigated[28,26], with most studies focusing on postoperative pain levels, anxiety or medication requirement in the first few days after surgery. To date, only four small studies in elective knee and hip replacement surgery with sample sizes of 60 patients or less examined the effect of music on confusion and cognitive functioning in adult surgical patients[29-31]. Only two used a delirium screening tool[32,33], but positive results were reported in all studies.

This multicentre randomised controlled trial will investigate whether perioperative music can reduce the occurrence of postoperative delirium in elderly proximal femur fracture patients undergoing surgery. Secondary objectives are to assess the effects of perioperative music on pain, anxiety, medication use, postoperative complications, neurohormonal stress response, hospital length of stay, nursing home length of stay, 30-day mortality, 90-day readmission, 90-day functional ability to perform daily living activities, costs, and cost-effectiveness.

Methods and Analysis

Trial design and setting

The MCHOPIN study is an investigator-initiated, multicentre, randomised controlled, open-label, clinical trial. Proximal femur fracture patients meeting eligibility criteria will be randomised to the music intervention or control group using a secure web-based, computerized randomisation system with concealed allocation in a 1:1 ratio, stratified by hospital site. Only study staff members and their delegates will have login credentials. The randomisation code for allocation will be kept concealed from the study staff recruiting patients. The music group will receive recorded music as an intervention before, during and after surgery, whilst the control group will not but will wear headphones without music during surgery instead. The study will take place in four non-academic hospitals and one academic hospital. Patients will be followed until 90 days after the proximal femur fracture surgical procedure.

Eligibility, recruitment and consent

Potential eligible patients will be informed about the MCHOPIN study while in the emergency department or upon admission to the surgical ward. Information will be provided verbally as well as on paper through a patient information folder with an informed consent form. Patients meeting eligibility criteria and willing to participate will be randomised after written informed consent obtainment. In general, proximal femur fracture patients will be operated within 48 hours of hospital admission based on guidelines set by the Dutch Health Care Inspectorate (in Dutch: Inspectie voor de Gezondheidszorg (IGZ)). Therefore, it is not possible to give patients more than a day to consider participation. However, the intervention is non-invasive and not associated with any risks or adverse events[26]. As beneficial effects of music on disruptive behaviour and cognition in dementia patients have been reported[34], proximal femur fracture surgery patients with dementia are not excluded from study participation, although written informed consent by the proxy is necessary. Patients with hearing aids can also readily participate, which has been consulted with the Erasmus MC auditory centre.

Inclusion criteria:
1. Patients with a proximal femur fracture undergoing surgical treatment
2. Age ≥ 65 years old
3. Provision of written informed consent by patient or proxy

Exclusion criteria
1. Additional serious injuries or additional surgical procedures that may affect any of the outcome parameters
2. Simultaneous bilateral hip fracture
3. Implant in situ in the affected hip
4. Severe hearing impairment, defined as no verbal communication possible
5. Patients unwilling or unable to comply with the intervention
6. Preoperative planned hospital discharge and return to nursing home within 48 hours of admission
7. Insufficient knowledge of the Dutch or English language to understand the study documents in the judgement of the attending physician or researcher
8. Participation in another intervention study that might influence the duration of surgery or any of the outcome parameters

Primary outcome

The primary outcome measure is postoperative delirium. Participating patients will be screened using the Delirium Observation Screening (DOS) scale, a diagnostic nursing screening tool. The DOS scale is a 13-item scale facilitated in order to recognize delirium early, with valid consistency and reliability in both geriatric patients and elderly hip fracture patients[35,36].

The DOS end score is the sum of the three DOS scales, assessed during each shift by the nurse, divided by 3. A DOS end score ranges between 0 and 13. In a study of 92 hip fracture patients, a DOS end score of 3 or more had a 94.4% sensitivity of delirium, while a score less than 3 had a 76.6% specificity[35,36]. Because the DOS scale is easy in use, requires no active patient participation and has been validated in several trials[37,38], it is a standard part of multidisciplinary delirium prevention measures in proximal femur fracture patients in the Dutch National Guidelines on delirium. In case of a DOS end score of 3 or more, the geriatrician will be consulted for patient assessment to confirm clinical diagnosis of delirium using the Diagnostic Statistical Manual-IV (DSM-IV) criteria. These criteria define delirium as an acute, fluctuating disturbance of consciousness with inability to focus and shift of attention, caused by a general medical condition. In all participating hospitals, a geriatrician is part of and actively involved in the proximal femur fracture surgery patient care team.

Secondary outcomes

Secondary outcome measures are:

- Postoperative pain, assessed using an 11-point numeric rating scale (NRS), in which 0 implies no pain and 10 implies the worst pain possible.
- Anxiety, assessed using the State-Trait Anxiety Inventory-6 (STAI-6)[39]. Feelings of anxiety are reported on a four-point Likert scale for each item, with a score between 20 and 80 points for each questionnaire. Scoring is achieved by reverse scoring the 3 positive items, sum all 6 scores, and multiply the total score by 20/6. A higher score correlates to a higher level of anxiety. The State-Trait Anxiety Inventory (STAI), consisting of two 20-item subscale questionnaires, is one of the most frequently used anxiety questionnaires in clinical research[40]. The state subscale measures situation related anxiety, anxiety at the very moment, while the trait subscale measures disposition related anxiety, anxiety as a general personal characteristic trait). A major drawback of the STAI is its length, especially in a study population of elderly patients with frequent cognitive impairment, pain and opioid requirement. In order to increase compliance and minimize unanswered items, the 6-item short form of the STAI-state by Marteau and Bekker (1992) will be used[39]. The STAI-6 has a high internal reliability and correlation with the full-form STAI[39,41,42], has been used in clinical research in elderly patients[43,44], and has been validated in Dutch[45].
- Medication use, consisting of intraoperative and postoperative opioid medication, as well as postoperative benzodiazepines and postoperative antipsychotic medication for the treatment of delirium. Data will be collected from the electronic patient file. Analgesic opioid medication will be converted to milligrams of morphine equivalents (1 mg ME = 1 mg parenteral morphine).
- Postoperative complication rate. Data will be collected from the electronic patient database and classified according to the Clavien-Dindo classification[46].
- Neurohormonal stress response, assessed by measuring serum cortisol. An increased stress response after surgery has been associated with an increased risk of postoperative delirium[24]. The duration until peak cortisol level depends on the surgical severity and is an indicator of intrinsic physiological stress[47]. Peak levels of cortisol are observed 4 hours after start of surgery in moderate and after 8 hours in major surgical procedures. Proximal femur fracture surgery is generally classified as a major surgical procedure. Therefore, the second serum cortisol will be drawn 6 hours after the first sample. This will be combined with the blood draw postoperatively for the postoperative serum haemoglobin measurement, which is part of standard surgical care.
- Hospital length of stay in days, as calculated from the hospital admission date until declared 'medically ready for discharge' by the attending physician as recorded in the patient's medical file. Also the full length of stay until the actual discharge from hospital will be assessed.

- 30-day mortality, as calculated from date of admission.
- Nursing home length of stay in days, as calculated from nursing home admission date until discharge.
- 90-day readmission, as calculated from date of admission.
- 90-day functional ability to perform daily living activities, which will be assessed during standard postoperative outpatient visit 3 months postoperatively using the Katz Index of Activities of Daily Living (Katz-ADL6). This 6-item instrument assesses basic activities of daily living in 6 functions, with a total score of 6 indicating full function and a score of 2 or less severe functional impairment[48].
- Through an economic evaluation, the cost-effectiveness of the music intervention will be investigated, using the method of cost-effectiveness analysis (CEA). The evaluation will be conducted from a healthcare perspective, with a time horizon of 90 days. It will make a comparison between the intervention and the control group by identifying, measuring, and valuing the costs and patient outcomes of both treatment strategies. The costs will include costs of the initial hospital admission (either on the ward or on the intensive care unit), primary surgery and additional procedures (including surgical re-interventions), medications, diagnostic imaging, in-hospital consultations, and costs for headphones and sound equipment. The analysis will take into account costs after hospital discharge, including costs of outpatient consultations, visits to the emergency room, consultations with the general practitioner, home care, and nursing home admissions. Data on resource consumption will be collected from the electronic patient database and using a custom follow-up questionnaire. These data will then be combined with unit costs to generate patient-level costs. Costs of productivity losses will be ignored in this study, because these are expected to be minor, given the age range of the patients. Regarding patient outcomes, the CEA will consider the occurrence of delirium (as defined above). An incremental cost-effectiveness ratio (ICER) will be calculated as the difference in cost between the two treatment strategies divided by the difference in effectiveness, unless one treatment dominates the other (i.e., has lower costs and greater effects). This ICER will be expressed as incremental costs per case of delirium prevented.

Additional study parameters assessed will be patient demographic characteristics, preoperative medication use, medical and surgical patient history, living situation prior to hospital admission, education level, injury and treatment characteristics, and music preferences and its importance in daily life. Cognitive functioning, a prominent risk factor for delirium[49], will be screened preoperatively using the Mini-Cog, a three-item screening questionnaire with high correlation to cognitive functioning assessment by the Mini-Mental State Examination (MMSE)[50,51].

Study intervention

The music group will listen to music preoperatively, intraoperatively and postoperatively during the first five days after surgery. The preoperative music intervention will be 15 minutes. The intraoperative music intervention will start after anaesthesia induction until the patient choses to remove the headphone in the recovery room. Postoperatively, the music group will listen to music twice a day for 30 minutes, starting from the first until the fifth postoperative day or until patient discharge. The control group will receive standard patient care and in addition wear headphones intraoperatively without music, in order to prevent that the potential beneficial effect of music is attributed solely to noise reduction. Previous studies have reported noise levels exceeding 100 decibels adjusted during surgery[52], with higher noise levels reportedly increasing postoperative complications rate and stress hormone levels[53-55].

The music intervention consists of preselected music divided in four playlists (classical, jazz and blues, pop, and Dutch music) providing approximately 30 hours of music using a tablet. Patients are allowed to choose music from these list, as the largest beneficial effects were previously observed when patients selected music from a preselected playlist[25]. Moreover, it is unlikely that the elderly proximal femur fracture surgery patients admitted through the emergency department will bring their own favourite music. Music was selected by a panel of five research physicians with extensive knowledge of perioperative music, based on literature recommendations and music used in previous studies. Care was taken to choose popular music from the patients' youth and early adulthood (50's to 80's) which would likely be familiar to the patient, as a familiar environment can reduce the occurrence of delirium[56]. Consent was obtained from the music copyright managing organizations in the Netherlands, Buma Association and Stemra Foundation (Dutch: Vereniging Buma and Stichting Stemra), to use recorded music for study research purposes.

Study procedures

A timeline detailing study procedures and outcome measures is presented in Figure 1. After signing informed consent and computerized randomisation, the Mini-Cog will be administered and baseline NRS for pain and STAI-6 will be filled out also by all participants, followed by preoperative geriatric consult and DOS scores as part of standard care. A custom-made demographic questionnaire on preoperative living situation, education level and music will be provided as well.

The preoperative music intervention for the music group will start from the surgical ward when the patient is called up for surgery and continue until arrival in the operating room, whereas the control group will receive standard care preoperatively. The anaesthesiologist and surgical team will be free to decide whether general or locoregional anaesthesia will be used, as well as the anaesthesia regimen. Preferably, anaesthesia administration will be guided by using a bispectral index monitor or comparable anaesthesia depth monitoring device. After induction, the first cortisol blood sample will be drawn and all subjects will receive headphones. The control group will wear headphones in order to assess the music intervention and not noise reduction. All participants will wear headphones until arrival in the recovery room, where they can chose to remove them when they wish. No corticosteroids will be administered between the first and second cortisol blood sample drawing (6 hours after the first blood sample), unless this is deemed clinically necessary by the patient care team. As previously mentioned, cortisol will not be assessed in a selected group of patients participating in his trial.

For all participating patients postoperatively, the DOS will be assessed thrice daily, with the geriatrician actively involved in proximal femur fracture surgery patient care. The NRS for pain will be assessed daily and postoperative opioid dosage will be administered based on the NRS and care team observations. The STAI-6 will be filled out by all participants during the first and second postoperative day. Data on the NRS for pain, DOS, postoperative medication requirement, postoperative complication rate, hospital length of stay and 30-day mortality rate will be retrieved from the electronic patient database. All participants will be followed until three months postoperatively. Two questionnaires, the custom-made follow-up questionnaire and the Katz-ADL6 questionnaire, will be administered during either the outpatient follow-up visit or by phone. The follow-up questionnaire will assess nursing home length of stay, 90-day readmission rate, and information needed for the economic evaluation.

Figure 1. MCHOPIN Study Procedures Timeline

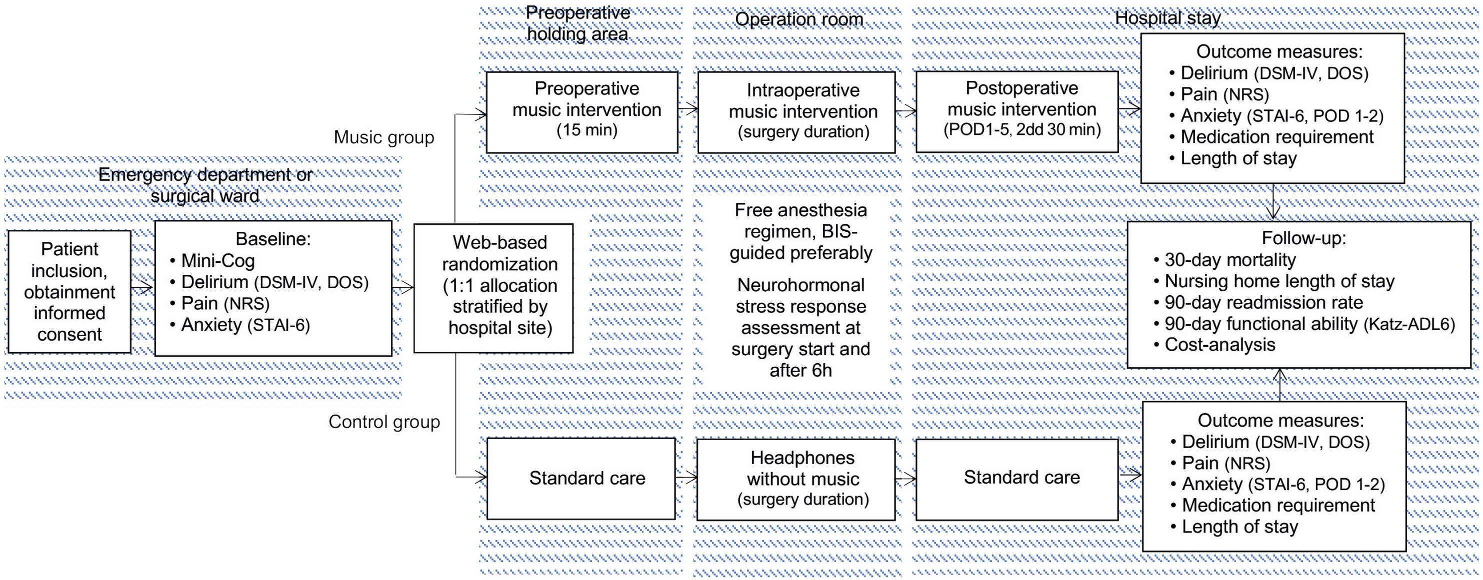

Figure 1 legend. MCHOPIN study overview detailing study procedures. The music intervention consists of approximately 30 hours of preselected music divided in four playlists (classical, jazz and blues, pop and Dutch music), allowing patients to choose from these lists.

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Sample size calculation

Literature on the frequency of postoperative delirium in proximal femur fracture surgery patients varies between 15 and 60 percent[2], with a recent meta-analysis reporting an accumulated prevalence of 24 percent[57]. Delirium in Dutch proximal femur fracture surgery patients over 65 years of age has been observed in 19 to 37 percent of patients[58,59]. Previously, a meta-analysis assessing effectiveness of different, mostly non-pharmacological interventions reported a reduction in delirium rates of 13%[60]. In order to assess a minimally clinical relevant reduction of 13% in delirium frequency when taking 15-60% of delirium into account, with a power of 80%, alpha of 5% and planned two-sided testing, taking into account possible in-hospital mortality and loss-to-follow-up of 10% overall, 508 patients should be enrolled (254 per group).

Data collection and management

Clinical research assistants will be available at participating hospital sites to assist in executing study procedures and data collection. Research data will be collected using questionnaires and with a case report forms with data from the electronic patient database. The handling of personal data will comply with the Dutch Personal Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming, AVG). Research data will be stored electronically in a database with an audit trail that meets Good Clinical Practice standards (OpenClinica) and will be handled confidentially. Any information on paper collected during this study will be placed in a research folder, which will be filed in locked cabinets in research offices at the participating hospitals. Data will be stored during the study period and for a period of 15 years after completion of the study.

Monitoring, safety and auditing

An appointed monitor will develop standard procedures and details on the monitoring activities. The sponsor/investigator has a liability insurance which is in accordance with the Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch wetenschappelijk Onderzoek met Mensen, WMO). The Medical Research Ethics Committee Erasmus MC has given dispensation from the statutory obligation to provide insurance for subjects participating in medical research, as participation in this study is considered to be without risks.

No deleterious or negative adverse side-effects associated with listening to music as a perioperative intervention are known[26]. In accordance, the investigator will report all serious adverse events to the sponsor, except for the specific serious adverse events which are considered not related to the music intervention and common in proximal femur fracture surgery patients. A maximum sound level will be ensured to prevent hearing damage. The headphones and sound equipment will be cleaned with a damp microfiber cloth and the ear pads or buds replaced after use by a patient during hospital stay, in order to reuse the devices, in accordance with the Erasmus MC Infection Prevention Unit and local hospital protocols. No additional or enhanced hygiene measures will be needed concerning the use of headphones and sound equipment in the operating room complex and the same sound equipment set will be used on the ward.

Statistical analysis

Data will be analysed using the Statistical Package for the Social Sciences (SPSS) version 24.0 or higher (SPSS, Chicago, Ill., USA). Normality of continuous data will be tested with the Shapiro-Wilk test. Homogeneity of variances will be tested using the Levene's test. A two-sided p-value <0.05 will be taken as threshold of statistical significance in all statistical tests. The analyses will be performed on an intention to treat basis. Should there be 5% crossovers, a per protocol analysis will also be done. If necessary, missing values will be replaced using multiple imputations following the predictive mean matching method, using ten imputations.

Descriptive analysis will be performed in order to report the outcome measures for both treatment groups. For continuous data, the mean and SD (parametric data) or the median and percentiles (non-parametric data) will be reported per treatment group. For categorical data, numbers and frequencies will be reported per treatment group. The only exception is that costs will be reported as mean with 95% confidence interval (95% CI). The 95% CI around the mean costs will be approximated by nonparametric bootstrapping. Continuous data will be tested using the Student's T-test or the Mann-Whitney U-test, as appropriate. Categorical data will be tested using the Chi-squared or Fisher's Exact test, as applicable. Both univariable and multivariable analysis will be performed. A binary logistic regression model (for binary outcomes) or multivariable linear regression model (for continuous outcomes) will be developed, with the outcome as dependent variable and the study group (i.e., intervention or control) as covariate. Patient, injury, and treatment variables that differ between the groups and may confound the association of the intervention and outcome will be entered into the model. Variables will be entered into the model if univariate analysis produces a p-value of 0.05 or lower. The unadjusted and adjusted odds ratio's (for binary outcomes) and beta values (for continuous outcomes) will be reported with 95% confidence interval. A subanalysis for all outcome measures will be performed by stratifying patients according to their age (<80 and ≥ 80 years).

Blinding

Patients enrolled in the MCHOPIN study will not be blinded to the music intervention. While the surgical team will be blinded intraoperatively on paper as all patients will wear headphones during surgery, in practice it will not be possible to blind the surgical team as patients can adjust the music volume or ask for a different playlist whilst in the operating room or postoperatively on the surgical ward. The clinical chemist and laboratory site concerned with the analysis of the neurohormonal cortisol stress response samples will be blinded to the intervention. Also, a part of the statistical analysis, which includes the primary and almost all of the secondary outcome measures except the economic analysis, will be performed by a statistician blinded to the music intervention.

Patient and Public Involvement

No patients and public were involved in the study design.

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Patient and Public Involvement

No patients and public were involved in the study design.

Ethics and Dissemination

This study will be conducted in accordance to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, 2013) and in accordance to the Medical Research Involving Human Subjects Act (in Dutch: WMO). Written informed consent will be obtained from each patient or proxy.

Ethics approval and trial registration

Approval by the Medical Research Ethics Committee Erasmus MC was obtained on October 8, 2018 (MEC-2018-110; NL64721.078.18). Local approval in the participating hospitals followed suite and the study was open for inclusion starting from March 5, 2019. The trial protocol has had no substantial amendments to the original protocol. This trial has been registered in the Dutch Trial Register (NTR7036).

Dissemination policy

Research data will be reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[61] No research data that can be traced to individual persons will be presented or published. On completion of the trial, the research team aims to publish the manuscript in a peer-reviewed journal and present results in national and international conferences. Each participating hospital will be invited to provide co-authors for a collaborator group authorship, consisting of one trauma surgeon and one anaesthesiologist, provided that 15 percent of the total required study sample size is included at that site. All participating hospitals will be acknowledged for their participation.

Discussion

Delirium is a prevalent complication in in-hospital elderly patients and is associated with prolonged hospitalisation due to an increased risk of postoperative complications and mortality. It also leads to long-term cognitive and functional impairment[3,6,7,10,11]. Therefore, an increasing research interest in delirium prevention and treatment has developed over the past two decades. Delirium prevention is currently a health care quality indicator in many countries worldwide[62]. Several non-pharmacological multimodal intervention programs have reported beneficial results on reducing delirium[3,16], especially since the pharmacological prevention and treatment of delirium remains somewhat controversial[3,16,17 63]. Given the multifactorial factors involved in delirium development, current guidelines consist of both multimodal pharmacological and non-pharmacological interventions. While no clinical useful biomarker for delirium has currently been identified yet[64], serum cortisol reportedly has delirious effects when increased[65-68]. It has been theorized that overstimulation of the hippocampus, rich in glucocorticoid receptors and therefore susceptible for cortisol and stress, plays a role in delirium development[69]. Given that perioperative music can attenuate the neurohormonal cortisol stress response[26], combined with the significant beneficial effects of perioperative music on postoperative pain, anxiety, intraoperative sedative requirement and postoperative opioid usage[25,26], the multicentre, randomised controlled, clinical MCHOPIN trial will assess the effect of perioperative recorded music on postoperative delirium, patient outcome and recovery in elderly proximal femur fracture surgery patients.

An exhaustive literature search with a biomedical information specialist was performed on October 16th, 2020 in order to assess current literature on perioperative music and postoperative delirium in adult surgical patients. Only four randomised controlled trials evaluated the effect of music on postoperative cognitive functioning and delirium. McCaffrey and Locsin *et al.* reported significant lower acute confusion episodes in two trials with 190 elderly patients undergoing elective hip or knee surgery[30,31]. However, confusion was ascertained by reading the nurse's narrative notes without use of screening tools for delirium recognition. Two other studies observed significantly lower rates of postoperative acute confusion ascertained using the validated NEECHAM Acute Confusion Scale when patients listened to music postoperatively compared to standard care. Sample sizes were relatively small, with only 22 and 60 elective hip and knee surgery patients included[32,33].

In the MCHOPIN study, the DOS score will be used to pro-actively screen for delirium in all participants during each nursing shift[35,37]. Given that delirium is often not recognized or misdiagnosed, a strong point of this trial is that all participating hospitals are high volume centres which actively involve the geriatrician in the care of all admitted proximal femur fracture surgery patients. Both patients and practitioners will not be blinded, as the beneficial effects of perioperative music seem largest when music is applied before, during and after surgery instead of only intraoperatively during general anaesthesia[25,26]. Also, a significant portion of proximal femur fracture surgery patients is operated on while receiving locoregional anaesthesia.

We believe it acceptable that no blinding is applied, as patients cannot be blinded in many surgical trials. Only 3 and 37% of practitioners and patients were blinded in high impact surgical randomised controlled trials[70]. Moreover, primary prevention of delirium is generally accepted to be most effective with non-pharmacological interventions[3], meaning blinding is not possible. The anaesthesiologist and surgical team will be free to decide the manner of anaesthesia and perioperative analgesia regimen. Given the number of patients that will be enrolled in this trial and the stratification per hospital site, it is assumed that this will balance itself out and no differences in locoregional or general anaesthesia and analgesia medication will be observed between the intervention and the control group.

To our knowledge, this is the first large, multicentre, randomised controlled trial investigating the effect of perioperative recorded music on postoperative clinical patient outcome and recovery which also employs a reasonable follow-up time after patient discharge. Moreover, only a limited number of studies evaluating perioperative music involved acute care or elderly surgical patients. Perioperative recorded music is an attractive intervention specifically in this patient group, as it is safe, well-liked and reduces sedative and opioid medication requirement[26]. The study population of patients undergoing proximal femur fracture surgery was chosen because of the prevalent occurrence of postoperative delirium and high levels of postoperative pain and stress. Results of this trial will give insight in reduction of delirium in a prevalent and vulnerable patient group, as well as clarify the relation between neurohormonal stress response to surgery activity, the occurrence of delirium and postoperative complication rate.

Trial Status

The current protocol is version 3.0, dated August 15, 2018. The first patient was included on March 5, 2019 and inclusion is expected to continue until December 2021. The study is open for patient inclusion.

Funding

This work was supported by Vergroot Bonekei Fonds, no grant number specified, Marez Oyens – van Ittersum Stichting, no grant number specified, Dokter Izak Wessel Stichting, no grant number specified, Swaenenborgh Stichting, no grant number specified and Van Leeuwen Van Lignac Stichting, grant number TLC/ew/133-T/Nr.689. Also, proceedings from a benefit concert of the 2018 European Medical Students' Orchestra and Choir (EMSOC) were donated in support of this study. All funders do not have a role in the study design, data collection and analysis, data interpretation, results, and publicized manuscripts generated from this trial. The authors declare no conflicts of interest.

Acknowledgements

The authors would like to thank the following people of the Erasmus MC, University Medical Center Rotterdam: W. Bramer, PhD, biomedical information specialist, for assisting in the systematic literature search; S.A.A. van den Berg, PhD, clinical chemist, and R.A. Feelders, MD, PhD, endocrinologist, for advice on the method and timing of the stress response to surgery assessment; M. Klimek, anesthesiologist, for advice on the intraoperative anesthesia protocol; P.E. Wessels, BSc, W.M. Borst, BSc, D. Gačević, BSc, medical research students, for assisting in literature screening, executing study procedures and data collection. Also, the authors would like to acknowledge A.J. Arendse, MD, geriatrician Maasstad Hospital, and A.J.H. Vochteloo, MD, PhD, orthopedic surgeon Orthopedic Centrum Oost-Nederland, for their advice on study procedures and protocol.

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Chapter 7

Implementation of perioperative music in day care surgery (IMAGINE): an implementation study

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Acta Chirurgica Belgica, *Accepted*

"Perioperative music is highly appreciated by both patients and surgeons"

Abstract

Background: Perioperative music can have a significant beneficial effect on postoperative pain, reduce postoperative opioid medication requirement in surgical patients. The aim was to assess implementation feasibility and its effect in day care surgery patients.

Methods: This implementation study employed a prospective single-center study design. The perioperative music intervention consisted of preselected playlists. Primary outcome was adherence to implementation. Barriers and attitudes towards music of patients and perioperative care providers were evaluated. Furthermore, the effects of music implementation were assessed through a matched cohort analysis. This study was registered with the Netherlands Trial Register(NL8213).

Results: From January to May 2020, 109 included day care surgery patients received the music intervention and 97 were analyzed after matching to retrospective controls. Adherence rate to the music intervention was 92% preoperatively, 81% intraoperatively, and 86% postoperatively, with 83% of patients satisfied with the preselected music, and 93% finding music to be beneficial to surgical care. Headphones quality was a potential improvement point. All health care providers believed perioperative music to be beneficial (63%) or were neutral (37%) towards its use. Postoperative pain was not significantly different (mean music numeric rating scale 0.74 for the music intervention group versus 0.68 for the control group, p=0.363). Although not statistically significant, postoperative opioid requirement in the music group was lower (30% versus 40%, p=0.132).

Conclusions: Perioperative music implementation in day care surgery is feasible with high adherence rates, patient satisfaction levels, and easy applicability, with positive attitudes of health care providers towards its use.

Authorship

MR, VF, GS, JJ and ED made substantial contributions to conception and study design. MR, VF and KM made substantial contributions to the acquisition and / or analysis of data. MR, VF, and KM interpreted the data. MR and VF primarily drafted the manuscript. JJ, KM, GS, and EM critically revised it for important intellectual content. All authors gave final approval for this version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abbreviation list

ASA	American College of Anesthesiologists classification
BMI	Body-mass index
CCI	Charlson comorbidity index
ERAS	Enhanced Recovery After surgery
ME	Morphine Equivalent
NRS	Numeric Rating Scale
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

Introduction

Perioperative music can have a beneficial effect on preoperative anxiety and postoperative pain[1,2], reduce intraoperative sedative and postoperative opioid medication requirement[3], and attenuate the physiological stress response to surgery in adult surgical patients[4]. Therefore, it is an attractive non-pharmacological intervention that fits into current perioperative fast-track surgery patient care, especially since no deleterious effects of perioperative music are known[3]. However, perioperative music is still not part of daily perioperative care.

Currently, the most well-known fast track protocols are collectively known as the Enhanced Recovery After Surgery (ERAS) protocols, which primarily aim to attenuate the stress response and reduce opioid requirement[5,6]. Such new care protocols take years to become part of active daily practice and repetitive evaluation and reimplementation is necessary to maintain its beneficial effects[7,8], especially in a fast paced environment like the surgical department. Implementation research that assesses contextual factors and barriers at the level of the patient, physician, surgical team, and organization can ultimately influence implementation in daily practice and therefore the outcome of an intervention[9].

The aim of this study is to analyze the implementation feasibility of perioperative music in day care surgery through adherence to implementation. Secondary outcome measures consisted of 1) patient reported experience, assessed through a custom made satisfaction questionnaire, 2) barriers and facilitators of implementation, as well as attitudes of perioperative health care providers towards the use of perioperative music. Finally, the effect of perioperative music was evaluated, which included postoperative pain, medication requirement, and postoperative in-hospital complication rate.

Methods

The study was approved by the Medical Research Ethics Committee of the Máxima Medical Center, Veldhoven, the Netherlands (L19.117 / N19.102). It was prospectively registered with the Netherlands Trial Register (NL8213) and adhered to the Declaration of Helsinki. The current study is reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Study design

This implementation study employed a prospective single-center study design with prospective included patients matched to a retrospective control group. Perioperative music was implemented as part of standard surgical care during day care surgery procedures. Day care surgery procedures were chosen to ensure a great expansion of the implementation due to the high patient turnover rate. Furthermore, patients undergoing day care surgery are both admitted to and discharged from the same ward, which minimized logistical problems during initiation of the implementation. Given that beneficial effects were also observed when music was solely applied during general anesthesia[1], all adult patients scheduled for elective day care surgery from January 2020 to April 2020, admitted and discharged on the same day, were eligible for inclusion. Patients with severe hearing impairment, defined as no verbal communication possible, insufficient knowledge of the Dutch or English language to understand the study documents, or patients who did not provide oral and written informed consent were excluded.

Included patients received music before, during, and after surgery according to the predefined implementation protocol. The implementation protocol was written with input by a multidisciplinary implementation team, with representatives of the surgical and anesthesiological department, as well as the nursing group, operation room assistants, and the management. Regular meetings of the implementation team every eight weeks were conducted throughout the study. Before implementation start, perioperative health care providers were asked if they were ready to change routine practice through interviews at staff meetings. Additionally, in order to inform all perioperative health care workers, a kick-off day was organised in January 2020, approximately four months after the first team meeting (Figure 1). In our regular team meetings, members were asked for their feedback on the implementation process in order to overcome barriers that arise at different levels in the health care system.

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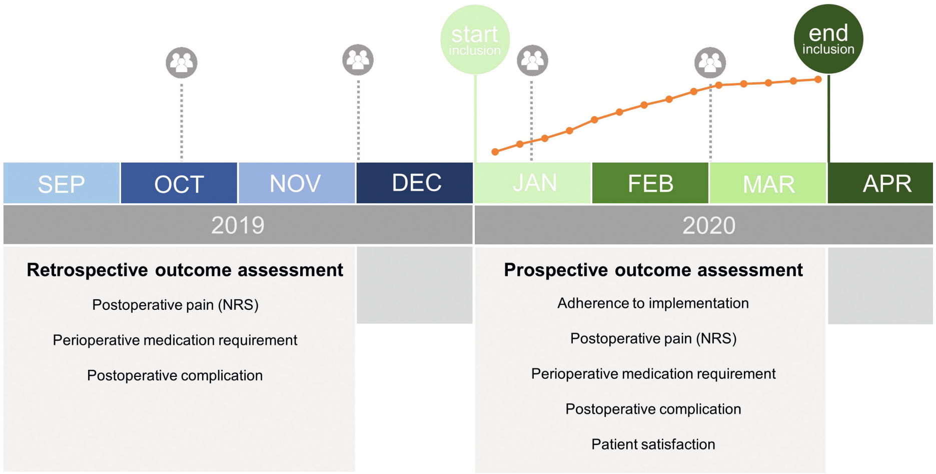
Figure 1. Implementation timeline



Music intervention

The music intervention was provided by using a Lenova Tab E7 and disposable headphones. Patients were able to choose from different music genres (e.g. pop, jazz, blues, classical, national). A preselected list of playlists was used based on recommendations from literature[1], with patients being allowed to choose their own preferred music. The lists included the following genres: blues/jazz (4:30 hours), classical (5:02 hours), pop (9:10 hours) and Dutch songs (5:50 hours). The music intervention was started after admission to the surgical ward and continued throughout the surgical procedure until discharge from hospital. In regards to copyright concerning music, Buma Association and Stemra Foundation gave permission to use the preselected music for research purposes.

Outcome measures

The primary outcome measure was adherence to implementation, calculated as the percentage of performed music interventions relative to the number of total possible interventions. Previous studies investigating ERAS have defined success of implementation when 80% of adherence is obtained[10]. Secondary outcome measures consisted of patient reported experience, assessed through a custom-made satisfaction questionnaire (Appendix A). Furthermore the effect of perioperative music was investigated. A matched-cohort analysis was conducted to compare outcomes of patients who received the music intervention and patients who did not (patients that underwent surgery prior to implementation start). Evaluated outcomes were postoperative pain (11 point Numeric Rating Scale (NRS) in which 0 implies no pain and 10 implies the worst pain possible), intraoperative and postoperative opioid medication requirement (converted to morphine equivalents (ME), with 1 mg ME = 1 mg of parenteral morphine[11], and in-hospital postoperative complication rate. Baseline characteristics were prospectively collected from the electronic patient database and included sex, age, body-mass index (BMI), American College of Anesthesiologists (ASA) classification and the Charlson comorbidity Index (CCI). Treatment characteristics included type of surgery, duration of surgery (net operation time from moment of skin incision until moment immediately after wound closure, without time required for induction of anesthesia), the time (minutes) spent on the recovery unit, and anesthesia type (general, spinal, regional, local). Finally, a custom-made questionnaire was distributed to perioperative health care providers to evaluate the implementation after inclusion end (Appendix B).

Statistical analysis and blinding

Statistical analysis was performed using SPSS version 22 (SPSS Inc. Chicago, IL, USA). Categorical variables were summarized as absolute number and percentage. Continuous data were presented as mean and standard deviation (SD) if normally distributed, and median and interquartile range (IQR) if not. Normality of data was assessed using the Kolmogorov-Smirnov test and visually in Q-Q plots.

Prospectively included patients undergoing the music intervention were matched according to surgical procedure first, and (if possible) age at surgery, in a one to one ratio to patients who underwent day care surgery (September – November 2019) prior to implementation start (Figure 1). If insufficient pre-test controls were available, matching was eased on type of surgery.

Continuous variables were compared using an independent samples student's T-test or a Mann-Whitney U-test, as appropriate. Discrete variables were compared using a Fisher's exact test or Chi-Square test. Two tailed testing was used with statistical significance inferred at $p<0.05$. In case of five percent missing data or more, both a case complete analysis and missing data imputation using the median and lower and upper interquartile ranges[12]. No sample size calculation was performed, as a predefined inclusion period was chosen for this implementation study. Due to the nature of the intervention, participating patients could not be blinded to the intervention. Perioperative health care providers were also not blinded, given the implementation study design. All data was collected by the coordinating investigator (M.R.) or research assistants, who were not blinded to the intervention.

Results

From January 1, 2020 to April 1, 2020, 110 patients were assessed for eligibility and gave written informed consent. Of these, 109 patients participated and completed the music intervention protocol. One patient could eventually not listen to music due to a technical problem of the music device. Twelve patients could not be matched according type of surgery and age because insufficient controls were available from the retrospective patient cohort. Therefore, effect analysis was performed of 97 matched patients.

Adherence to Implementation and Patient satisfaction

Of the 110 patients, 59 (54%) filled out the custom-made satisfaction questionnaire.
A total of 54 patients (92%) listened to music in the preoperative period, 48 patients (81%) intraoperatively and 51 patients (86%) in the postoperative period. Median patient satisfaction on a visual analogue scale was 8, with 6 patients (10%) giving the maximum score of 10 when surveyed (Figure 2). Median rating score for satisfaction did not change after imputation of missing values. Fifty-five patients (93%) considered the music intervention to be beneficial to perioperative patient care, 56 (95%) would like to listen to music again if they would be operated again in the future.

Figure 2. Patient satisfaction

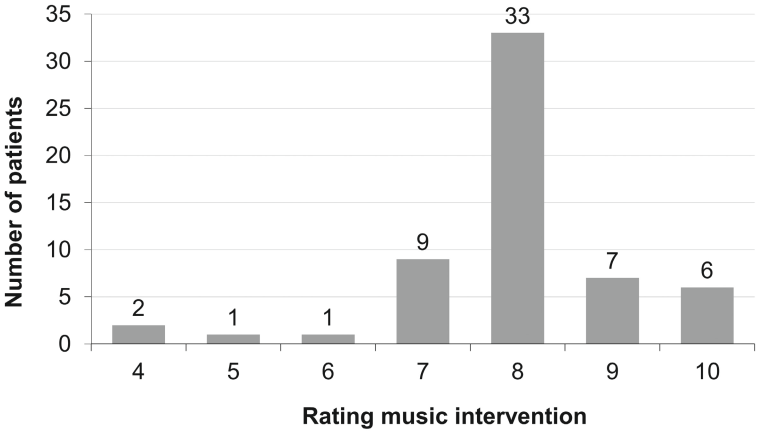


Table 1.

	Bad	Poor	Fair	Good	Excellent
Music genres	0 (0%)	5 (9%)	5 (9%)	41 (7%)	8 (14%)
Songs	1 (2%)	4 (7%)	4 (7%)	45 (76%)	5 (9%)
Information provided by staff	1 (12%)	2 (3%)	3 (5%)	40 (68%)	13 (22%)
Quality of medium	4 (67%)	14 (24%)	10 (17%)	31 (53%)	0 (0%)
Self-control device	2 (3%)	2 (3%)	14 (24%)	38 (64%)	3 (5%)

Table 1 legend. Ratings of several factors regarding patient satisfaction (n = 59)*
*59 of 110 patients filled out the custom-made satisfaction questionnaire.

Shown in Table 1, 49 patients (83%) were satisfied with the preselected music. Two patients (3%) additionally stated that they preferred their own choice of music (in addition to preselected music playlists). The majority of the patients (90%) was satisfied with the information provided by staff regarding the music intervention. The quality of the medium (tablet and headphone) was rated '*bad*' or '*medium*' by one third of the patients. Fourteen patients (24%) mentioned the volume of the headphones being too low. Finally, the self-control of the music device was rated '*fair*', '*good*' or '*excellent*' by nearly all patients (95%). Four patients (7%) experienced technical difficulties with the tablet.

Table 2.

Questions	Answers	*n* (%)
Sex		
	Male	14 (26%)
	Female	40 (74%)
What is your occupation?		
	Day-care nurse	8 (15%)
	Recovery nurse	3 (6%)
	Nurse anesthetist	6 (11%)
	Surgeon assistant	9 (17%)
	Medical doctor	17 (31%)
	Resident not in training	2 (4%)
	Resident in training	7 (13%)
	Preoperative screening assistant	2 (4%)
How much extra time do you spend on the music intervention?		
	0-10 minutes	41 (76%)
	10-20 minutes	2 (4%)
	20-30 minutes	0 (0%)
	20-30 minutes	0 (0%)
	NA	8 (15%)
	Other	3 (5%)
Do you believe that the patient experiences a positive effect of the music intervention?		
	Yes	34 (63%)
	Neutral	20 (37%)
Does the music intervention impair you to do your own work?		
	Yes	7 (13%)
	Neutral	16 (30%)
	No	31 (57%)
How likely are you to recommend the music intervention to others? *		
	1-2	0 (0%)
	3-4	1 (2%)
	5-6	12 (23%
	7-8	29 (54%)
	9-10	12 (23%)
Do you think music should be standard perioperative care?		
	Yes	40 (74%)
	No	8 (15%)
	NA	2 (4%)
	Other	4 (7%)

Table 2 legend. Results of questionnaire that assessed attitudes and barriers towards the implementation of perioperative music among perioperative health care providers ($n = 54$). Abbreviations: NA not applicable. *Scores ranges from 1 (not at all likely) to 10 (extremely likely)

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Attitudes and barriers towards perioperative music implementation

Table 2 represents the results of the questionnaire that assessed attitudes and barriers towards the implementation of perioperative music of perioperative health care providers at the end of the study period (*n*=54). Most of the respondents were medical doctors (31%), surgeon assistants (17%) or day-care nurses (15%). The majority of respondents reported that they usually spend little extra time (0-10 minutes) on the music intervention. All respondents were either convinced or neutral about the positive impact of perioperative music on the patient (respectively 63% and 37%). Six respondents (11%) reported that the music should not negatively influence patient communication at crucial moments, especially during the time-out procedure in the operating room. The majority of the respondents (74%) thought perioperative music should be standard perioperative care, whereas four respondents (7%) stated that patients should always be able to choose freely.

Demographic and perioperative characteristics

No differences in age (50 (16) versus 51 (18) years, p=0.707) and sex (female 55% versus 59%, p=0.562) were found between patients in the music intervention and control group (Table 3). Although not statistically different, patients in the control group were more often classified as ASA score III-IV (10% versus 18%, p=0.155) and had a higher CCI score[13] (median 1 (0-6) versus 2 (0-9), p=0.285). The majority of surgeries that were performed for both groups consisted of abdominal, plastic and gynecological surgical procedures. Duration of surgery (47 versus 43 minutes, p=0.131) and time spend on the recovery ward (53 versus 52 minutes, p=0.562) were comparable between groups. The majority of patients received general anaesthesia (74% in the music intervention group versus 84% in the control group, p=0.113).

Effect of perioperative music implementation

Postoperative pain did not differ significantly between the music intervention group and retrospective matched control group (mean music NRS 0.74 (1.26) versus 0.68 (0.90), p=0.363) (Table 4). Although total amount of opioid requirement did not differ significantly (2.53 mg ME (6.24) versus 3.33 mg (2.47), p=0.511), it seemed that less patients who received the music intervention required postoperative opioids (30% versus 40%, p=0.132) (Table 5). Only one patient (1%) in the intervention group experienced postoperative bleeding after breast surgery, a complication which was unrelated to the music intervention.

Table 3

	Music intervention group (*n* = 97)	Control group (*n* = 97)	*P*-value
Age (years)	50 (16)	51 (18)	0.707
Sex, male	44 (45%)	40 (41%)	0.562
Body-mass index (kg/m²)	25.7 (4.6)	26.1 (5.4)	0.556
ASA-classification			0.155
I - II	86 (89%)	80 (82%)	
III-IV	10 (10%)	17 (18%)	
Missing	1	0	
Charlson comorbidity index (CCI)	1 (0-6)	2 (0-9)	0.285
Surgery type			0.875
Abdominal surgery	27 (28%)	25 (26%)	
Gynecology	16 (17%)	16 (17%)	
Orthopedics and trauma surgery	11 (11%)	13 (13%)	
Plastic surgery	21 (22%)	19 (20%)	
Urology	10 (10%)	9 (9%)	
Vascular surgery	5 (5%)	5 (5%)	
Other *	7 (7%)	10 (10%)	
Duration of surgery (min)	47 (31)	43 (34)	0.131
Time on recovery (min)	53 (22)	52 (18)	0.562
Anesthesia type			0.113
General	72 (74%)	81 (84%)	
Other (spinal, regional, local, sedative)	25 (26%)	16 (16%)	

Table 3 legend. Demographic and clinical characteristics of patients receiving the perioperative music intervention (*n* = 97) and patients in the control group (*n* = 97). Values are in numbers (percentages), mean (standard deviation) or median (interquartile range). * Other: ear, nose and throat, oral, breast or neurosurgery. Abbreviations: ASA, American Society of Anesthesia score; kg, kilograms; m, meters.

Table 4

	Music intervention group (*n* = 97)		Control group (*n* = 97)		*P*-value
NRS*	***n*** (%)		***n*** (%)		
Maximum NRS	88	1.07 (1.55)	94	1.19 (1.54)	0.455
First NRS	88	0.48 (1.30)	94	0.32 (0.78)	0.671
Second NRS	77	1.05 (1.46)	83	1.14 (1.56)	0.755
Mean NRS	88	0.74 (1.26)	94	0.68 (0.90)	0.636

Table 4 legend. Postoperative pain scores of patients receiving the perioperative music intervention (*n*=97) and the control group (*n*=97). For a more suitable display of results pain scores are in mean (standard deviation), differences are based upon nonparametric tests. *Numeric Rating Scale ranges from 0 to 10.

Table 5

	Music intervention group (n = 97)	Control group (n = 97)	*P*- value
Intraoperative analgesic medication requirement			
Sufentanil	66 (68%)	78 (80%)	**0.049**
ug	25.00 (13.13)	20.00 (11.25)	0.990
Morphine	5 (5%)	5 (5%)	-
mg	8.00 (5.00)	5.00 (4.00)	0.496
Remifentanil	8 (8%)	3 (3%)	0.121
mg	0.81 (0.54)	1.20 (-)	0.149
Alfentanil	4 (4%)	8 (8%)	0.233
mg	0.75 (1.28)	0.45 (0.68)	0.343
Postoperative analgesic medication requirement			
Total recovery	15 (15%)	25 (26%)	0.076
ME (mg)	5.86 (5.87)	3.33 (1.67)	0.139
Total ward	16 (16%)	17 (18%)	0.848
ME (mg)	2.53 (1.85)	2.53 (0.00)	0.106
Total recovery + ward	29 (30%)	39 (40%)	0.132
ME (mg)	2.53 (6.24)	3.33 (2.47)	0.511

Table 5 legend. Intraoperative and postoperative analgesic medication requirement of prospective and retrospective cohort. Values are in numbers (percentages) or in medians (interquartile range). Abbreviations: ME: morphine equivalent.

Discussion

Perioperative music has beneficial effects on postoperative pain[1], opioid requirement[3], and attenuates the physiological stress response to surgery[4]. Although these are important objectives of the fast track recovery protocols in current surgical patient care[6], music is still not part of routine perioperative care. As the true effect of an intervention depends partly on whether or not it can be successfully implemented, the aim of this study was to evaluate the implementation feasibility of music in day care surgery through adherence to implementation, as well as its effects.

Implementation was deemed successful, given that adherence was over 80%. Furthermore, patient satisfaction was high and attitude of health care providers towards the perioperative music intervention was positive, with minimal time and effort (less than 10 minutes) required by the latter to perform the intervention. A potential improvement point were the headphones used, which consisted of low-quality, disposable, over-ear headphones. As they were already standardly provided to each admitted patient, these headphones were considered to be safe for patient use and also reduced costs. Given the implementation success, we have continued to provide perioperative music and have procured headphones that offer improved audio quality. Furthermore, these are easy to clean and reusable, with the latter being important in an era of increased consumption and waste production by hospitals[14]. According to local guidelines of infection prevention, disposable hygiene headphone covers are being switched after every user. Although it seemed that the provided, pre-selected music was well liked in general, the use of music streaming services could be considered in order to offer a broader music spectrum. Moreover, it avoids problems regarding copyright and music streaming services are already commonly used by the majority of patients outside of the hospital. In line with previous studies[3], no adverse side effects of the perioperative music intervention were observed, making perioperative music a viable, easily applicable, well-liked, non-pharmacological intervention for perioperative patient care.

Although several systematic reviews and meta-analyses have previously described the positive role of music on pain and analgesia needs[1,3,15], no statistically significant beneficial effects on postoperative pain and opioid requirement were observed in the current study. Several reasons seem apparent for the lack of results. No sample size calculation was performed, given that the primary outcome measure was implementation adherence. Therefore, this study was not adequately powered to evaluate a significant clinical effect. Furthermore, implementation was performed in day care surgery, as this was considered to involve straightforward surgical procedures minimizing logistical planning issues in the hospitals' infrastructure. Postoperative pain levels and opioid requirement are usually low, making it hard to find a clinically relevant, beneficial effect in the first place. However, it should be noted that a trend towards less patients needing postoperative opioids when listening to perioperative music was observed. Previous research revealed that regional anesthesia, compared to general anesthetic techniques, decreases postoperative pain. This could also possibly explain the finding that more patients in the control group required more postoperative opioids since a higher proportion of patients in the control group received general anaesthesia[16]. Especially in light of the current opioid epidemic[17], music could be an attractive non-pharmacological additive to opioid-free analgesia, which is unfortunately limited studied[18].

This study has several strengths and limitations. Several key factors of implementation were thoroughly assessed in this study, taking into account both the opinions of surgical patients and staff alike. This led to an easily applicable, perioperative music intervention, which is apparent given the high adherence rate and minimal time and effort required. Unfortunately, not all patients filled out the postoperative satisfaction questionnaire due to either being drowsy or forgetting about it altogether, which was to be completed in the recovery ward before returning to the surgical ward. However, imputation of missing values according to common statistical methods did not change the outcome, even when the lowest quartile scores were used for imputation. Therefore, we do not believe that the true values would be different. The duration of the music intervention was not truly evaluated through a comprehensive music report. In theory this could mean that the actual adherence was either underreported or over reported. Moreover, the COVID-19 pandemic, which started to spread in the Netherlands at the end of February 2020, limited patient inclusion and the final sample size. Finally, due to the nature of the music intervention, patients and health care providers were not blinded. However, a previous report observed blinding in surgical trials to be the case in only three percent of studies published in high impact journals[19].

This implementation study of perioperative music in day care surgery observed a high adherence rate, an easy applicability, high patient satisfaction levels both with the perioperative music intervention and the preselected music as well, a positive attitude of health care providers towards the music intervention, and a trend towards a reduced postoperative opioid requirement need. This success has led to an expansion towards other surgical procedures, improvement of the music devices, the provision of music streaming services for surgical patients, and perhaps more importantly, a role model for other Dutch hospitals. Future studies should further evaluate implementation of perioperative music and its effect during more complex surgical procedures, which will also involve more care providers and possibly increase barriers to implementation.

Author Disclosure Statement

No external funding was received for this study. The authors declare no conflicts of interest.

Acknowledgements

We thank all patients, health care providers and research assistants for their participation in the study.

Appendix A. Satisfaction questionnaire

You have been listening to music during your perioperative stay. We would like to know your opinion and experience regarding this project. It will take approximately 3 minutes to complete the survey.

1. Do you use hearing aids?
   - ☐ No
   - ☐ Yes

2. How often do you listen to music in daily life?
   - ☐ Almost the whole day
   - ☐ A few hours a day
   - ☐ A few hours a week
   - ☐ Rarely/never

3. On a scale from 0-10, how important is music to you

	0	1	2	3	4	5	6	7	8	9	10	
Totally not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

4. Please rate your satisfaction for each of the following:

	Bad	Poor	Fair	Good	Excellent
The music genres	☐	☐	☐	☐	☐
The music songs	☐	☐	☐	☐	☐
Information provided by the staff	☐	☐	☐	☐	☐
Quality of the medium	☐	☐	☐	☐	☐
Self-control of the device	☐	☐	☐	☐	☐

5. Where have you been listening to music during your perioperative stay? (multiple selections are allowed)
   - ☐ Waiting room
   - ☐ Holding area
   - ☐ Operating room
   - ☐ Recovery area

6. Where there problems with the music devices?
   - ☐ No
   - ☐ Yes, please specify: ________________________________

7. Do you consider the music intervention to be beneficial to perioperative patient care?
   ☐ Yes, please specify: ________________________________
   ☐ No

8. Would you like to listen to music again if you would be operated again in the future?
   ☐ Yes, please specify: ________________________________
   ☐ No

9. On a scale from 0-10, with 1 being very poor and 10 being excellent, how would you rate the music intervention?

	0	1	2	3	4	5	6	7	8	9	10	
Very poor	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Excellent

10. If you have any additional comments, questions or concerns, please leave it here

Appendix B. Questionnaire for perioperative health care providers

We would like to invite you to participate in a short survey to gather your opinion and feedback on the implementation of music in perioperative care in the Máxima Medical Center. It will take approximately 3 minutes to complete the survey.

1. Wat is your sex?
   - ☐ Female
   - ☐ Male

2. What is your occupation?
   - ☐ Day-care nurse
   - ☐ Recovery nurse
   - ☐ Nurse anesthetist
   - ☐ Surgeon assistant
   - ☐ Medical doctor
   - ☐ Resident not in training
   - ☐ Resident in training
   - ☐ Preoperative screening assistant
   - ☐ Other: ____________________________

3. How much extra time do you spend on the music intervention?
   - ☐ 0-10 minutes
   - ☐ 10-20 minutes
   - ☐ 20-30 minutes
   - ☐ >30 minutes
   - ☐ Other: ____________________________

4. Do you believe that the patient experiences a positive effect of the music intervention?
   - ☐ Yes
   - ☐ Neutral
   - ☐ No, please specify: ____________________________

5. Does the music intervention impair you to do your own work?
   - ☐ No
   - ☐ Neutral
   - ☐ Yes, please specify: ____________________________

6. On a scale from 0-10, how likely are you to recommend the music intervention to family or friends?

	0	1	2	3	4	5	6	7	8	9	10	
Not at all likely	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely likely

7. On a scale from 0-10, how likely is it that you want to listen to music yourself if you were to undergo an operation in the future?

	0	1	2	3	4	5	6	7	8	9	10	
Not at all likely	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely likely

8. Do you think music should be part of standard perioperative care?
   - ☐ Yes
   - ☐ Neutral
   - ☐ No, please specify: ___________________________

9. If you have any additional comments, questions or concerns, please leave it here

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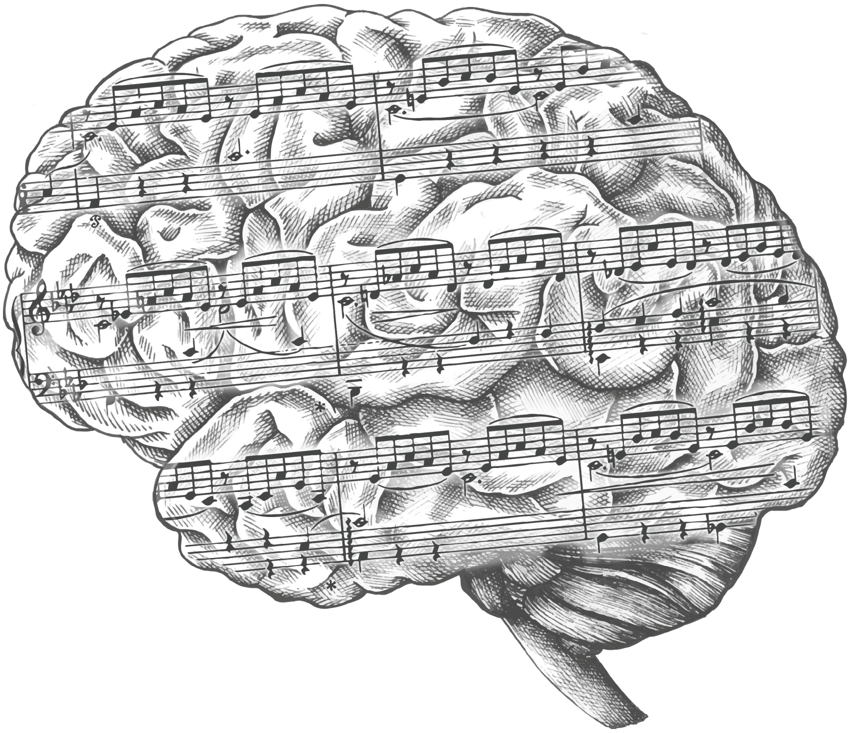
Part II

The Effect of Perioperative Music on Surgical Performance



Chapter 8

The effect of music on simulated surgical performance: a systematic review

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Surgical Endoscopy, 33(9): 2774 – 2784, 2019.

"The Mozart Effect is much bigger. It's more of the universal effects of what sound and music can do to improve our lives."
Don Campbell, 1997, author of "The Mozart Effect".

Abstract

Introduction: Beneficial effects of music have been described on several cognitive domains, task performance, stress, anxiety and pain. Greater surgical skill is a factor that has been associated with improved patient outcome. The aim of this systematic review is to assess the effect of music on surgical performance.

Methods: An exhaustive literature search was performed. The following databases were searched: Embase, Medline Ovid, Web of Science, Cochrane CENTAL, PsycINFO Ovid, CINAHL EBSCOhost, ERIC EBSCOhost and Google Scholar. All prospective studies that assessed the effect of a music intervention compared to either another auditory condition or silence on surgical performance were included in a qualitative synthesis. The study was registered in the PROSPERO-database (CRD42018092021).

Results: The literature search identified 3492 articles of which 9 studies (212 participants) were included. Beneficial effects of music were reported on time to task completion, instrument handling, quality of surgical task performance and general surgical performance. Furthermore, a beneficial effect of music on muscle activation was observed.

Conclusion: Although beneficial effects of music on surgical performance have been observed, there is insufficient evidence to definitively conclude that music has a beneficial effect on surgical performance in the simulated setting. Future studies should be conducted using greater numbers of participants focusing on a more limited range of tasks, as well as validation in the live operating environment.

Abbreviation list

EMG	Electromyography
FLS	Fundamentals of laparoscopic surgery
HRV	Heart rate variability
OR	Operation room or operating theatre
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
TTC	Time to task completion

8

Introduction

Music is played during surgery in many operating rooms (OR) worldwide. A majority of physicians and nurses reported that they listen to music on a regular basis in the OR[1,2]. Respondents stated that music makes them feel calmer and work more efficient. Rauscher *et al.* first described beneficial effects of music on spatial task performance[3]. Since then, much has been published on this so-called Mozart effect. A meta-analysis concluded that there is a small but statistically significant beneficial effect of listening to Mozart on task performance. Moreover, this effect can also be observed with other types of music[4]. Beneficial effects of music have been reported on task performance and cognitive abilities in both rodents and humans[5-8]. Furthermore, anxiolytic and analgesic effects of music during surgery have been observed[9]. Also, stress-reductive effects of music in healthcare professionals have been described[10].

Greater surgical skill has been associated with a reduction in postoperative complications[11] and high stress levels in the operating theatre can negatively affect surgical performance and team performance[12]. According to a survey, nearly 80% of the responding surgeons experience pain on a regular basis while performing surgery[13]. Since music can improve task performance, reduce stress and has analgesic effects, it could potentially benefit surgical performance and therefore patient outcome. The primary objective of this systematic review is to assess the effect of music on surgical performance. Secondary outcomes are the effect of music on vital parameters, stress and electromyography (EMG).

Methods

The study protocol was registered in the PROSPERO database (CRD42018092021)[14]. All aspects of the PRISMA-statement were followed[15]. Neither IRB approval nor written informed was necessary to obtain, as this paper is a systematic review.

Search strategy:

The databases Embase, Medline Ovid, Web of Science, Cochrane CENTAL, PsycINFO Ovid, CINAHL EBSCOhost, ERIC EBSCOhost and Google Scholar were searched on March 1st, 2018 with keywords like "surgery" "surgical skill" "music" and "auditory stimulation". The syntax construction and database search were executed in collaboration with a biomedical information specialist using the exhaustive search method[16]. The full search and syntax is presented in Appendix A. Two independent reviewers (PO and VF) identified eligible studies. First, all identified articles were screened by title and abstract. Subsequently, the full text articles were screened to assess if eligibility criteria were matched. Only full text peer-reviewed published articles in the English language were included. Inclusion criteria for this systematic review were prospective studies that assessed the effect of music compared to another auditory condition or to silence on surgical performance. Secondary outcomes were the effect of music on heart rate, blood pressure, stress response and electromyography (EMG). Studies were excluded if multiple concomitant interventions were used. Discrepancies were resolved through mutual discussion or by referring to a senior author (JJ).

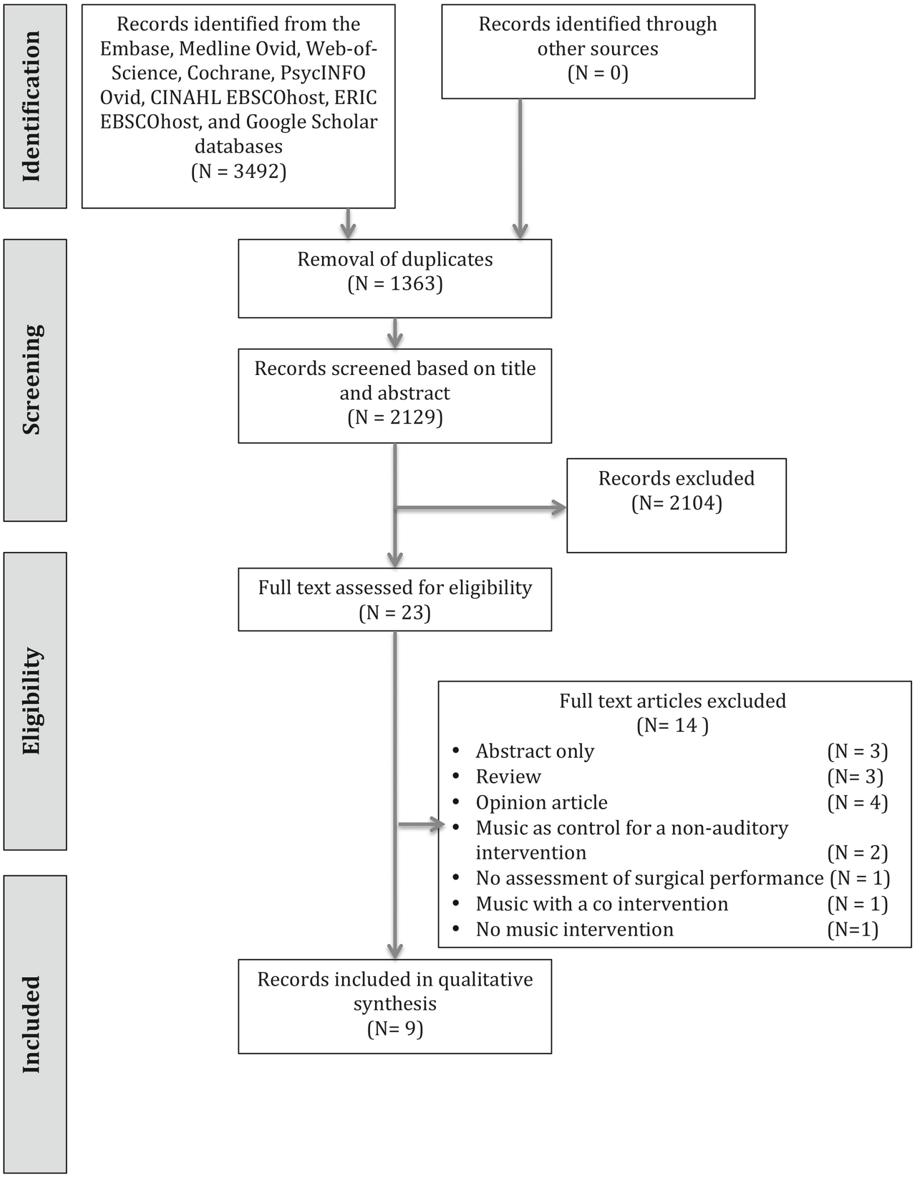
Data collection and quality assessment

Data collection was performed independently by two researchers (PO and VF) using custom made forms. If data was available in plots or images, data was estimated using the online available data extraction software WebPlotDigitizer (version 4.1)[17]. If necessary, authors were contacted to obtain additional data. Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias[18]. Disagreements between reviewers were resolved through mutual discussion or by referring to a senior author (JJ).

Data analysis

The overall group path length and time to task completion means were calculated if individual data were presented. Standard error was converted to standard deviation as described in the Cochrane handbook[18]. If a study contained several music interventions, the means and standard deviations of the different music groups were pooled to an approximated mean and standard deviation of the entire group. If several tasks were used to assess surgical performance, approximated means and standard deviations were pooled for the outcomes time to task completion and path length. If absolute means were presented, mean differences and percentages of mean differences were computed. Only the percentage of improvement was extracted in studies where the task that was used in the intervention group was different from the task in the control group, as parameters such as time to task completion and path length inherently differ between the different tasks.

Figure 1. PRISMA flow diagram



Results

The PRISMA flow diagram of the search strategy is presented in Figure 1. Initial database searching resulted in 3492 articles (2129 after removal of duplicates). Nine articles (212 participants) were included in this review. An overview of the study characteristics is presentedin Table 1. All studies assessed surgical performance in a simulated setting. In eight studies, the music intervention was applied during the assessment of the surgical performance[19-26]. One study applied the music intervention prior to performing the simulation tasks[27]. Motion analysis software was used to assess surgical performance in six studies[19-21,23-26].

Classical music was used as a music intervention in six studies, while preferred music of the participant was used in two studies. All studies used silence or 'no music' as a control intervention. Additional auditory intervention groups consisted of dichotic music[19,20], defined as two different types of music applied through each ear, and OR noise[24].

Bias assessment

Risk of bias of the included studies is presented in Figure 2 and Figure 3. Several studies lacked information to adequately assess all quality domains. Participants could inherently not be blinded due to the nature of the intervention; therefore risk of performance bias was high in all studies. Detection bias was low in all studies since either motion analysis software or predefined criteria by blinded observers were used to assess surgical performance. The condition (i.e. surgical task performance) was considered to be suitable for a crossover study if subjects were allowed to practice the task first, or if subjects were experienced with the type of task that was performed, or if a learning effect was assessed and was absent. Carryover effect was assessed as low risk of bias in one study as the time between periods was at least 24 hours with a median time of 15.5 days. All other crossover studies did not specify the washout period and carryover effect was therefore assessed as unclear risk of bias in these studies.

Other bias has been assessed in one study as high risk of bias, since the study design was changed during the experiment[27]. In this study two music interventions were compared in a crossover study. An additional cohort with no music was added after analysis of the two music interventions.

Table 1. Study characteristics of the included studies

Study	Study design	Participants	Technique	Music intervention	Control intervention	Simulation used	Performance assessment
Conrad 2010	Crossover	8 Experienced surgeons	Laparoscopy	Classical (Mozart piano sonatas)	Silence Dichotic music[a] Mental loading	Surgical SIM VR Tasks not specified	Time to task completion Path length
Conrad 2012	Crossover	31 Junior surgeons[b]	Laparoscopy	Classical (Mozart piano sonatas)	Silence Dichotic music[a] Mental loading	Surgical SIM VR Lifting a structure and cutting Targeting objects Feeding a rope Aligning objects	Time to task completion Path length
Kyrillos 2017	Crossover	12 Residents 14 Ophtalmologists	Intraocular surgery	Classical (Mozart KV 448)	No music	EyeSI VRmagic CAT-A Anti tremor task CAT-C Capsulorhexis	Time to task completion Total score Percentage out of bound Deviation from radius Roundness Centering
Lies 2015	Crossover	12 Residents	Open surgery	Preferred music	No music	Pig's foot Layered wound closure	Time to task completion Quality
Miskovic 2007	Randomized controlled trial	45 Junior surgeons[b]	Laparoscopy	Activating music Deactivating music	No music	Xitact LS500 Clipping and cutting cystic duct	Time to task completion Path length Global score
Moorthy 2004	Crossover	12 Experienced surgeons	Laparoscopy	Classical	OR-noise No music	Pelvitrainer Placing of a suture	Time to task completion Path length Global rating scale Accuracy count Knot quality

Table 1. Continued.

Study	Study design	Participants	Technique	Music intervention	Control intervention	Simulation used	Performance assessment
Shakir 2017	Crossover	9 Residents 3 Fellows	Microsurgery	Preferred music	No music	Chicken's foot Arterial anastomosis	Motion analysis score
Siu 2010	Crossover	10 Medical students	Robotic surgery	Classical Hiphop Jamaican Jazz	No music	daVinci Skills Simulator Tying three knots Mesh alignment	Time to task completion Path length
Wiseman 2012	Crossover + Cohort	55 Novices	Laparoscopy	Classical (Mozart KV 448) Progressive Metal (Dream Theater – Stream of Consciousness)	No music	Custom laparoscopic box Peg transfer Rope transfer Removal of a pen cap	Time to task completion Error score

Table 1 legend. [a]: German Folk music in one ear, deathmetal music in the other ear; [b]: Residents without prior laparoscopic experience

Figure 2. Risk of bias summary

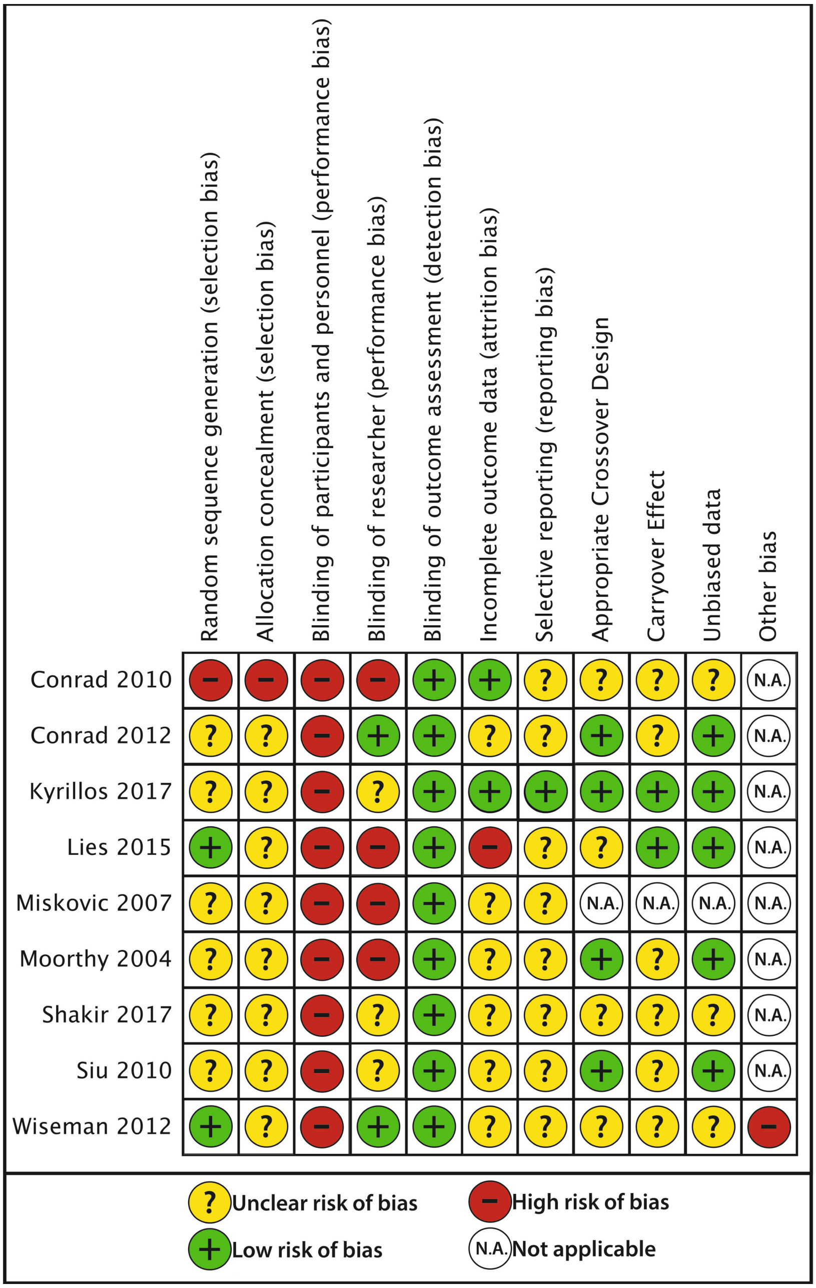


Figure 2 legend. Review authors' judgements about each risk of bias item for included study

Figure 3. Risk of bias graph

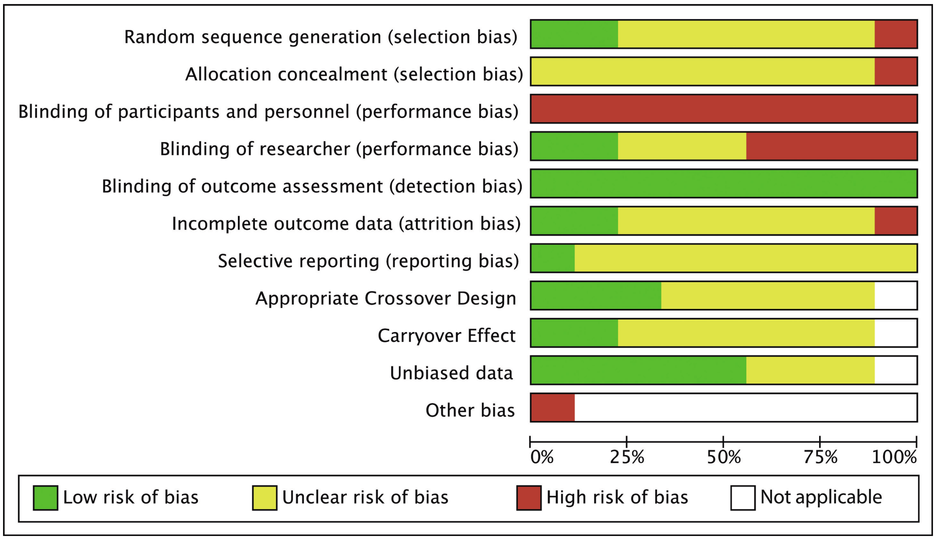


Figure 3 legend. Review authors' judgements about each risk of bias item presented as percentages across all included studies.

Effects of music on time to task completion

Eight studies assessed the effect of music on time to task completion (Table 2) [19-24,26,27]. Three studies evaluated whether the relative improvement in time to task completion was higher, when participants repeated a task and were exposed to either music, no music, silence or another auditory intervention[19,20,27]. In the study by Wiseman *et al.*, each participant completed a series of three tasks[27]. The music cohort was exposed to classical music or progressive metal music during the second and third task, while the control cohort was not exposed to music. The percentage of improvement was not significantly different between the music groups and control group. In two studies by Conrad *et al.* with a similar set-up, classical music was played throughout the entire experiment during both the first and second task. One of the two studies showed a statistically significant higher percentage of improvement when participants listened to music compared to the improvement measured during silence[20]. The other study did not report a level of significance as the study consisted of only eight participants[19].

Four studies evaluated the mean time to task completion with and without music [21,22,24,26]. Two studies reported a statistically beneficial effect of both preferred music, hiphop and Jamaican music on time to task completion[22,26]. One study did not present exact values, but reported no significant difference between groups[23].

Table 2. Effects of music on time to task completion

Study	Intervention		Measure	Results		Mean difference
Assessment of improvement of TTC						
	Music	Control		Music	Control	
Conrad 2010	Mozart piano sonatas	Silence	Mean percentage of improvement	10.51	26.06	15,55
Conrad 2012	Mozart piano sonatas	Silence	Median percentage of improvement	61.29*	39.27	Not applicable
Wiseman 2012	Pooled music groups[a] (n=39)	No music (n=15)	Mean percentage of improvement	22.78 ± 22.93	20.4 ± 9.1	-2.38
Assessment of absolute TTC						
Study	Intervention		Measure	Results		Mean difference (% of mean difference)
	Music	Control		Music	Control	
Kyrillos 2017	Mozart KV 448	No music	Mean TTC(sec.)	81.97	81.79	0.18 (-0.2%)
Lies 2015	Preferred music	No music	Mean TTC(min.) ± SD	10.6 ± 2.6*	11.5 ± 2.9	-0.9 (7.8%)
Miskovic 2008	Activating music Deactivating music	No music	Mean TTC	Not specified		Not applicable
Moorthy 2004	Classical	Silence OR-noise	Median TTC(sec.) (IQR)	529 (210.8)	585.5 (149.6) 526.8 (275.1)	Not applicable
Siu 2010	Pooled music groups[b]	No music	Mean TTC(sec.)± SD	70.36 ± 29.25**	88.56 ± 31.09	-18.20 (20.6%)

Table 2 legend. If the number of participants is not equally divided between groups, the number of participants is specified between parentheses in the intervention columns

[a]: Mozart KV448 and Dream Theater-Stream of Consciousness; [b]: Classical, hiphop, Jamaican, and Jazz; TTC: Time to task completion; *: $p<0.05$; **: $p<0.05$ in both hiphop and Jamaican music compared to control

Effects of music on instrument handling

Instrument handling, defined as path length (i.e. the total distance travelled by the instrument tip) or as the percentage of time that the instrument was out of a predefined boundary, was assessed in six studies (Table 3) [19-21,23,24,26].

Two studies with a similar setup assessed whether improvement of path length was higher when participants repeated a task and were exposed to either classical music, no music, another auditory intervention or silence[19,20]. One study found that improvement of path length upon repetition was statistically significantly increased during exposure to classical music in comparison to any other control condition[20]. The other study did not report a level of statistical significance, as only eight participants were included[19].

Four studies evaluated the mean path length or percentage out of bound with and without exposure to music. A statistically significant beneficial effect of Jamaican music was found on path length in the study conducted by Siu *et al.*[26]. One study did not present exact values, but reported no significant difference between groups [23].

Effects of music on surgical task performance quality

The quality of the performed surgical task was assessed in two studies by blinded observers using predefined criteria[22,24]. Wound, repair graded on a 1-5 scale by blinded plastic surgeons, was performed with significantly better quality when participants listened to their preferred music genre[22]. There was no statistically significant effect of classical music on the quality of a laparoscopically tied knot[24].

8

Effects of music on general surgical task performance

Four studies assessed the effect of music on a general score rating surgical task performance [21,23-25]. Two studies used the total score, generated by the simulator's built-in software[21,23]. One study used a validated global rating scale developed by Reznick *et al.*[28,24]. Shakir *et al.* used a validated general motion analysis score based on the parameters time to task completion, tremor, extreme movements and overall movement pattern. This general motion analysis score was significantly improved during exposure to preferred music[25]. Significant beneficial effect of classical music on the total score was also observed in simulated intra-ocular surgery[21]. Two studies did not find a statistically significant effect of classical music, activating or deactivating music on the total score[23,24].

Table 3. Effects of music on instrument handling

Study ID	Interventions: Music	Interventions: Control	Parameter of assessment	Measure	Results: Music	Results: Control	Mean difference
Assessment of improvement of instrument handling							
Conrad 2010	Mozart piano sonatas	Silence	Path length[b]	Mean percentage of improvement	-5.29	21.56	-26,85
Conrad 2012	Mozart piano sonatas	Silence	Path length[b]	Median percentage of improvement[f]	57.00*	32.02	Not applicable
Assessment of instrument handling							
Study ID	**Interventions: Music**	**Interventions: Control**	**Parameter of assessment**	**Measure**	**Results: Music**	**Results: Control**	**Mean difference (% of mean difference)**
Kyrillos 2017	Mozart KV. 448	No music	Percentage out of bound[c]	Mean (percentage)	18.83	20.24	-1,68 (8,3%)
Moorthy 2004	Classical	Silence OR-noise	Path length[b]	Median (cm) (IQR)	7124.4 (15809.4)	6608.2 (3233.5) 7192.2 (5732.9)	Not applicable
Miskovic 2008	Activating music Deactivating music	No music	Path length[b]	Not specified	Not specified		Not applicable
Siu 2010	Pooled music groups[a]	No music	Path length[b]	Mean (cm) ± SD	1130.81 ± 414.80**	1398.26 ± 417.97	-267,45 (19,13%)

Table 3 legend. [a]: Classical, hiphop, Jamaican and Jazz; [b]: The total distance travelled by the instrument tip; [c]: The percentage of time the instrument was out of a predefined boundary; *: p <0.05; **: p<0.05 in Jamaican music compared to control

Effect of music on vital parameters and muscle activation

One study assessed the effect of music on heart rate and heart rate variability (HRV) during surgical performance[23]. Listening to activating music during surgical performance led to an increased heart rate compared to deactivating music and 'no music'. There were no significant differences in HRV.

One study assessed the effects of music on muscle activation in the dominant hand using electromyography (EMG) as an indication of muscle fatigue[26]. Mean electromyography activation of the extensor digitorum muscle was significantly reduced when participants listened to any type of researcher-selected music (i.e. classical, hiphop, Jamaican or jazz) while median electromyography frequency did not differ statistically significantly between groups. Music did not have a statistically significant effect on mean electromyography activation of the flexor carpi radialis, but did decrease median electromyography frequency.

Discussion

This systematic review provides an overview of the effect of music on surgical performance. Five out of nine studies reported beneficial effects of music on different surgical performance domains. Beneficial effects of music were observed on TTC[20,22,26], instrument handling[20,22,26], task performance quality[22] and general surgical task performance[21,25]. Moreover, one study also observed an attenuating effect of music on muscle activation, which can be correlated to muscle fatigue[26,29].

All included studies assessed the effect of music on surgical skill in a simulated setting. Surgical skill acquired in a simulated setting translates to and correlates with surgical performance in a clinical setting[30-35]. Greater surgical skill is associated with a lower mortality and complication rate in surgical patients, including surgical site infections, pulmonary complications, readmissions and reoperations[11]. Several studies reported a beneficial effect of music on time to task completion. Prolonged operation duration has been associated with a higher postoperative complication rate and increases medical costs[36,37]. Therefore, the use of music during surgical procedures could potentially improve patient outcome and reduce costs, as one minute of OR-time is estimated to cost $36-37[37,38]. Implementing music interventions in training modules might also benefit residents. Simulation based training is an essential part of surgical education, as the American Board of Surgery Graduating requires graduating residents to successfully pass the FLS program (Fundamentals of Laparoscopic Surgery)[39,40].

The type of music that is most beneficial is unclear, but we believe it to be unlikely that a surgeon would listen to music that they dislike. Perhaps the beneficial effect of music on surgical performance is more profound if participants can choose music of their preference. This would coincide with earlier observations where the beneficial effect of music on the surgeon's physiological response was larger under self-selected music compared to researcher-selected music[41]. Out of the nine included studies in this review, two used preferred music of the participants. Both these studies observed statistically significant beneficial effects of music on time to task completion, task performance, quality of repair and on general surgical task performance[22,25]. Siu *et al.* used several researcher-selected music genres. Significant beneficial effects of hiphop were observed on time to task completion, hiphop was in the top two favourite genres of 70% of the participants[26]. In another study, a tendency towards improved surgical performance was observed in participants that rated the music as pleasant, compared to unpleasant or to silence[23].

There are several limitations of this review. One limitation is the low number of included studies and participants. While time to task completion was assessed as the primary outcome measure by most studies, it was not reported in a consistent manner. Some studies reported within-subject improvement, while others reported absolute means of the groups. Moreover, the studies contained different simulated tasks. Therefore no meta-analysis could be performed and no absolute values (i.e. time reduction in minutes) could be calculated. Other endpoints were reported less frequently. This limits the strength of conclusions that could be drawn.

None of the included studies was performed in a live operating environment. There is contradicting evidence with regard to the use of music in the operating theatre. Music has been reported report to reduce stress and increase working efficiency in OR-staff[1,2]. Music has also been reported to impair surgeon's auditory processing and team communication[42,43]. The majority of anaesthetists generally like music in the operating theatre, but also consider it to be distracting if anaesthesiological problems were to occur[44]. However, in a simulated setting, no adverse effects of music were observed on anaesthetist's psychomotor performance[45]. Many factors can potentially affect surgical performance in a live operating environment, including leadership skills, communication level and cooperation[46-50]. How music affects all these factors and thus surgical performance in a live operating environment is unclear. Nonetheless, several studies have reported a correlation between improved surgical performance in a simulated setting and performance in the live operating environment[30-35].

Conclusion

There is not sufficient evidence to definitively determine whether music has a beneficial effect on surgical performance in the simulated setting. However, the results suggest that preferred music of the participant does improve surgical performance in a simulated setting.. Future studies should be conducted using greater numbers of participants, participant preferred music, and focusing on a more limited range of tasks. Furthermore the effects of music on surgical team performance and patient outcome should be assessed, in order to answer the question whether music improves surgical performance in the live operating environment.

Author Disclosure Statement

No external funding was received for this study. The authors declare no conflicts of interest.

Acknowledgements

The authors would like to thank W.M. Bramer, biomedical information specialist at the library of the Erasmus University Medical Centre, for his aid and expertise with the literature research.

8

Appendix A. Literature search

Database	Years of Coverage	Before deduplication	After deduplication
Embase.com	1971 – March 1, 2018	1157	1127
Medline Ovid	1946 – March 1, 2018	658	160
Web of Science	1900 – March 1, 2018	1050	566
Cochrane Central	1992 – March 1, 2018	101	7
PsycINFO	1887 – March 1, 2018	67	41
Cinahl	1937 – March 1, 2018	249	70
ERIC EBSCOhost	1996 – March 1, 2018	10	8
Google Scholar	Not applicable	200	150
Total		**3492**	**2129**

Embase.com
(music/de OR 'auditory stimulation'/de OR 'noise'/de OR (music OR musical OR musicotherap* OR (rhythm NEAR/3 (perception* OR accompan*)) OR melod* OR ((auditor* OR acoustic*) NEAR/3 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise):ab,ti) AND ('surgical skill'/exp OR 'suture'/de OR 'wound closure'/de OR 'suture technique'/de OR 'surgeon'/exp OR (('motor system'/de OR 'psychomotor performance'/de OR 'motor performance'/de OR 'motor function test'/de OR 'task performance'/de OR 'eye hand coordination'/de OR 'motor activity'/de OR 'motor coordination'/de) AND (surgery/exp OR 'operating room'/exp)) OR (((motor* OR psychomotor* OR performan* OR abilit* OR function* OR skill* OR train* OR entrain* OR education* OR learn* OR simulat* OR improv* OR sequence* OR process* OR interaction* OR coordinat* OR task*) NEAR/3 (surgic* OR surger* OR operating-room* OR operating-theat* OR laparoscop* OR perioperat* OR peroperat* OR peri-operat* OR per-operat*)) OR surgeon* OR stitch* OR sutur* OR laparoscop* OR davinci OR da-vinci):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND [english]/lim

Medline Ovid
(music/ OR Acoustic Stimulation/ OR noise/ OR (music OR musical OR musicotherap* OR (rhythm ADJ3 (perception* OR accompan*)) OR melod* OR ((auditor* OR acoustic*) ADJ3 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise).ab,ti.) AND (sutures/ OR Suture Techniques/ OR Wound Closure Techniques/ OR exp surgeons/ OR (("Task Performance and Analysis"/ OR Psychomotor Performance/ OR motor activity/) AND (exp Surgical Procedures, Operative/ OR Operating Rooms/)) OR (((motor* OR psychomotor* OR performan* OR abilit* OR function* OR skill* OR train* OR entrain* OR education* OR learn* OR simulat* OR improv* OR sequence* OR process* OR interaction* OR coordinat* OR task*) ADJ3 (surgic* OR surger* OR

operating-room* OR operating-theat* OR laparoscop* OR perioperat* OR peroperat* OR peri-operat* OR per-operat*)) OR surgeon* OR stitch* OR sutur* OR laparoscop* OR davinci OR da-vinci).ab,ti.) NOT (exp animals/ NOT humans/) AND english.la.

Web of Science
TS=(((music OR musical OR musicotherap* OR (rhythm NEAR/2 (perception* OR accompan*)) OR melod* OR ((auditor* OR acoustic*) NEAR/2 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise)) AND ((((motor* OR psychomotor* OR performan* OR abilit* OR function* OR skill* OR train* OR entrain* OR education* OR learn* OR simulat* OR improv* OR sequence* OR process* OR interaction* OR coordinat* OR task*) NEAR/2 (surgic* OR surger* OR operating-room* OR operating-theat* OR laparoscop* OR perioperat* OR peroperat* OR peri-operat* OR per-operat*)) OR surgeon* OR stitch* OR sutur* OR laparoscop* OR davinci OR da-vinci))) AND LA=(english)

Cochrane Central
((music OR musical OR musicotherap* OR (rhythm NEAR/3 (perception* OR accompan*)) OR melod* OR ((auditor* OR acoustic*) NEAR/3 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise):ab,ti) AND ((((motor* OR psychomotor* OR performan* OR abilit* OR function* OR skill* OR train* OR entrain* OR education* OR learn* OR simulat* OR improv* OR sequence* OR process* OR interaction* OR coordinat* OR task*) NEAR/3 (surgic* OR surger* OR operating-room* OR operating-theat* OR laparoscop* OR perioperat* OR peroperat* OR peri-operat* OR per-operat*)) OR surgeon* OR stitch* OR sutur* OR laparoscop* OR davinci OR da-vinci):ab,ti)

8

PsycINFO
(music/ OR Auditory Stimulation/ OR noise effects/ OR (music OR musical OR musicotherap* OR (rhythm ADJ3 (perception* OR accompan*)) OR melod* OR ((auditor* OR acoustic*) ADJ3 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise).ab,ti.) AND (exp surgeons/ OR (((motor* OR psychomotor* OR performan* OR abilit* OR function* OR skill* OR train* OR entrain* OR education* OR learn* OR simulat* OR improv* OR sequence* OR process* OR interaction* OR coordinat* OR task*) ADJ3 (surgic* OR surger* OR operating-room* OR operating-theat* OR laparoscop* OR perioperat* OR peroperat* OR peri-operat* OR per-operat*)) OR surgeon* OR stitch* OR sutur* OR laparoscop* OR davinci OR da-vinci).ab,ti.) NOT (exp animals/ NOT humans/) AND english.la.

Cinahl
(MH music OR MH Acoustic Stimulation OR MH noise OR TI (music OR musical OR musicotherap* OR (rhythm N2 (perception* OR accompan*)) OR melod* OR ((auditor* OR acoustic*) N2 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise) OR AB (music OR musical OR musicotherap* OR (rhythm N2 (perception*

OR accompan*)) OR melod* OR ((auditor* OR acoustic*) N2 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise)) AND (MH sutures OR MH Suture Techniques OR MH surgeons+ OR ((MH "Task Performance and Analysis" OR MH Psychomotor Performance+ OR MH motor activity) AND (MH Operating Rooms OR MH Surgery, Operative+)) OR TI (((motor* OR psychomotor* OR performan* OR abilit* OR function* OR skill* OR train* OR entrain* OR education* OR learn* OR simulat* OR improv* OR sequence* OR process* OR interaction* OR coordinat* OR task*) N2 (surgic* OR surger* OR operating-room* OR operating-theat* OR laparoscop* OR perioperat* OR peroperat* OR peri-operat* OR per-operat*)) OR surgeon* OR stitch* OR sutur* OR laparoscop* OR davinci OR da-vinci) OR AB (((motor* OR psychomotor* OR performan* OR abilit* OR function* OR skill* OR train* OR entrain* OR education* OR learn* OR simulat* OR improv* OR sequence* OR process* OR interaction* OR coordinat* OR task*) N2 (surgic* OR surger* OR operating-room* OR operating-theat* OR laparoscop* OR perioperat* OR peroperat* OR peri-operat* OR per-operat*)) OR surgeon* OR stitch* OR sutur* OR laparoscop* OR davinci OR da-vinci)) NOT (MH animals+ NOT humans+) AND LA (english)

ERIC EBSCOhost

(MH music OR TI (music OR musical OR musicotherap* OR (rhythm N2 (perception* OR accompan*)) OR melod* OR ((auditor* OR acoustic*) N2 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise) OR AB (music OR musical OR musicotherap* OR (rhythm N2 (perception* OR accompan*)) OR melod* OR ((auditor* OR acoustic*) N2 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise)) AND (TI (((motor* OR psychomotor* OR performan* OR abilit* OR function* OR skill* OR train* OR entrain* OR education* OR learn* OR simulat* OR improv* OR sequence* OR process* OR interaction* OR coordinat* OR task*) N2 (surgic* OR surger* OR operating-room* OR operating-theat* OR laparoscop* OR perioperat* OR peroperat* OR peri-operat* OR per-operat*)) OR surgeon* OR stitch* OR sutur* OR laparoscop* OR davinci OR da-vinci) OR AB (((motor* OR psychomotor* OR performan* OR abilit* OR function* OR skill* OR train* OR entrain* OR education* OR learn* OR simulat* OR improv* OR sequence* OR process* OR interaction* OR coordinat* OR task*) N2 (surgic* OR surger* OR operating-room* OR operating-theat* OR laparoscop* OR perioperat* OR peroperat* OR peri-operat* OR per-operat*)) OR surgeon* OR stitch* OR sutur* OR laparoscop* OR davinci OR da-vinci)) NOT (MH animals+ NOT humans+) AND LA (english)

Google Scholar

music|musical||"auditory|acoustic distraction|stress|relaxation"|noise surgeon|"surgical skills|tasks"

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Chapter 9

The Effects of Preferred Music on Laparoscopic Surgical Performance (ENSEMBLE): A Randomized Crossover Study

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World Journal of Surgery, 44(8):2614 – 2619, 2020.

"Participant-preferred music can improve laparoscopic surgical task performance, depending on mental workload and task complexity"

Abstract

Introduction: Music can have a positive effect on stress and general task performance. This randomized crossover study assessed the effects of preferred music on laparoscopic surgical performance in a simulated setting.

Methods: Sixty medical students, inexperienced in laparoscopy, were included between June 2018 and November 2018. A randomized, 4-period, 4-sequence, 2-treatment crossover study design was used, with each participant acting as its own control. Participants performed four periods, consisting of five peg transfer tasks each period, on a laparoscopic box trainer; two periods while wearing active noise-cancelling headphones and two periods during music exposure. The parameters time to task completion, path length and normalized jerk were assessed. Mental workload was assessed using the Surgical Task Load Index questionnaire. Also heart rate and blood pressure were assessed.

Results: Participants performed the peg transfer task significantly faster [median difference: -0.81s(interquartile range: -3.44 – 0.69) p=0.037] and handled their instruments significantly more efficient as path length was reduced [median difference: -52.24mm (interquartile range: -196.97 – 89.81) p=0.019] when exposed to music. Also, mental workload was significantly reduced during music [median difference: -2.41(interquartile range: -7.17- 1.83) p=0.021)]. No statistically significant effect was observed on heart rate and blood pressure

Conclusion: Listening to preferred music improves laparoscopic surgical performance and reduces mental workload in a simulated setting.

Introduction

In many operating theatres worldwide, music is played. The surgical staff perceives that music reduces stress and increases efficiency[1,2]. Much has been published on performance-enhancing effects of music after the observation of a beneficial effect of Mozart's music on visuospatial task performance[3]. A previous meta-analysis found a small but significant beneficial effect of multiple types of music, not exclusively Mozart's music, on task performance[4]. Improved task performance could benefit patient outcome. However, earlier studies assessing the effect of recorded music on surgical task performance did not provide conclusive evidence. Two out of nine studies used preferred music, and seven studies used researcher-selected music[5-13]. The available evidence suggests that the participant's preference could play an essential role in the effects of music on surgical performance[14]. The primary objective of this randomized crossover study is therefore to assess the effect of preferred music on laparoscopic performance in a simulated setting. Secondary objectives are to assess the effect of music on mental workload and vital parameters.

Methods

This study was approved by the institutional review board of the Erasmus University Medical Center (MEC-2018-1134) and registered at clinicaltrials.gov (NCT04111679). Written informed consent was obtained from 60 healthy medical students, all inexperienced in laparoscopy, who were included between June 2018 and November 2018.

Laparoscopic surgical performance assessment

A laparoscopic box trainer was used, which was developed by the skills laboratory of the Erasmus University Medical Center Rotterdam. A shortened version of the peg transfer task was designed to assess laparoscopic surgical performance. The peg transfer task is part of the Fundamentals of Laparoscopic Surgery program, a validated training course mandatory for all surgical residents in the United States[15,16]. This task consists of moving two colored pegs with grasper forceps using the dominant hand. A sequence of goal positions of the pegs was designated on the screen by colored squares. To assess surgical performance, a leap motion device recorded the following parameters: time to task completion (total time used to complete the peg transfer, path length (total distance travelled by the instrument tip during the peg transfer task), and motion smoothness (normalized jerk, i.e. the rate of change in acceleration of instrument tip)[17].

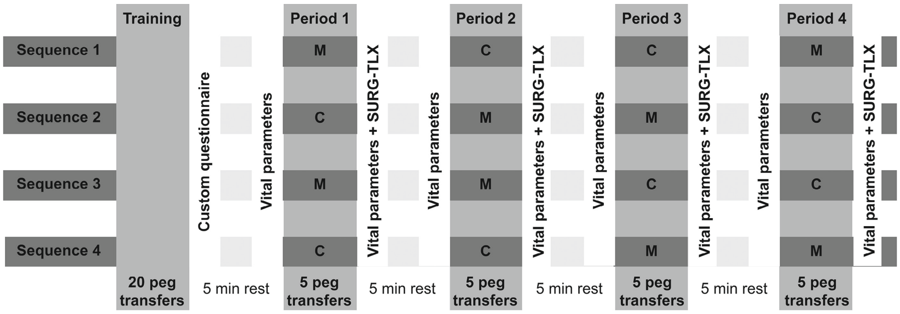
Mental workload, vital parameters, and music listening behavior

Mental workload was assessed using the Surgical Task Load Index (SURG-TLX), a modified version of the National Aeronautics and Space Administration Task Load Index (NASA-TLX)[18]. The SURG-TLX is a weighed 0-100 score based on six subscales that assess mental demands, physical demands, temporal demands, situational stress, task complexity and distractions. After every period, participants completed a SURG-TLX questionnaire. Heart rate and blood pressure were assessed before and immediately after every period, using a Philips© DL8760/15 blood pressure monitor. All participants completed a custom-made demographic questionnaire assessing dexterity, their music listening behavior, whether the participant masters a musical instrument, and whether the participant plays or has played video games, and whether the participants listens to music while studying.

Study design

A 4-period, 4-sequence, 2-treatment crossover design was used in order to reduce a possible learning effect19. Participants competed four periods, each consisting of five peg transfer tasks. In total, the peg transfer task was performed 10 times while listening to music selected by the participant (M) and 10 times in silent conditions (C), with every participant serving as their own control. All participants wore noise-cancelling headphones (Bose QuietComfort 35 II) during each period in order to minimize observer bias. Participants were randomly allocated to a sequence Participants were randomly allocated to a sequence that determined the order of the experiment using opaque sealed envelopes. Participants were allowed to rest for 5 minutes between every period. To get acquainted with the setup and to practice the tasks, all participants completed 20 peg transfers prior to the experiment, as it was observed during the development of the research setup that the learning curve starts to flatten after 20 repetitions. Figure 1 provides an overview of the used sequences as well as a time line of the experiment.

Figure 1. Experiment timeline



This figure provides a timeline of the experiment for each sequence. M = music: participant-selected music via noise-cancelling headphones; C = control: noise-canceling headphones without music; SURG-TLX: Surgical Task Load Index questionnaire

Statistical analysis and sample size calculation.

Based on the available literature, effect size was estimated at 0.40[9,10,13]. Therefore, a sample size of 52 would be sufficient ($\alpha = 0.05$, $\beta = 0.8$). Sample size was set at 60 to account for an estimated 10% exclusion rate and to evenly distribute participants over the four sequences in order to maintain a balanced crossover design. Statistical analysis was performed using IBM SPSS Statistics for windows, version 24.0, Armonk, NY: IBM Corp. Normality was assessed using the Kolmogorov-Smirnov test and visually in Q-Q plots. Continuous variable was compared using a paired-samples T-test if the data were normally distributed or the Wilcoxon signed rank test if the data were non-normally distributed. Within-subject differences were computed by subtracting the control values from the music values. Within-subject differences of path length, time to task completion and normalized jerk were presented in percentages. Data were presented as median and (interquartile range) if the data was non-normally distributed, or mean ± standard deviation if normally distributed. Between subgroup differences were calculated using the Student's T-test if the data were normally distributed and the Mann-Whitney U test if the data were not normally distributed.

Results

Sixty participants completed the experiment. Demographic characteristics of the included participants are presented in Table 1. The median age was 19 years, and the majority of the participants were first year medical students. Ninety-five percent was right-handed, and the top three favorite musical genres in general were pop, classical and rock music.

Table 1. Demographic characteristics

	Full Cohort (n = 60)
Age: years (IQR)	19 (18-21)
Sex: Male	19 (31,7)
Dexterity: right handed (%)	57 (95)
Year of study (IQR)	1 (1 – 3)
Current or previous video game experience	25 (41,7)
Importance of music on a 0-10 scale (IQR)	8 (7 – 9)
Plays or has played a musical instrument (%)	42 (70)
Top 3 favorite genres	Pop: 23,90% Classical: 17,90% Rock: 14,10%
Listens to music while studying (%)	48 (80)
Top 3 favorite genres when studying	Classical: 30,10% Pop: 18,30% Instrumental: 17,20%

The musical preference of the participants seemed to depend on the situation, as the top three favorite music genres participants listen to while studying differed, being classical, pop and instrumental music, respectively. Twelve participants never listened to music while studying.

Laparoscopic surgical performance

A statistically significant beneficial effect was observed of music on laparoscopic surgical performance (Table 2). Participants performed the peg transfer task 4.68% (– 4.35-16.59) (p= 0.019) faster during music exposure compared to silence. Laparoscopic instrument handling was significantly improved during music exposure as path length was reduced by 6.35% (-17.15-7.54) (p = 0.037). No statistically significant effect of music on normalized jerk was observed (p = 0.171).

Table 2. Laparoscopic surgical performance data

Full cohort (N=57)	Music	Control	Median of differences	IQR of differences	*p*
Path length (mm)	1141.47 ± 357.42	1216.18 ± 419.81	-52.24	(-196.97 – 89.81)	0.019[a]
Time to task completion (s)	19.16 (16.10 – 22.68)	19.72 (16.77 – 24.43)	-0.81	(-3.44 – 0.66)	0.037[b]
Normalized jerk (mm/s^3)	9595.16 (5885.91 – 13934.26)	9538.07 (6394.45 – 15631.07)	-982.12	(-4635.70 – 2673.27)	0.171

Table 2 legend. Continuous variables presented as median (interquartile range) or mean ± standard if the data were normally distributed.
Median of differences: median of within-subject differences. IQR of differences: interquartile range of within-subject differences.
[a] Paired samples t-test. [b] Wilcoxon signed-rank test

Table 3. Mental workload

	Full Cohort (N=60)		Within subject	
	Music	**Control**	***p***	**Differences**
SURG-TLX	26.00 (14.75 – 38.00)	28.33 (18.75 – 42.67)	0.021	-2.41 (-7.17 – 1.83)
Mental demands	20.00 (12.50 – 35.00)	22.50 (13.75 – 35.00)	0.160	0.00 (-6.25 – 0.00)
Physical demands	15.00 (7.50 – 18.75)	17.50 (12.50 – 25.00)	0.003	-2.50 (-7.50 – 0.00)
Temporal demands	22.50 (15.00 – 52.50)	37.50 (17.50 – 51.25)	0.156	-2.50 (-12.50 – 7.50)
Situational Stress	12.50 (7.50 – 31.25)	22.50 (10.00 – 37.50)	0.005	-2.50 (-11.25 – 2.50)
Complexity	22.50 (12.50 – 35.00)	27.50 (17.50 – 35.00)	0.008	-2.50 (-7.50 – 2.50)
Distraction	12.50 (8.75 – 25.00)	15.00 (10.00 – 25.00)	0.513	0.00 (-7.50 – 0.00)

Table 3 legend. Surgical Task Load Index (SURG-TLX) is a weighted score comprised of six subscales ranging from 0 to 100 representing general mental workload. Continuous variables presented in medians and (interquartile ranges). *p*: Wilcoxon signed-rank test.

Mental workload

A statistically significant beneficial effect was observed on the mental workload, as the weighed SURG-TLX score was reduced when participants were exposed to music – 2,41 (– 7,17-1,83)(Table 3). Physical demands were reduced during exposure to music – 2,50 (– 7,50-0,00). Situational stress levels were lower during music exposure – 2,50 (– 11,25-2,50), and the laparoscopic task was perceived as less complex during music exposure – 2,50 (– 7,50-2,50). Music did not reduce distractions or affect mental and temporal demands.

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Heart rate and blood pressure

No statistically significant effect of music was observed on heart rate, systolic blood pressure and diastolic blood pressure.

Discussion

To our knowledge, this is the largest published study to date assessing the effect of preferred music on laparoscopic surgical performance in a simulated setting and the first to use participant-preferred music during simulated laparoscopic task performance[14]. Participants performed the laparoscopic task on average 4,68% faster, and their instrument handling was more efficient, as path length was reduced by 6,35% during exposure to music of their choice. To our knowledge, this is also the first published study that observed a beneficial effect of music on mental workload, as it was significantly reduced during exposure to music. The beneficial effect of music was most profound on situational stress, physical demands and task complexity subscales. Therefore, both laparoscopic surgical task performance and the subjective experience of the participants were significantly improved during music exposure.

In surveys assessing healthcare provider's attitudes towards music in the operating room, the operating room staff reported that music made them feel less stressed and a majority considered music not distracting[2,20]. In the present study using a simulated setting, we observed similar effects. Music reduced the situational stress and was not found to be distracting. In fact, a majority of our cohort experienced music as less distracting than silence. The present observations using participant-preferred music confirm earlier observations by Miskovic *et al*[9], who observed a trend towards a statistically significant beneficial effect on laparoscopic surgical performance when participants considered the researcher-selected music as pleasant. Our results confirm earlier suggestions that participant-preferred music improves simulated surgical performance[21]. Perioperative music has been observed to reduce stress in patients undergoing surgery[22]. We observed comparable effects during laparoscopic surgical task performance when participants were exposed to music in situational stress. High levels of stress and anxiety in the operating room are associated with impaired surgical performance, team performance and an increased risk of adverse events; music might help to reduce these stress levels[22-24].

Preferred music reduced subjective physical demands during laparoscopic performance. This could be of importance, as surgery is a physically demanding task. Musculoskeletal disease is highly prevalent in surgeons, often leading to a leave of absence, practice restriction or even early retirement[25,26]. High levels of workload and perceived physical demands have been associated with the incidence of musculoskeletal disease in healthcare workers[27-30].

This study has strengths and limitations. Our sample size is large compared to earlier studies that assessed the effect of music on surgical performance[5-13]. Our crossover design is well-balanced and minimizes possible learning effects[19]. To further reduce this effect, all participants practiced the laparoscopic task prior to the experiment to the point where it has been observed that the learning curve starts to flatten during development of our research setup. Our study assessed laparoscopic surgical performance in a simulated setting, which has been observed to translate to, and correlate with real-world surgical performance[31-34]. Music was not considered to be distracting and positively affected laparoscopic surgical task. However, music during surgery has been reported to impair team communication, which could not be assessed in our experimental setup. It cannot be ruled out that the beneficial effects we observed can be attributed to auditory stimulation and not music per se, given that the control condition was silence. As it has been reported that noise cancellation could induce anxiety[35], it could be possible that we observed an adverse effect of silence instead of a beneficial effect of music. Furthermore, in a live operating environment, it is hardly ever silent in the operating room[36]. It is unclear how music would affect laparoscopic performance in a noisy environment such as the operating theatre or when controlling for another form of auditory stimulation. However, given that music is generally well liked and prevalently played during surgery, we do not believe it clinically relevant to assess the effects of other forms of auditory stimulation for surgical task performance, except recorded operating room noise. The study population consisted of medical students who were inexperienced in laparoscopy, performing a relatively simple laparoscopic peg transfer task, as it has been reported that more experienced surgeons can more effectively block out noise and music. Also, several practical barriers would hinder the inclusion of a significant number of surgeons for laparoscopic task performance in a simulated setting, like time constraints due to busy schedules. How music would affect performance while performing more complex surgical tasks is unclear. Unfortunately, we could not identify any personal factors that enhance or diminish the effects of music on laparoscopic surgical performance, due to our sample size.

Surgical residents report that the largest barrier to attend simulation based training is a lack of free time[37]. Implementing music interventions could assist surgical residents in completing their mandatory training modules more quickly and efficiently[15]. In our opinion, future research should focus on the effects of music while controlling for the noisy environment of the operating theater and the effects of music on laparoscopic tasks with a higher level of complexity. A follow-up study is currently being conducted investigating aforementioned fields of interests (Dutch Trial Register (Trial NL7961) www.trialregister.nl/trial/7961). Also, it would be interesting to investigate the effect of music on surgical performance in more experienced surgeons, at it is hypothesized that they block out distracting noises more effectively[10].

Conclusion

Preferred music improves laparoscopic surgical performance and reduces mental workload in a simulated setting.

Author Disclosure Statement

No external funding was received for this study. The authors declare no conflicts of interest.

Appendix A.

Vital Parameters	Music			Control			*p*
	Pretest	Post-test	Difference	Pretest	Post-test	Difference	
Heartrate (BPM)	77.75 (72.50 – 84.13)	75.50 (70.38 – 84.63)	1.00 (-1.50 – 3.63)	78.75 (70.88 – 87.50)	77.50 (68.88 – 83.13)	1.50 (-2.00 – 4.13)	0.987
Systolic blood pressure (mm/hg)	124.25 (117.25 – 130.63)	125.50 (120.88 – 130.00)	-1.25 (-4.00 – 2.00)	123.25 (117.00 – 130.25)	123.25 (115.88 – 132.13)	-0.50 (-2.50 – 2.50)	0.465
Diastolic blood pressure (mm/hg)	73.25 (68.75 – 79.88)	73.25 (69.38 – 79.25)	-0.50 (-2.50 – 2.50)	72.50 (68.25 – 80.75)	73.00 (69.88 – 78.38)	-0.50 (-2.50 – 2.50)	0.386

Appendix A legend. Data presented as medians and (interquartile range). BPM: Beats per minute; mm/hg: millimeter of mercury; *p*: Wilcoxon signed rank test of pre- and post-test differences in both music and control.

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Chapter 10

The Effect of Preferred Music on Mental Workload and Laparoscopic Surgical Performance in a Simulated Setting (OPTIMISE): A Randomized Controlled Crossover Study

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Surgical Endoscopy, 35(9): 5051 – 5061, 2021.

"Music attenuates stress in both surgeons and patients"

Abstract

Background: Worldwide, music is commonly played in the operation room. The effect of music on surgical performance reportedly has varying results, while its effect on mental workload and key surgical stressor domains has only sparingly been investigated. Therefore, the aim is to assess the effect of recorded preferred music versus operating room noise on laparoscopic task performance and mental workload in a simulated setting.

Methods: A four-sequence, four-period, two-treatment, randomized controlled crossover study design was used. Medical students, novices to laparoscopy, were eligible for inclusion. Participants were randomly allocated to one of four sequences, which decided the exposure order to music and operation room noise during the four periods. Laparoscopic task performance was assessed through motion analysis with a laparoscopic box simulator. Each period consisted of 10 alternating peg transfer tasks. To account for the learning curve, a preparation phase was employed. Mental workload was assessed using the Surgery Task Load Index. This study was registered with the Netherlands Trial Register (NL7961).

Results: From October 29, 2019 until March 12, 2020, 107 participants completed the study, with 97 included for analyzation. Laparoscopic task performance increased significantly during the preparation phase. No significant beneficial effect of music versus operating room noise was observed on time to task completion, path length, speed or motion smoothness. Music significantly decreased mental workload, reflected by a lower score of the total weighted Surgery Task Load Index in all but one of the six workload dimensions.

Conclusion: Music significantly reduced mental workload overall and of several previously identified key surgical stressor domains, and its use in the operating room is reportedly viewed favorably. Music did not significantly improve laparoscopic task performance of novice laparoscopists in a simulated setting. Although varying results have been reported previously, it seems that surgical experience and task demand are more determinative.

Authorship

VF, PO and VK made substantial contributions to conception and design of the study. KS, WB and PW carried out the experiment for the acquisition of data. VF, PO and KS made substantial contributions to overall data analysis. VK processed the motion data for analyzation. WB focused primarily on motion analysis and PW on mental workload and heart rate variability analysis. VF, PO, JL, GK and JJ interpreted the data. VF primarily drafted the manuscript, with substantial contribution by PO, VK, KS, WB and PW, whilst JL, GK and JJ critically revised it for important intellectual content. All authors gave final approval of the version to be published.

Abbreviation list

bpm	Beats per minutes
CONSORT	Consolidated standard of reporting trials
ECG	Electrocardiography
HRV	Heart rate variability
IQR	Interquartile range
mm	Millimeter
ms	Millisecond
NASA-TLX	National aeronautics and space administration task load index
NN	Interval between two heartbeats
NRS	Numeric rating scale
OR	Operating room
RCT	Randomized controlled trial
s	Second
SD	Standard deviation
SDNN	Standard deviation of all NN intervals, representing HRV median variability
SPSS	Statistical package for the social sciences
SURG-TLX	Surgery task load index
VAS	Visual analog scale

Introduction

Worldwide, music is commonly played during surgery[1]. Perioperative music has been extensively investigated in adult surgical patients with several beneficial effects[2-4]. However, no definitive conclusion on the effect of music on surgical task performance can currently be drawn due to conflicting study results, inconsistent data reporting methods, and varying study designs in previously published studies[5]. To date, all these studies have been conducted in a simulated setting[5], as surgical performance in a simulated setting correlates to performance during actual real-world surgery and influences postoperative patient outcome[6-9]. It is unclear whether the reported beneficial effects of music on surgical performance are due to an auditory stimulus and not music per se, as all but one[10] of the previous studies used silence as a control[11-18]. Given that high noise level settings are commonly prevalent in the operation room (OR)[19], it could be argued that using silence as a control factor is therefore not appropriate when evaluating the effect of music on surgical performance.

Some surveys have shown that music is well-liked by surgical personnel and can improve focus during surgery[1], while others mentioned that it can be distracting and reduce vigilance[20,21]. Therefore, music during surgery could potentially influence mental workload, which can be defined as the attention that can be directed to a surgical task and the balance of the attention amount used and additionally available when necessary. Increased mental workload is associated with decreased surgical task performance[22]. Whilst perioperative music has a significant beneficial attenuating effect on the physiological stress response in adult surgical patients[3], its effect on mental workload and stress while performing a surgical task has only sparingly been investigated[23].

Laparoscopic surgery requires different skills compared to conventional open surgery due to the use of long instruments and the fulcrum effect, two-dimensional screen visualization which can impair depth perception, and limited tactile feedback[24]. Therefore, simulation using either a box trainer or virtual reality is increasingly used to provide a safe environment for the early learning curve phase. Successfully completing the Fundamentals of Laparoscopic Surgery program is required to become board certified as a general surgeon in the United States[25]. The acquired competencies in a simulated setting seem to be transferable to the real word setting with favorable effects on skill, knowledge and patient outcome[26,9,6]. The purpose of this randomized crossover study is to investigate the effect of participant-selected recorded music versus recorded OR noise on laparoscopic task performance, mental workload and heart rate variability (HRV) in a simulated setting.

Methods

This study was approved in September 2019 by the Medical Ethics Committee Erasmus MC (MEC-2019-0537) and prospectively registered with the Netherlands Trial Register

(Trial NL7961). The study was performed in accordance with the ethical standards of the Helsinki Declaration of 1975. No study protocol amendments were required. Reporting adhered to the 2010 Consolidated Standard of Reporting Trials (CONSORT) extension for randomized crossover trials[27].

Study design

A study procedure timeline overview is presented in Figure 1. A four-sequence, four-period, two-treatment, randomized controlled crossover study design was used to investigate the effects of recorded, participant-selected music versus recorded OR noise on laparoscopic task performance, mental workload and HRV. Medical students who were novices to laparoscopy and provided written informed consent were eligible for study participation. Severe hearing impairment, visual impairment, physical handicap that impairs laparoscopic task performance, or use of cardiac medication were considered as exclusion criteria. Participants were instructed to bring music they would like to listen to while performing a laparoscopic task and to abstain from alcohol for 12 hours prior to the experiment. The 10 minute OR noise recording was selected from a list by three authors (VF, PO and JJ) with prior surgical experience in the OR to represent noise during a routine laparoscopic surgical procedure (i.e. no orthopedic drilling noise). Laparoscopic task performance was assessed with a validated, custom-made laparoscopic box simulator using the peg transfer task[23], during which a blue and red peg are moved with a grasper forceps to a predefined location shown on a monitor. This task is part of the Fundamentals of Laparoscopic Surgery program for surgical residents in the United States[28]. Motion data to assess laparoscopic task performance was captured using a Leap Motion Device (LMC, Leap Motion Inc., LM-010), a compact sensor modified and customized for motion analysis, connected to a computer with monitor, and a webcam (Gemini Gembird) functioning as camera with a frame rate of 60 Hertz. Motion data was progressed using a custom made software program (OCRAM technologies) combined with Python version 2.7.

After signing the informed consent form, a chest band was fitted to continuously measure HRV throughout the entire experimental session[29]. A custom demographic questionnaire evaluating music importance and preferences, listening to music while studying, and whether a music instrument is or was played, was filled out. Participants were randomly allocated using the sealed envelope method and a 1:1:1:1 allocation ratio to one of four sequences. Each sequence consisted of a preparation phase followed by two periods of recorded, participant-selected music and two periods recorded OR noise, with the order of exposure decided by the previously mentioned randomization. To account for the learning curve, all participants completed a preparation phase consisting of 30 peg transfer tasks, alternating between the right and left hand (i.e. the first peg transfer is performed using the right hand, the second using the left hand, the third using the right hand again and so on), as it was previously observed that the learning curve flattened after 20 repetitions[23].

Figure 1. Study procedure overview timeline

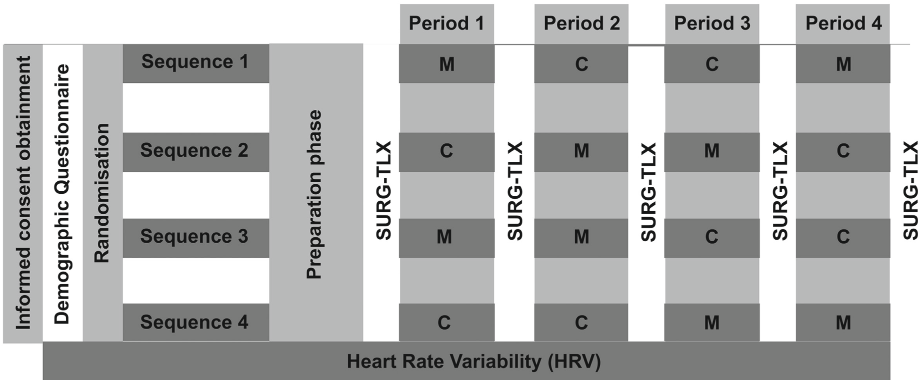

Figure 1 legend. Timeline detailing study procedures. Depending on the sequence, consisting of 4 periods, participants were exposed to either music or operation room noise.
Preparation phase = 30 alternating peg transfer tasks; Period = 10 alternating peg transfer tasks; M = Exposure to recorded, participant-selected music; C = Exposure to recorded operation room noise; SURG-TLX = Surgery Task Load Index; HRV = Heart rate variability, measured continuously throughout the experiment

During each period, 10 alternating peg transfer tasks were performed whilst listening to either music or OR noise using noise-cancelling headphones (Bose Quietcomfort 35ii). Volume level was adjusted at the start by the participant and was therefore consistent during the entire experiment. The Surgery Task Load Index (SURG-TLX) questionnaire evaluating mental workload was filled out after the preparation phase and each period for a total of five times, which led to a washout period of at least several minutes.

Outcome parameters

The primary outcome measure was time to task completion, defined as the time in seconds (s) required to complete a 10 peg transfer task period, consisting of alternating peg transfers with the dominant and non-dominant hand. Time to task completion of the peg transfer task is the main score attribute in the Fundamentals of Laparoscopic Surgery program[28]. Furthermore, path length, the total distance traveled in millimeters (mm) by the instrument tip, speed, the ratio of path length and time to task completion (mm/s), and motion smoothness, the normalized jerk or the rate of instrument tip acceleration change (mm/s^3) were measured. To assess the benefit of the preparation phase, motion analysis of the first 10 peg transfers in this phase was compared to the last 10 peg transfers additionally.

Mental workload was assessed using the SURG-TLX, an in laparoscopic surgery validated, adapted version of the National Aeronautics and Space Administration Task Load Index (NASA-TLX) questionnaire[30]. This weighted questionnaire assesses six dimensions of workload (mental demands, physical demands, temporal demands, task complexity, situation stress and distractions) using a visual analogue scale (VAS) and was filled out by all participants after the preparation phase and each period.

Heart rate and HRV, defined as the variation in time between each heartbeat (NN), were continuously measured from the preparation phase start until experiment end using the commercially available, validated BM-CS5EU wireless chest band (BM innovations, Acentas GmbH)[29]. Short-term HRV measurements[31], lasting approximately five minute during each of the four periods as well as the first five and last five minutes of the preparation phase, were analyzed (ATS 2.4.6., BM Innovations). HRV can represent the physiological state of autonomic nervous system activity and has been used to assess mental strain in surgeons during laparoscopic task performance[32]. A lower HRV implicates dominance by the sympathetic nervous system and has been regarded as higher mental strain. HRV quantification was presented using the time-domain variable standard deviation of all NN intervals (SDNN) in milliseconds (ms).

Blinding and data analysis

Obviously, the participants in this experiment could not be blinded. Headphones were employed partly to blind the research assistant overseeing the experiment. However, as participants brought their preferred music using different devices, transferring music to the laptop which contained the OR noise recording in order to be played during the experiment was impractical. Therefore, the music intervention was directly played whilst the headphones were attached to the participant's phone or music player. Although the research assistant was separated from the participant by an opaque screen during the experiment in order to reduce any influence to the fullest extent, the assistant was not considered to be blinded. All questionnaires were filled out using a secure, computerized questionnaire by the participants themselves and were therefore not administered by the research assistant. Heart rate and HRV data was processed through a validated software program. Motion data analysis was computerized using a software script validated in previous studies, whilst the person responsible for data retrieval and preparing it for analysis was blinded to the allocation sequence. All data were only analyzed after the last participant had completed the experiment.

Data were statistically analyzed using the IBM Statistical Package for the Social Sciences (SPSS) version 24.0. Data were presented as mean and standard deviation (SD) if data were normally distributed, and median and interquartile range (IQR) if not. Normality of data was assessed using the Kolmogorov-Smirnov test and visually in Q-Q plots. Continuous variables were compared using a paired-samples T-test or Wilcoxon signed rank test, as appropriate. Within subject differences were presented by subtracting the control group from the intervention group. Categorical variables were presented as absolute number and percentage. Two tailed testing was used with statistical significance inferred at $p<0.05$.

Sample size calculation

Based on our previous study using the same laparoscopic box simulator[23], an effect size of 0.3 was deemed clinically relevant. With alpha set at 0.05, power of 0.80 and two-sided dependent testing, 90 participants would be required. Given that there were four randomization sequences, we chose to set the sample size at 92 participants to allow for equal distribution among the sequences. Taking into account a 10 percentage exclusion rate, total sample size was set at 104 participants.

Figure 2. CONSORT Flow diagram

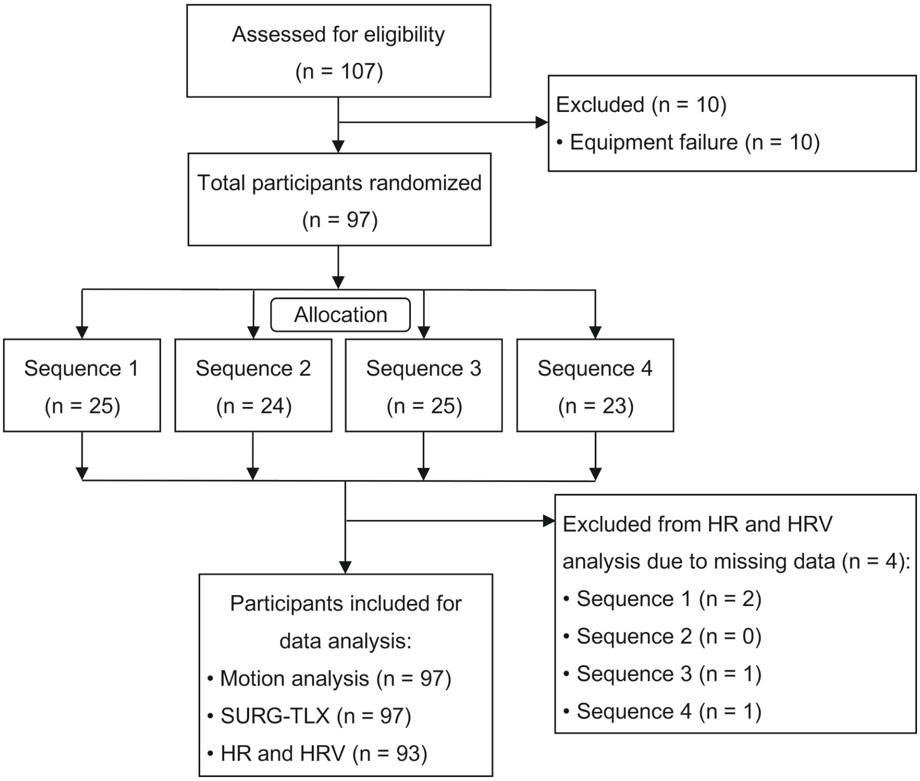

Figure 2 legend. Inclusion flowchart
n = number of participants; SURG-TLX = Surgery Task Load Index; HR = Heart rate; HRV = Heart rate variability

Results

From October 29, 2019 until March 12, 2020, 107 participants were recruited. Ten participants were excluded because of equipment failure at the start of the study. Motion analysis and mental workload assessment using the SURG-TLX was performed of all 97 participants who completed the study. Due to missing data, heart rate and HRV analysis was performed of 93 participants (Figure 2).

Demographic characteristics

An overview of demographic characteristics of the full cohort (N=97) can be found in Table 1. Median age was 20 (IQR 18 to 21), with the majority of the medical students being in their first three years of study (77%), right-handed (85%) and female (57%). A little over half of participants (54%) had experience with a musical instrument, with 31 (32%) currently playing and 21 (22%) previously playing an instrument. Music was deemed important in daily life with a median numeric rating scale (NRS) of 8 (IQR 7 to 8), with 68 (70%) participants listening to music while studying. Favorite genres while studying were classical (20%) and pop (16%), while 18% specified music that could not be classified under commonly described genres. Top music genres chosen for this experiment were pop (47%), classical (21%) and hip hop (9.3%) (Appendix A).

Laparoscopic task performance

Laparoscopic task performance improved during the preparation phase (Table 2), with time to task completion of the last 10 alternating peg transfer tasks being significantly faster compared to the first 10 tasks (median 250 s [IQR 218 to 327] versus 433 s [335 to 532], $p<.001$). A significant reduction in path length of the last 10 compared to the first 10 tasks during the preparation phase (8375 mm [6107 to 12397] versus 12810 mm [8813 to 18168], $p<.001$) and improved motion smoothness in the form of normalized jerk was also observed (236596 mm/s^3 [102441 to 471534] versus 857493 mm/s^3 [407460 to 1833467], $p<.001$).

Table 1. Demographic characteristics

Characteristic		Full cohort (n = 97)
Age (years)		20 (18-21)
Sex	Male	42 (43.3%)
	Female	55 (56.7%)
Dexterity	Right	82 (84.5%)
	Left	14 (14.4%)
	Bimanual	1 (1.0%)
Year of Medical School	1	34 (35.1%)
	2	20 (20.6%)
	3	21 (21.6%)
	4	16 (16.5%)
	5	1 (1.0%)
	6	5 (5.2%)
Importance of music (NRS)		8 (7-8)
Listens to music while studying	Yes	68 (70.1%)
	No	29 (29.9%)
Top-three favorite music genre while studying	1	Classical (19.6%)
	2	Other (17.5%)
	3	Pop (15.5%)
Plays a musical instrument	Yes	31 (32.0%)
	Used to	21 (21.6%)
	No	45 (46.4%)
Top-three chosen music genre for OPTIMISE study	1	Pop (42.3%)
	2	Classical (19.6%)
	3	Hip hop (9.3%)
Sequence randomization	1	25 (25.8%)
	2	24 (24.7%)
	3	25 (25.8%)
	4	23 (23.7%)

Table 1 legend. Demographic characteristics of OPTIMISE study population. For categorical variables, absolute number (percentage of study population) is presented. For continuous variables, median (interquartile range) is presented. n = number of participants; NRS = Numeric rating scale

Table 2. Preparation phase

Motion analysis (n=97)	First 10 peg transfer tasks	Last 10 peg transfer tasks	Within subject differences	P
Time to task completion, median (IQR), s	433 (335 to 532)	250 (218 to 327)	163 (65.9 to 266)	0.000
Path length, median (IQR), mm	12810 (8813 to 18168)	8375 (6107 to 12397)	4018 (761.8 to 7354)	0.000
Average speed, median (IQR), mm/s	445 (321 to 540)	461 (325 to 561)	-6.21 (-81.7 to 72.9)	0.544
Normalized jerk, median (IQR), mm/s^3	857493 (407460 to 1833467)	236596 (102441 to 471534)	493611 (97813 to 1334364)	0.000
Heart rate and heart rate variability (n=93)	**First 5 minutes**	**Last 5 minutes**	**Within subject differences**	**P**
Heart rate, median (IQR), bpm	87 (75 to 101)	91 (80 to 106)	-4.0 (-8.0 to -0.50)	0.000
Heart rate variability, median (IQR), SDNN	52 (40 to 71)	48 (38 to 63)	7.0 (-1.5 to 13)	0.000

Table 2 legend. Learning curve overview reflected by comparing the motion analysis of the last 10 to the first 10 peg transfer tasks during the preparation phase, which consisted of 30 alternating peg transfer tasks in total. Data presented as median (interquartile range).
n = number of participants; IQR = interquartile range; s = seconds; mm = millimeters; bpm = beats per minutes; SDNN = standard deviation of the all NN intervals, representing a median of HRV variability

No statistically significant difference in laparoscopic task performance parameters were observed during exposure to the different auditory stimuli (Table 3). Time to task completion was not statistically significantly faster while listening to music compared to OR noise (210 s [191 to 262] versus 221 s [188 to 257], *p*=.518) and path length was not reduced (7606 mm [5725 to 9182] versus 7462 mm [5833 to 8952], *p*=.434). Speed did not differ (434 mm/s [321 to 552] versus 436 mm/s [324 to 556], *p*=.758), nor did motion smoothness in the form of normalized jerk (180687 mm/s^3 [83581 to 281566] versus 171957 mm/s^3 [95905 to 316327], *p*=.125). Additionally, there was no significant difference by music compared to OR noise in laparoscopic task performance parameters of the dominant and non-dominant hand, when these were assessed separately from each other. When assessing the participants who preferred to listen to music when studying (n=68) as a separate group, no significant difference was observed. No difference was observed when taking experience with playing a musical instrument into account, or gender (Table 4).

Table 3. Main study results

Motion analysis (n=97)	Music	Control	Within subject differences	P
Time to task completion, median (IQR), s	210 (191 to 262)	221 (188 to 257)	0.60 (-25.3 to 18.8)	0.518
Path length, median (IQR), mm	7606 (5725 to 9182)	7462 (5833 to 8952)	184.3 (-853.0 to 1219)	0.434
Average speed, median (IQR), mm/s	434 (321 to 552)	436 (324 to 556)	0.83 (-50.8 to 55.6)	0.758
Normalized jerk, median (IQR), mm/s^3	180687 (83581 to 281566)	171957 (95905 to 316327)	-9259 (-78294 to 45858)	0.125
Mental workload (n=97)	**Music**	**Control**	**Within subject differences**	**P**
SURG-TLX, median (IQR), VAS 0-100	27.0 (17.3 to 38.3)	33.7 (21.2 to 43.3)	-3.50 (-9.08 to 1.75)	0.000
Mental demands, median (IQR), VAS 0-100	25.0 (15.0 to 37.5)	30.0 (20.0 to 50.0)	-5.00 (-12.5 to 0.00)	0.000
Physical demands, median (IQR), VAS 0-100	20.0 (12.5 to 32.5)	22.5 (12.5 to 31.3)	0.00 (-5.00 to 2.50)	0.012
Temporal demands, median (IQR), VAS 0-100	35.0 (20.0 to 47.5)	37.5 (22.5 to 50.0)	-2.50 (-12.5 to 5.00)	0.010
Task complexity, median (IQR), VAS 0-100	25.0 (12.5 to 42.5)	25.0 (15.0 to 43.8)	0.00 (-5.00 to 2.50)	0.471
Situational stress, median (IQR), VAS 0-100	17.5 (10.0 to 30.0)	25.0 (12.5 to 40.0)	-2.50 (-10.0 to 0.00)	0.000
Distractions, median (IQR), VAS 0-100	15.0 (10.0 to 30.0)	32.5 (20.0 to 47.5)	-10.0 (-27.5 to 0.00)	0.000
Heart rate and heart rate variability (n=93)	**Music**	**Control**	**Within subject differences**	**P**
Heart rate, median (IQR), bpm	88 (78 to 102)	87 (77 to 102)	1.0 (-1.3 to 2.0)	0.046
Heart rate variability, median (IQR), SDNN	49 (40 to 63)	52 (41 to 68)	-2.5 (-6.8 to 2.8)	0.015

Table 3 legend. Overview of main study results with data presented as median (interquartile range). n = number of participants; IQR = interquartile range; s = seconds; mm = millimeters; bpm = beats per minutes; SDNN = standard deviation of the all NN intervals, representing a median of HRV variability

Table 4. Additional motion analysis

Motion analysis (n=96)		Music	Control	Within subject differences	P
Time to task completion, median (IQR), s	Dominant hand	102 (85.9 to 121)	104 (89.2 to 122)	-2.91 (-17.6 to 10.9)	0.271
	Non-dominant hand	111 (91.2 to 136)	110 (94.0 to 140)	-0.67 (-16.5 to 18.1)	0.953
Path length, median (IQR), mm	Dominant hand	3729 (2109 to 5300)	3685 (2446 to 5042)	-16.31 (-613.5 to 609.3)	0.852
	Non-dominant hand	3537 (2285 to 4594)	3415 (2187 to 4269)	10.94 (-431.9 to 673.5)	0.494
Average speed, median (IQR), mm/s	Dominant hand	224 (148 to 314)	221 (153 to 326)	-3.02 (-38.7 to 37.5)	0.924
	Non-dominant hand	199 (148 to 239)	200 (143 to 243)	2.02 (-19.2 to 18.1)	0.648
Normalized jerk, median (IQR), mm/s^3	Dominant hand	95520 (34549 to 179223)	91289 (38076 to 214895)	-5856 (-69945 to 37479)	0.116
	Non-dominant hand	48433 (27678 to 106052)	49010 (28656 to 94344)	-1642 (-30473 to 20571)	0.614
Motion analysis (n=97)		**Music**	**Control**	**Within subject differences**	**P**
Time to task completion, median (IQR), s	Listens music while studying (n=68)	208 (189 to 254)	222 (187 to 253)	-1.85 (-30.2 to 12.4)	0.248
	No music while studying (n=29)	222 (200 to 271)	211 (188 to 262)	5.18 (-20.1 to 34.8)	0.381
Time to task completion, median (IQR), s	Plays or played instrument (n=52)	205 (184 to 253)	216 (184 to 243)	-1.85 (-22.0 to 10.7)	0.377
	Never played instrument (n=45)	216 (201 to 267)	230 (194 to 270)	5.03 (-28.1 to 29.8)	0.861
Time to task completion, median (IQR), s	Male (n=42)	206 (183 to 262)	211 (180 to 244)	-7.72 (-23.2 to 26.3)	0.722
	Female (n=55)	214 (197 to 264)	231 (200 to 264)	2.34 (-26.5 to 16.2)	0.861

Table 4 legend. Effect of participant-selected music versus recorded operation room noise on laparoscopic task performance by the dominant and non-dominant hand (one participant was ambidextrous), and the influence of listening to music while studying or playing a musical instrument on time to task completion.
n = number of participants; IQR = interquartile range; s = seconds; mm = millimeters

Mental workload, heart rate and HRV

A significant beneficial effect of music was observed on mental workload as the weighted SURG-TLX score was lower (27.0 [17.3 to 38.3] versus 33.7 [21.2 to 43.3], $p<.001$). This was also reflected in all but one of the SURG-TLX dimensions (Table 3, Appendix B). Mental demands (25.0 [15.0 to 37.5] versus 30.0 [20.0 to 50.0], $p<.001$), physical demands (20.0 [12.5 to 32.5] versus 22.5 [12.5 to 31.3], $p=.012$), temporal demands (35.0 [20.0 to 47.5] versus 37.5 [22.5 to 50], $p=.010$), situational stress (17.5 [10.0 to 30.0] versus 25.0 [12.5 to 40.0], $p<.001$) and distractions (15.0 [10.0 to 30.0] versus 32.5 [20.0 to 47.5], $p<.001$) were all significantly lower when exposed to music. Only in the task complexity dimension, no significant difference was observed (25.0 [12.5 to 42.5] versus 25.0 [15.0 to 43.8], $p=.471$).

In four participants (4.1%), heart rate and HRV data was not registered and data was therefore analyzed of 93 participants. None of the included participants had known cardiac diseases or arrhythmias or used any cardiac medication. Median duration of HRV measurement was 4.25 minutes [3.59 to 5.11] over the experiment (93 measurements per period) as a whole. Of the 372 total heart rate and HRV measurements, the measurement duration of 173 (47%) were at least 4.5 minutes or more, 166 (45%) were between 3.5 and 4.5 minutes, and 33 were below 3.5 minutes (8.9%). Heart rate during the last 5 minutes of the preparation phase was statistically significantly increased compared to the first 5 minutes (91 [80 to 106] versus 87 [75 to 101], $p<.001$), while HRV was statistically significantly lower (48 [38 to 63] versus 52 [40 to 71], $p<.001$) (Table 2). During the experiment, heart rate was statistically significantly higher while exposed to music (88 [78 to 102] versus 87 [77 to 102], $p=.046$). HRV was statistically significantly lower while exposed to music (49 [40 to 63] versus 52 [41 to 68], $p=.015$) (Table 3).

No correlation was present between HRV and mental workload assessed using the SURG-TLX (Spearman's rho 0.060, $p=.565$), nor between heart rate and SURG-TLX (Spearman's rho -0.022, $p=.836$).

Discussion

This randomized controlled crossover study with the largest sample size to date assessed the effect of participant-selected recorded music on laparoscopic task performance and mental workload in a simulated setting. No statistically significant beneficial effect of participant-selected music was observed regarding laparoscopic task performance while compared to OR noise in novice laparoscopists. Previous studies, all performed in a simulated setting, reported varying results[5]. Two studies with a similar study design and comparable tasks by the same lead author evaluated the effect of music on laparoscopic task performance. A beneficial effect on task accuracy in expert surgeons was observed[11], but not in junior residents with no previous laparoscopic experience[12]. No beneficial effects were observed in junior novice surgeons asked to perform part of a laparoscopic cholecystectomy[15], nor in 12 surgeons with varying experience placing laparoscopic knots[10]. Although considered a basic skill, laparoscopic knot tying is reportedly the most difficult laparoscopic skill to master[33,34]. In aforementioned studies, preselected music by the research team was used. A positive trend between likability of the music and a beneficial effect was noted[15]. In practice, it seems less likely that surgeons would listen to music that they do not prefer. Surgeons did choose the music played in the OR in a majority of cases[35-37]. Hence, participant-selected preferred music was used which we believe to be more clinically relevant. Recently, we observed a significant beneficial effect on time to task completion (4.68%, $p = 0.037$) and path length (6.35%, $p = 0.019$) of participant-selected music versus silence in 60 medical students in our previous study. Surgical experience level was comparable, as they were also novices of laparoscopy, and a similar study setup was employed, although the modified peg transfer task was only performed 5 times with solely the dominant hand[23]. It could be argued that the different results compared to this study on task performance can partly be attributed due to a more demanding task, with a higher SURG-TLX, and heart rate in this study[23]. Therefore, given the previously mentioned studies, it might be possible that depending on experience and task complexity, music could be beneficial when the surgical task is considered to be relatively easy and manageable, but that this effect disappears when the motor task is more difficult and increasingly demanding on mental workload.

An important component during laparoscopic surgery besides motor task execution and performance is the cognitive decision making to determine which motor steps should be executed. Reducing mental workload, often reported as stress by the surgeon, will leave more mental resource capacity for both components[38]. Indeed, laparoscopic task performance has been correlated to stress experienced by the surgeon[39], with identified key stressors in the form of time pressure, noise and distractions impairing dexterity and increasing error rate[40]. Mental workload assessed using the SURG-TLX questionnaire was significantly reduced by music, which was especially profound in the domains mental demands (within subject difference -5.0, $p = 0.000$) and distractions (within subject difference -10.0, $p = 0.000$), while reflected to a slightly lower but still significant degree in temporal demands (within subject difference -2.5, $p = 0.010$). Whilst secondary outcome measure results should always be interpreted with caution, these findings mimic our previous study which also observed a beneficial effect by music on mental workload during laparoscopic task performance[23].. Previous surveys also observed favorable responses in general towards the use of music by surgeons, especially in regard to stress[41,36,42]. Although reporting bias cannot be entirely ruled out, the SURG-TLX follows the trend of objective parameters like salivary cortisol levels[43]. HRV seems to be an adequate method to assess mental surgical stress as well[44]. Whilst heart rate was statistically significantly higher (within subject difference 1.0 bpm, $p = 0.046$) and HRV lower (within subject difference -2.5, $p = 0.015$) in the music group, the absolute difference observed cannot be considered clinically relevant. It was expected that each period in this experiment would allow for short-term HRV analysis (nominal 5 min duration), but 54% of HRV measurements lasted 4.5 minutes or less. Given that the validity of ultra short-term HRV analysis has been questioned[31], as well

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as the lack of correlation with mental workload in this study, interpretation of these results as a reflection of mental strain in our study should be done with caution.

Major strong points of this study was the largest sample size to date and the rigorous study design, which reduces a potential carry-over effect[45]. Whilst computerized randomization would preferably be used, we considered non-random allocation risk to be minimal. All participants acted as their own control. The research assistant overseeing the experiment execution had no incentive to influence allocation as they had no information on the participant during the experiment, given that all questionnaires were filled out using secure computerized questionnaire. These data were only revealed and analyzed after all inclusions had been completed. The envelope deciding allocation sequence was chosen before the preparation phase, preventing any potential influence of this phase on the allocation sequence. A maximum envelope number per sequence based on the sample size calculation assured equal allocation. A previously validated, custom-made laparoscopic box trainer was used[23], with real surgical instruments and pegs allowing for realistic tactile sense and haptic feedback that is not provided by all virtual reality simulators. To get acquainted with the box trainer and eliminate the learning curve as the foremost potential biasing factor, a preparation phase was incorporated. The number of peg transfer tasks necessary for this was based on a previously conducted study with the same box trainer[23]. Its success is evident through the fact that time to task completion rapidly decreased in the preparation phase, while staying almost consistent during the experiment (for either treatment factor). Since previous studies did not employ a preparation phase, it is difficult to ascertain whether the previously reported effects partly reflect the learning curve. Moreover, participant-selected instead of researcher-selected recorded music was used and the volume adjusted by the participants themselves to more accurately represent the real-world setting, whilst recorded OR noise acted as a control instead of silence in order to account for auditory stimulation as a factor. Nonetheless, several limitations can still be observed. The peg transfer task was chosen, which does not require surgical knowledge that could potentially influence task performance. However, this task with an average observed duration of approximately 3.5 minutes per period takes significantly shorter than any surgical procedure. Still, earlier studies reported that even relatively simple, short lasting tasks and drills like these can improve relevant laparoscopic surgical tasks and should therefore not be disregarded[46,47]. We chose to perform the study in medical students who were inexperienced with laparoscopy in order to reduce potential previous experience influencing laparoscopic task performance. Studies evaluating noise in the OR found higher subjective distraction levels in assisting surgeons with less experience compared to the main, more experienced surgeons[48], whilst the negative impact on clinical reasoning was lower when anesthesiological residents were more experienced[49]. It has been theorized that more experienced surgeons can block out noise and music more effectively[10], theoretically decreasing potential effect size and increasing the required number of participants. It would have been impractical therefore to try to investigate the effects of music using more experienced residents or surgeons in such large numbers without the present data and our recently published study[23]. Finally, a major factor affecting teamwork in the OR is communication, with a considerable percentage of surgical errors involving communication between surgical personnel[50]. This factor could not be evaluated. These limitations make extrapolation of the observed results to the real-world setting less appropriate, limiting conclusions to a simulated setting.

Although varying results regarding the effects of music on laparoscopic task performance have been reported, it seems that surgical experience and task demand can be more determinative. Future studies should take these factors into account and evaluate surgeons with different experience levels in a more lifelike setting. Whilst several studies evaluated the effect of music on laparoscopic task performance through short-lasting laparoscopic and surgical tasks to date[5], important elements like simulated surgical procedures, communication, and performance of the entire OR team have only sparingly been investigated[51,52]. Auditory intervention should preferably consist of music combined with OR noise versus OR noise through speakers, with music chosen by both the surgeon and OR team. Music did significantly reduce mental workload and several previously identified key stressors of surgery, and its use in the operating theatre is reportedly viewed favorably. Higher perceived stress is associated with a decreased HRV even throughout the night, indicative of a protracted recovery time[44]. As music can attenuate the stress response to surgery in patients undergoing surgery, future research should incorporate its effect on mental workload through HRV with attention to recovery from surgical task performance as well.

Conclusion

In this four-sequence, four-period, two-treatment, randomized controlled crossover study of 97 laparoscopy novices, recorded preferred music significantly reduced mental workload overall and in key surgical stressor domains during laparoscopic task performance in a simulated setting when compared to OR noise, but no beneficial effect on task performance itself was observed.

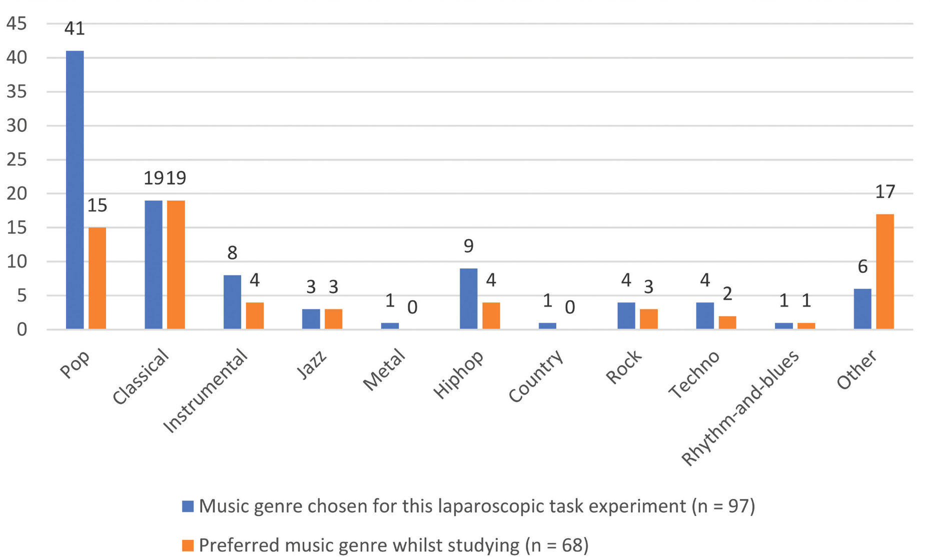
Author Disclosure Statement

No external funding was received for this study. Equipment and software to analyze heart rate variability was kindly provided by BioCheck, which had no role in study design, data analysis, data interpretation or manuscript drafting. The authors declare no conflicts of interest.

Acknowledgements

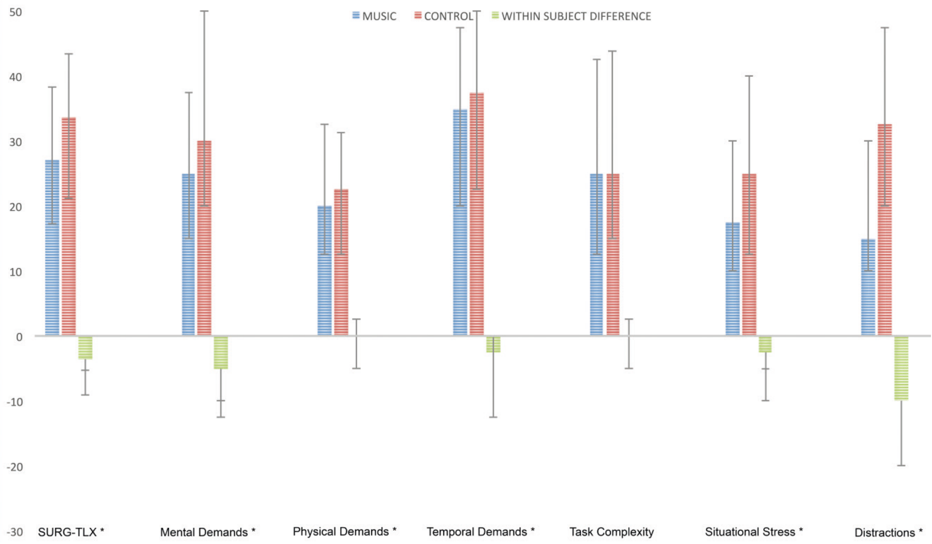
The authors would like to thank Biocheck for providing the equipment and software to assess heart rate and HRV.

Appendix A. Music Genres



Appendix A legend. Figure summarizing the music genre chosen for the experiment by the 97 participants (left bar), as well as the preferred genre while studying by 68 participants who like to listen to music while studying (right bar). Data presented are absolute numbers.

Appendix B. Mental Workload



Appendix B legend. Effect of participant-selected music and operation room noise on mental workload (Surgery Task Load Index (Surg-TLX)) during laparoscopic task performance. Data is presented as median and interquartile range. Of the three paired bars of the total weighted SURG-TLX and its workload dimensions, the left bar reflects absolute score during participant-selected music exposure, the middle bar during operation room noise exposure, and the right bar the within subject difference. All were statistically significant in favor of music ($p<0.05$, marked with *), except the dimension task complexity.

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Chapter 11

The Perception and Attitude towards Noise and Music in the Operation Room: A Systematic Review

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Journal of Surgical Research 263: 193 – 206, 2021

"Unnecessary noise is the most cruel absence of care which can be inflicted either on sick or on well."

Florence Nightingale, 1859, founder of modern nursing.

Abstract

Background: Environmental noise pollution is regarded as a general stressor. Noise levels frequently exceed recommended noise levels by the World Health Organization in hospitals, especially in the operation room. The aim of this systematic review was to assess the effects of noise pollution on patient outcome and performance by operation room staff. In addition, the perception of and attitude towards playing music in the operation room, which can increase noise levels, was assessed as well.

Materials and Methods: A systematic literature search of the databases Embase, Medline Ovid and Cochrane from date of database inception until October 16th, 2020 using the exhaustive literature search method was performed. Prospective studies evaluating the effect of noise on the patient, surgeons, anesthesiologists, nurses, and other operation room staff, or perception and attitude towards playing music in the operation room, were included. This systematic review adhered to the PRISMA guidelines and was registered with PROSPERO (ID: 208282).

Results: The literature search generated 4758 articles and 22 prospective studies (3507 participants) were included. Three of the four studies that investigated the effect of noise on patient outcome reported a significant reduction of complication rate in surgical patients, when noise levels were lower. Six studies assessed the effect of noise in the operation room on the staff (1383 participants). Over half of the surveyed staff found noise levels to be a disturbing stressor and negatively impact performance. Although music increased decibel levels in the operation room, the majority of surveyed staff was positively predisposed towards playing music during surgery, believing it to improve both individual and team performance. In general, music was not considered to be distracting or impairing communication.

Conclusion: Higher noise levels seem to have a negative effect on patient outcome and adversely affect performance by members in the operation room. Further research is needed to assess whether this knowledge can benefit patient outcome and surgical performance. Notably, attitude of surgical team members towards music during surgery is generally regarded favorable.

Author contributions

VF and PO made substantial contributions to conception and study design. VF, PO and NM made substantial contributions to the acquisition and analysis of data. VF, PO, NM, and JJ interpreted the data. VF and PO primarily drafted the manuscript, with substantial contributions by NM. JJ critically revised it for important intellectual content. All authors gave final approval of this version to be published.

Abbreviation list

dB	Decibels
dBA	Decibels adjusted
OR	Operation room
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis

Introduction

Noise is defined as an unpleasant and unwanted sound. Environmental noise pollution is regarded as a general stressor, increasing mental stress, the development of cerebral cardiovascular disease, and the risk of hearing loss[1,2]. During the past decades, noise pollution has increased exponentially in hospitals[3,4]. High noise levels are nowadays prevalent in the operation room (OR) and frequently exceed both the recommended threshold of 30 dBA set by the World Health Organization[5], as well as the American Occupational Safety and Health Administration standard[6]. Peak levels have been noted to vary between 80 and 119 dBA[5,4,7]. During neurosurgery and orthopedic surgery, noise levels exceed 95 dBA for the majority of surgery duration[7], which equals standing next to a lawn mower. Noise pollution was observed to be mainly caused by staff-related behavior and surgical equipment, increasing as the day progressed[5,8-10]. Playing music in the OR deserves a specific mention. It increases decibel levels and some have questioned its safety in regard to communication and distraction[11].

Previous studies mainly focused on solely measuring decibel levels in the OR and several recent reviews explored this topic[4]. Therefore, the aim of this systematic review was to assess the effect of noise pollution on patient outcome, as well as staff perception and performance in the OR. Besides potential negative health effects on members of the surgical team, high noise levels can also increase stress, impair communication, reduce concentration and affect performance[2]. Whilst beneficial effects of music regarding patient outcome, patient satisfaction, and surgical performance have extensively been investigated[12-15], the subjective perception by OR staff regarding music in the OR has not. Therefore, the attitude of OR staff, including surgeons, anesthesiologists and nurses will be evaluated as well, taking aforementioned domains into account.

Methods

This systematic review was prospectively recorded with the PROSPERO database (ID: 208282). The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were followed[16].

Literature search and study selection

A systematic literature search was performed with assistance of a biomedical information specialist. The exhaustive literature search method was used in order to search the databases Embase, Medline Ovid and Cochrane from date of database inception until October 16th, 2020[17]. Full search syntax is available in Appendix A. Three reviewers (VF, PO, and NM) independently assessed which of the retrieved articles were eligible for inclusion according to prospectively recorded inclusion criteria. Published, prospective studies in the English language evaluating the effect of noise in the OR on patient outcome, defined as postoperative complication rate and length of stay, as well as performance by members of the OR team were eligible for inclusion. Furthermore, the perception of and attitude towards noise in the OR by members of the OR regarding the domains performance, team performance and team work, stress, communication and distraction were assessed as well. Finally, given that music increases decibel levels and can be considered to be a type of noise, studies evaluating the perception of and attitude by members of the OR team towards music in the OR were included as well. Studies solely evaluating decibel levels in the OR were not included. Manual cross-referencing of included studies was performed additionally.

Risk of bias assessment, data extraction and data analysis

Risk of bias was independently assessed by the three reviewers (V.F., P.O. and N.M.). Different risk of bias assessment methods were used depending on the study type. For prospective randomized controlled and crossover trials, the Cochrane Collaboration's tool for assessing risk of bias in randomized trials was used[18]. Risk of bias in observational studies without interventions was assessed using the Newcastle-Ottawa Scale[19]. For risk of bias assessment of surveys, the Risk of Bias Instrument for Cross-Sectional Surveys of Attitudes and Practices by the CLARITY Group was used[20].

Study data extraction was independently performed using a custom made data extraction sheet and mutually discussed among the three reviewers (V.F., P.O. and N.M.). Data regarding the outcome measures of interest as stated previously which were presented as means and standard deviations, medians and interquartile ranges, and percentages in the included studies was extracted. In case study data were only presented through plots or images, the online available data extraction software WebPlotDigitizer (Version 4.1) was used to plot the figures and estimate the data, with at least two reviewers independently performing this task[21]. Attitude towards, and perception of music in the OR concerning the domains performance, team performance and team work, stress, communication and distraction were presented using a 5 point Likert scale, which was the most frequently employed survey method. The low end (1 and 2) of the scale represented a negative or disagreeing answer, the middle scale (3) a neutral answer, and the high end (4 and 5) a positive or agreeing answer in regard to the survey question. In some cases, an additional 'don't know' option was presented. Due to the different ways questions were asked, as well as the difference in proportion of surveyed surgical, anesthesiological and nursing staff in each study (i.e. one study assessed the opinion of anesthesiologists only, whilst another received twice as many responses from nurses compared to surgeons), we did not calculate an overall mean or perform additional statistical analysis. No meta-analysis could be performed due to the limited number of studies, clinical heterogeneity, and varying methods of data presentation.

Results

The literature search generated 4758 articles, with 3631 remaining after deduplication. Ninety-three articles were assessed full text by the three reviewers, with 71 being excluded according to the predefined exclusion criteria after full text assessment as they were not written in the English language (n = 3), not conducted in the surgical setting (n = 2), not prospective studies (n = 10), did not contain relevant outcome measures (n = 23), only measured decibel levels (n = 29) or other reasons (n = 4). As a result, 22 prospective studies (3508 participants) were included in this review, with four assessing the effect of noise in the operation room on the patient, six the effect of, perception of, and attitude towards noise by members of the operation room team, and 13 the perception of and attitude of the operation room team towards music in the operation room (Figure 1) (Table 1). One study assessed the effect of noise both on the patient and the surgical team[8]. There were no disagreements concerning study inclusion or data extraction among the three reviewers.

The effect of noise in the OR on the patient

The effect of noise on patient outcome was assessed in four studies (350 patients)[22,8,23,24]. Three studies reported a significant reduction in postoperative complication rate, when noise levels were lower. Two prospective observational studies observed significantly higher noise levels during surgery in patients who developed surgical-site infection after elective hernia repairs and open abdominal surgery[22,23]. Surgical-site infection occurred in five out of 64 (7.8%) hernia patients, with a mean increase in noise of 11.3 dB when comparing the infection and no infection group[22]. After open abdominal surgery, surgical-site infection occurred in six out of 35 (17%) patients, whilst median sound levels were 43.5 dB (26.0-60.0) on average in these six patients versus 25.0 (25.0 – 60.0) in the patients that did not have a surgical-site infection[23]. In the third study[8], a noise reduction program was implemented in the pediatric surgery department, which consisted of sound-reduction devices and behavioral rules limiting

Figure 1. PRISMA Flow chart

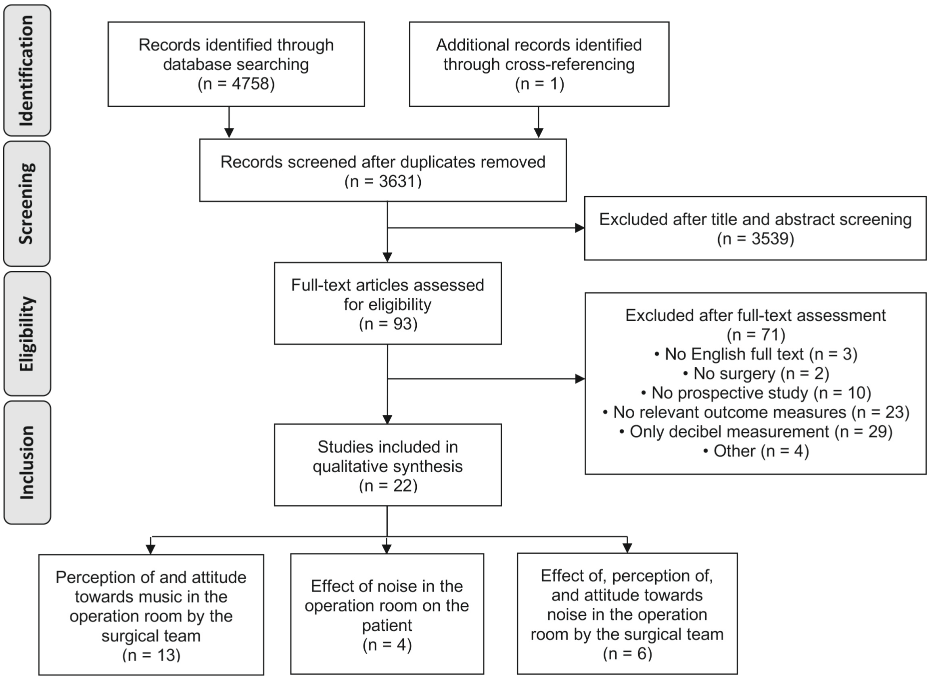

Figure 1 legend.
n = number of studies

One study (Engelmann *et al.*, 2014) assessed the effect of noise both on the patient and surgical team conversation, opening of the operation room door, and monitor alarms. This noise reduction program significantly reduced both decibel levels during 114 pediatric surgical procedures by approximately 50% (3dBA, equivalent to a twofold increase in perceived sound level), as well as peak noise levels by over 50%. Postoperative complication rate was also significantly lower in the noise-reduction group (17.9% versus 34.5%, $p < 0.05$). The fourth study included that investigated the effect of noise reduction on patient outcome employed the use of a wireless audio system during 69 robot-assisted surgical procedures, which reduced peak noise level events above 70 dB, but not average noise levels during surgery. No statistically significant differences were observed regarding postoperative complication rate or length of hospital stay when comparing these to 68 control cases[24].

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Table 1. Study Characteristics

Study	Study type	Surgical procedure	Setting	N	Study population	Outcome assessed
Cheriyan 2016	Repeated measure design	Simulated setting, 5 trials with 20 words	Simulated setting with ambient, ambient and equipment, ambient and equipment and music sound setting	4 (1 OR team)	Operation room team members	Auditory processing under 3 different noise conditions (percentage correct response rate)
Dholakia 2015	Observational study	Elective hernia repair	Operation room	64	Adult patients	Relation between noise levels and 30-day surgical-site infection rate
Engelmann 2014	Non-randomized, two-armed clinical trial	Pediatric surgery	Non-operation related noise reduction program in operation room	114	Pediatric patients	Postoperative complication rate
				16	Pediatric surgeons	Stress response (salivary cortisol, electrodermal activity) Distraction and communication
Enser 2010	Randomized crossover trial	Simulated setting	Noisy versus quiet environment	42	Anesthesiology residents	Performance (clinical reasoning through script concordance test)
Faraj 2014	Cross-sectional survey study	*Not applicable*	Single center, general hospital survey (United Kingdom)	52 (102)	Surgeons, nurses, anesthesiologists, other OR assisting staff	Perception and attitude on music in the OR (prevalence, effect on enjoyment, efficiency, (team) performance and distraction)
George 2011	Cross-sectional survey study	*Not applicable*	Single-center hospital survey (India)	100	Surgeons, nurses, anesthesiologists	Perception and attitude on music in the OR (prevalence, enjoyment, stress, performance, communication)
Hawksworth 1997	Cross-sectional survey study	*Not applicable*	Nationwide survey (United Kingdom)	144 (200)	Anesthesiologists	Perception and attitude on music in the OR (prevalence, enjoyment, performance, communication, distraction)
Keller 2018	Prospective Observational study	Elective open abdominal surgery	Operation room	110	Surgeons, nurses, anesthesiologists	Self-reported distraction levels of noise in the OR

Table 1. Continued.

Study	Study type	Surgical procedure	Setting	N	Study population	Outcome assessed
Kumar 2013	Cross-sectional survey study	*Not applicable*	International survey	68 (110)	Neuroanesthesiologists	Appropriateness of playing music in the OR
Kurmann 2011	Prospective Observational study	Elective open abdominal surgery	Operation room	35	Not specified	Relation between noise levels and 30-day surgical-site infection rate
Lee 2013	Cross-sectional survey study	*Not applicable*	International survey	523 (2057)	Urologists	Prevalence of music in the OR
Makama 2010	Cross-sectional survey study	*Not applicable*	Survey (Nigeria)	162 (167)	Surgeons, nurses, anesthesiologists, other OR assisting staff	Perception and attitude on music in the OR (enjoyment, performance, stress, distraction)
Moorthy 2004	Randomized crossover trial	Laparoscopic suturing (Pelvi laparoscopic box trainer)	Simulated setting with quiet, noise at 80-85 decibels, and music sound setting	12	Surgeons	Laparoscopic task performance (task completion time, movements, path length, global score, accuracy, knot quality)
Narayanan and Gray 2018	Cross-sectional survey study	*Not applicable*	Single-center, tertiary teaching hospital survey (New Zealand)	106 (234)	Surgeons, nurses, anesthesiologists, other OR assisting staff	Perception and attitude on music in the OR (prevalence, enjoyment, (team) performance, communication, distraction)
Oliver 1999	Cross-sectional survey study	*Not applicable*	Single-center, tertiary teaching hospital survey (United Kingdom)	35 (45)	Surgeons, nurses, anesthesiologists	Perception and attitude on music in the OR (prevalence, enjoyment, performance, concentration, distraction)
Padmakumar 2017	Cross-sectional survey study	*Not applicable*	Nationwide survey (United Kingdom)	519	Surgeons, nurses, anesthesiologists, other OR assisting staff, medical students	Music adverse influence perception and attitude on noise in the OR ((team) performance, stress, communication, concentration)

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Table 1. Continued.

Study	Study type	Surgical procedure	Setting	N	Study population	Outcome assessed
Tsafrir 2020	Non-randomized, two-armed clinical trial	Gynaecological and urological robotic surgical procedures	Wireless audio headset	137	148 team members	Postoperative complication rate Self-report communication, performance, teamwork and mental workload quality
Tsiou 2008	Cross-sectional survey study	*Not applicable*	National multicenter survey (Greece)	684	Surgeons, nurses, anesthesiologists	Perception and attitude on noise in the OR (prevalence, performance)
Ullman 2008	Cross-sectional survey study	*Not applicable*	National multicenter survey (Israel)	171	Surgeons, nurses, anesthesiologists	Perception and attitude on music in the OR (prevalence, concentration, communication, distraction)
Way 2013	Randomized crossover trial	Peg transfer task (Ethicon Skill Kit)	Simulated setting with quiet, filtered, OR noise, OR noise and music condition	15	Surgeons with varying degree of experience	Auditory processing under 4 different noise conditions (Speech In Noise Test – Revised)
Weldon 2015	Prospective, non-randomized observational study	13 laparoscopic and 7 open surgical procedures	Two operating theaters	5 (5 OR teams)	Surgeons, scrub nurses	Repeated request number (univariate analysis) after dividing surgical procedures to with and without intraoperative music
Yamasaki 2016	Cross-sectional survey study	*Not applicable*	Single-center survey (United States)	390 (409)	Surgeons, nurses, anesthesiologists	Perception and attitude on music in the OR (prevalence, enjoyment, concentration, communication, distraction)

Table 1 legend. Study characteristics of included studies
N = Number of participants. For cross-sectional studies, the number to which the survey was distributed is presented in (brackets), if reported.;
OR = Operation room
Cheriyan 2016: 5 trials with 20 words were spoken by the surgeon and recorded by the first assistant, anesthesiologist and circulating nurse during three different sound level settings.
Weldon 2015: 20 surgical procedure video recordings were assessed.

The effect of noise in the OR on members of the OR team

Six studies assessed the effect on, perception towards, and attitude regarding noise in the OR of the health care staff (1383 participants)[8,25,10,26-28].

Two studies evaluated the stress-inducing effects of noise in the OR. Noise levels in the OR were regarded as a disturbing stressor by over half of the surgeons, anesthetists and OR nurses surveyed[28]. The aforementioned noise reduction program employed during pediatric surgery reduced both intraoperative salivary cortisol rise by 20%, as well as electrodermal potential peaks indicative of severe stress by 60% of the performing surgeons. However, these results were not statistically significant ($p > 0.05$)[8].

Four studies evaluated the effect of noise on performance. Noise levels in the OR negatively impacted performance and concentration according to more than half of the surveyed staff [27,28]. Laparoscopic task performance was not affected by a more noisy environment when 12 surgeons with different experience levels were evaluated during simulated laparoscopic suturing environment[26]. A noisier environment did significantly impact clinical reasoning by anesthesiological residents when compared to a quieter environment. Performance on the script concordance test was significantly reduced (59.0 (56.0 – 62.0) versus 62.8 (60.8 – 64.9), $p = 0.04$), although the difference in performance lessened with experience of the resident[25].

Two studies evaluated the effect of noise in the OR on communication and distraction. Communication was the factor believed to be most adversely affected by noise in the OR[27]. Self-reported distraction by noise seems to be more present in surgeons (39 and 43% of main and assisting surgeons) when compared to anesthesiologists (16%)[10].

Perception of and attitude towards playing music in the OR

Ten studies evaluated the perception by and attitude of the OR staff on playing music in the OR through cross-sectional surveys (1751 participants) (Table 2) [29-38], with an additional three studies assessing its effect on auditory perception and communication (24 participants)[39,40,11]. The prevalence of music in the OR was assessed in seven studies (1486 participants), with music being played during a majority of surgical procedures in hospitals around the world[29-31,35,37,38,33]. In general, the majority enjoyed music in the OR with positive approval rates varying between 60 and 90 percent (eight studies, 1057 participants)[29-31,34-36,38,32]. In six studies (949 participants) [29,34,30,31,35,38], individual performance or concentration was subjectively either improved or unaffected by music according to the majority of surgeons, anesthetists and OR nurses surveyed. Music was also deemed to be beneficial for team performance and team work (158 participants)[29,35]. Furthermore, music was perceived to reduce stress (398 participants)[30,34-36].

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Table 2. Attitude towards and perception of Music in the Operation Room

	Study	n	SUR	ANA	NUR	Survey question	Assessment method	Result (%) Disagree		⟷		Agree
Individual performance	Faraj 2014	52	27	6	8	"I feel I perform better when music is played in the operating theatre"	Likert scale 1-5 (with 6th option don't know)	7	12	32	17	30
								Don't know: 2				
	Makama 2010	162	94	18	22	Does familiar music enhance performance?	List of options	*NR*		*NR*	86.4	
	Narayanan and Gray 2018	101	37	29	35	How does music affect the surgeon's performance?	Likert scale 1-5 (Negative-positive)	0	6	59	34	2
Concentration	George 2011	100	44	25	31	"Do you think music improves concentration?"	Likert scale 1-5	11	16	10	50	13
		100	44	25	31	"Do you think music reduces your vigilance?"	Likert scale 1-5	35	20	19	22	4
	Hawksworth 1997	144	0	144	0	"Do you feel music affects your vigilance during an anaesthetic?" (negatively)	Likert scale 1-3	9.6		64.4	26	
	Narayanan and Gray 2018	101	37	29	35	Effect of music on own focus?	Likert scale 1-5 (Negative-positive)	4	13	58	25	1
						Effect of music on own vigilance?	Likert scale 1-5 (Negative-positive)	1	10	79	11	0
	Yamasaki 2016	390	99	97	194	"How does music impact your concentration?"	NRS 0 – 100 (Negative-positive)	Mean 59.9 (Standard deviation 24.6)				

Table 2. Continued

	Study	n	SUR	ANA	NUR	Survey question	Assessment method	Result (%)				
								Disagree		⟷		Agree
Team performance	Faraj 2014	52	27	6	8	"I feel the overall performance of the theatre team is better when music is played"	Likert scale 1-5 (with 6th option: don't know)	*NR*		*NR*	63	
								Don't know: *NR*				
	Narayanan and Gray 2018	101	37	29	35	Effect of music on overall team performance	Likert scale 1-5 (Negative-positive)	2	4	44	44	7
						Effect of music on mood in OR?	Likert scale 1-5 (Negative-positive)	0	3	12	64	22
Stress	George 2011	100	44	25	31	"Do you think it (music) reduces your autonomic reactivity in stressful surgeries?"	Likert scale 1-5	14	13	14	50	9
	Makama 2010	162	94	18	22	Does music reduce stress?	List of options (multiple options allowed)	*NR*		*NR*	91.4	
	Narayanan and Gray 2018	101	37	29	35	Effect of music on own calmness?	Likert scale 1-5 (Negative-positive)	1	8	43	46	3
	Oliver 1999	35	10	10	15	"Generally do you find it (music) relaxing?"	No, sometimes, yes (with 4th option: don't know)	11		3	74	
								Don't know: 11				

Table 2. Continued

	Study	n	SUR	ANA	NUR	Survey question	Assessment method	Result (%)			
								Disagree		⟷	Agree
Distraction	Faraj 2014	52	27	6	8	"I find music played in the operating theatre distracting"	Likert scale 1-5 (with 6th option: don't know)	*NR*	*NR*	*NR*	27
								Don't know: *NR*			
	Hawksworth 1997	144	0	144	0	"Does music distract you from alarms on the theatre monitors?"	Likert scale 1-3	63.5		24	11.5
						"If things aren't going well with the anaesthetic, do you find music distracting when it might not have been before?"	Likert scale 1-3	16.3		28.8	51
	Makama 2010	162	94	18	22	Does music prevent distraction?	Multiple options	*NR*		*NR*	79.6
	Narayanan and Gray 2018	101	37	29	35	Does music distract during a crisis?	*NR*	*NR*		*NR*	84
	Ullmann	171	*NR*	*NR*	*NR*	Do you view music as a distracting factor when played during a long, complicated or emergency procedure?	*NR*	*NR*		*NR*	20
	Yamasaki 2016	390	99	97	194	"Do you find music distracting?"	NRS 0 – 100 (Not at all - very much so)	Mean 32.2 (Standard deviation 22.2)			

Table 2. Continued

	Study	n	SUR	ANA	NUR	Survey question	Assessment method	Result (%)				
								Disagree		⟵⟶		Agree
Communication	George 2011	100	44	25	31	"Do you think music restricts your communication with other staff?"	Likert scale 1-5	42	24	6	23	5
	Hawksworth 1997	144	0	144	0	"Does music affect your communication with staff in theatre?" (negatively)	Likert scale 1-3	15.4		59.6	24	
	Narayanan and Gray 2018	101	37	29	35	Effect of music on own communication? (negatively)	Likert scale 1-5 (Negative-positive)	3	27	64	7	0
	Ullmann 2008	171	*NR*	*NR*	*NR*	"Do you think that music in the OR affects communication between staff?" (negatively)	Likert scale 1-3	63		28.6	8.4	
	Yamasaki 2016	390	99	97	194	"How does music impact communication between team members in the OR?"	NRS 0 – 100 (Negative-positive)	Mean 55 (Standard deviation 22.5)				

Table 2 legend. Survey results regarding the attitude towards and perception of music during surgery by staff in the operation room. Questions presented with quotation marks represent the exact phrasing used in the survey, whilst words in parenthesis have been added to clarify the question.
n = number of total survey participants; SUR = number of surgeons; ANA = number of anesthesiologists; NUR = number of OR team nurses or other members; NR = not reported; NRS = numeric rating scale; OR = operation room

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Table 3. Risk of bias in crossover studies

Study	Random Sequence Generation	Allocation concealment	Blinding of Participants and Staff	Blinding of outcome assessors	Incomplete outcome addressed	Selective reporting addressed	Appropriate crossover design	Carry-over effect addressed	Unbiased data addressed	Other bias addressed
Cheriyan 2016	No	No	No	No	Unclear	Unclear	Yes	Unclear	Yes	No
Engelmann 2014	No	No	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Enser 2010	Yes	Yes	No	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes
Moorthy 2004	Unclear	Unclear	No	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes
Tsafrir 2020	No	No	No	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes
Way 2013	Unclear	Unclear	No	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No

Table 3 legend.
No = high risk; Unclear = unclear risk; Yes = low risk; Engelmann 2014: the evaluation of staff can be classified as a non-randomized crossover design

Whether music was considered distracting differed. Music was not deemed to be distracting in general[34,38], but opinions differed in regard to critical situations when a problem was encountered[29,36,37,31,35]. Communication was regarded to be either unaffected or positively influenced by music by approximately 60% of respondents (911 participants)[30,31,35,37,38]. In contrast, two studies that respectively evaluated 15 surgeons and four physicians acting as an OR team reported a significant reduction in the correct rate of auditory speech perception in a simulated setting, when music was added[39,40]. An observational study using operation room video recordings observing five surgeons performing 20 surgical procedures reported a significantly increase in repeated request rate when music was played[11].

Risk of Bias Assessment

Six studies employed a crossover design[39,8,25,26,24,40] (Table 3). Whilst three employed a randomization, only one specified the randomization method (17%)[25], leaving risk of selection bias either unclear or high. Due to the intervention, blinding of participants was not possible. In three studies, outcome assessors were blinded (50%)[8,25,26]. All studies employed an appropriate crossover design, although carry-over effect addressment was not specified. In two studies, other bias risk category was deemed high as both studies failed to take the Lombard effect into account, the physiological phenomenon that speakers increase their voice level and adapt their speech manner when in the presence of increasing background noise levels[41].

In four observational studies[22,10,23,11], insufficient information was provided to adequately assess bias risk in regards to selection and comparability according to the Newcastle-Ottawa Scale and potential confounders were not addressed. Assessment, follow-up and adequacy of outcome was deemed to be appropriately assessed in all four studies.

Twelve studies employed a cross-sectional survey study design (Table 4)[29-36,27,28,37,38]. Bias risk in regard to sample representativeness was either low or probably low risk in ten studies (83%), as a random selection of OR staff was assessed in either a single hospital, multicenter, nationwide or international. It was deemed unclear in one (8.3%)[34], and probably high risk in one study (8.3%)[36]. Adequacy of response varied, with six studies (50%) reporting a response rate of at least 60%. Three studies (25% had a potential high risk of bias as less than half of potential participants filled out the survey[29,33,35]. In three studies (25%), response rate was not reported. In ten studies, risk of bias due to missing data in the completed questionnaires was considered low, whilst two studies (17%) did not specify the amount of missing data[29,28]. Although the universally known Likert scale was used in most questionnaires, only two studies (17%) employed a previously validated questionnaire[29,32]. One survey study reported conflicting results when comparing the numbers presented in the results paragraph with the figures, concerning the response rate and percentage of distraction[29]. In three studies[31-33], only a specific group of specialists were surveyed regarding the topic of playing music in the OR.

Table 4. Risk of bias of cross-sectional survey studies

Study	Representativeness of sample	Adequacy of response rate	Missing data in completed questionnaires	Clinical sensibility of survey	Validity of survey instrument	Other bias
Faraj 2014	Probably low risk (random selection of all OR staff, single center)	High risk (52 / 121, 43%, but reported rate 58%)	Unclear (not reported)	Probably low risk (ordered response categories)	Probably low risk (ordered response categories)	Contradicting results and figure on distraction
George 2011	Probably low risk (random selection of all OR staff, single center)	Unclear risk (not reported)	Low risk (100% response rate according to Table 1)	Unclear risk (not reported)	Unclear risk (not reported)	Not applicable
Hawksworth 1997	Low risk (random selection nationwide)	Probably low risk (72% response rate)	Probably low risk (not all questions answered)	Probably low risk (tested by colleagues)	Unclear risk (not reported)	Only anesthetists surveyed
Kumar 2013	Low risk (random selection of international anesthetists at conference)	Probably low risk (62% response rate)	Low risk (above 98% completed)	Probably low risk (previously used questionnaire)	Probably low risk (previously used questionnaire)	Only neuro-anesthetists surveyed
Lee 2013	Low risk (random selection of international urologists)	High risk (25% response rate)	Low risk (100% completed the online survey)	Unclear risk (not reported)	Unclear risk (not reported)	Only urologists surveyed
Makama 2010	Unclear risk (not reported)	Low risk (97%, completed)	Low risk (above 97% completed)	Unclear risk (not reported)	Unclear risk (not reported)	Not applicable
Narayanan and Gray 2018	Probably low risk (random selection of all OR staff, single center)	High risk (45% response rate)	Low risk (above 95% completed)	Unclear risk (not reported)	Unclear risk (not reported)	Not applicable

Table 4. Continued.

Study	Representativeness of sample	Adequacy of response rate	Missing data in completed questionnaires	Clinical sensibility of survey	Validity of survey instrument	Other bias
Oliver 1999	Probably high risk (random sample, but limited number surveyed)	Low risk (35 / 45, 78% response rate)	Probably low risk (1 / 8 questions not completely filled out)	Unclear risk (not reported)	Unclear risk (not reported)	Not applicable
Padmakumar 2017	Low risk (random selection of OR staff nationwide)	Unclear risk (not reported)	Low risk (100% completed according to tables)	Probably low risk (tested by sample OR staff)	Unclear risk (not reported)	Not applicable
Tsiou 2008	Low risk (random selection of OR staff nationwide)	Unclear risk (not reported)	Unclear risk (not reported)	Unclear risk (not reported)	Unclear risk (not reported)	Not applicable
Ullman 2008	Low risk (random selection of OR staff in three hospitals)	Probably low risk (171 / 250, 62% response rate)	Low risk (above 90% completed)	Unclear risk (not reported)	Unclear risk (not reported)	Not applicable
Yamasaki 2016	Low risk (random selection of OR staff nationwide)	Low risk (directed survey)	Low risk (above 99% completed)	Unclear risk (not reported)	Unclear risk (not reported)	Not applicable

Table 4 legend. Risk of bias of cross-sectional survey studies, assessed using Risk of bias instrument for cross-sectional surveys of attitudes and practices by the CLARITY Group. OR = operation room.

Discussion

Noise has been universally reported to act as a stressor, increasing autonomic nervous system activity and stress hormone levels[2,42-44]. Even relatively short-lasting, acute noise exposure has been associated with increased cardiovascular stress[45]. Attention to the attenuation of the stress response using Enhanced Recovery After Surgery and similar fast track protocols have significantly improved postoperative patient outcome[46]. A more vigorous response has been associated with a higher postoperative complication rate[14,47], with the stress hormone cortisol playing a role in wound healing and infection occurrence[48,49]. Only a very limited number of studies to date evaluated the effect of OR noise on surgical patients, as presented in this systematic review. Most previously conducted studies solely measured the presence of high decibel levels. However, it appears that higher noise levels during surgery are associated with an increased rate of surgical-site infections[22,23]. Although this does not infer causality, a noise reduction program can apparently significantly reduce the postoperative complication rate[8]. Recent studies revealed the auditory cortex of patients to be active and receptive during general anesthesia[50,51], whilst even low noise levels in sleeping individuals affect the cardiovascular system[2]. This could theoretically explain the negative effects of high noise levels in surgical patient during general anesthesia and should be further explored in future studies.

Noise pollution in the OR is perceived negatively by the staff as well. Current noise levels are subjectively perceived to be a disturbance in the operation room by over half of surveyed surgeons, anesthetists and nurses, with the majority considering it to have a negative influence on the job[28]. Furthermore, noise can increase stress both subjectively and objectively in an already stressful environment[8], plagued with high burnout levels[52]. Noise induced hearing loss seems to be prevalent in 50% of OR personnel involved in orthopedic surgery[53,54]. An extensive meta-analytic synthesis of 242 studies evaluating the effects of noise in healthy adults on task performance observed significant negative effects on cognitive task performance (effects size -0.34 [95%CI -0.42 to -0.25], 191 studies), psychomotor performance (-0.43 [95%CI -0.74 to -0.21], 11 studies), and communication tasks (-0.53 [95%CI -0.83 to -0.23], 17 studies)[55]. These effects on task performance were not only related to noise level intensity. The presence of intermittent noise, the type of noise and the task performed are important factors as well. Whether performance in the OR is affected by noise seems to be partially dependent on experience. Assisting surgeons with less experience report higher subjective distraction levels due to noise when compared to the primary, more experienced surgeons[10]. The negative impact of noise on clinical reasoning was lower in more experienced anesthesiological residents[25]. Although simulated laparoscopic task performance in 12 experienced surgeons was not negatively affected by noise at 80 to 85 dB, the sample size was relatively small and the comparator was either a clinically unnatural silent or music setting[26].

Of interest is the fact that music was not subjectively identified as a negative factor by OR staff, even though sound levels are doubled by music[39]. Therefore, it seems that not all increases in noise levels equal negative effects. Several recent extensive meta-analyses have observed beneficial effects of perioperative music on postoperative pain[12], intraoperative sedative medication requirement[13], postoperative opioid requirement[13], and the physiological stress response to surgery in adult surgical patients[14]. Moreover, music reduced mental workload in novice laparoscopists and improved laparoscopic task performance in the simulated setting depending on task demand as well [56,57]. In this review, we chose to only focus on the attitudes of and perception towards music in the operation room. The majority of OR staff are positively predisposed to playing music in the OR and have attributed positive influences of music on performance, teamwork, concentration and stress reduction. This general positivity appears to be irrespective of specialty (surgeon versus anesthesiologist), experience (residents versus attending physicians) or type of health care provider (attending versus nurse), although the degree of enjoyment varied[38]. It appears that in clinical practice, the music played is most often selected by the senior surgeon or through a team consensus[29,35,37]. Playing music during surgery was also widely considered to be a positive influence regarding work enjoyment. Higher satisfaction with the work environment is associated with a lower chance of burnout[58]. This is a vital factor for young physicians and nurses wishing to leave their profession[58,59]. Moreover, it seems that most health care staff in the OR do not believe that music negatively affected communication or acted as a distraction. However, when a problem is encountered, the opinions regarding music differ[29,31,35,36]. Miscommunication is a major cause for the occurrence of medical errors leading to injury in surgical patients, with 30% occurring intraoperatively[60]. Clearly, music in the OR should not affect communication, but whether this is the case has to date been insufficiently investigated in our opinion. The conclusions from two studies regarding auditory perception in a simulated setting should be taken with care[39,40]. Although participants were presented with increasing levels of background noise, followed by the addition of music, it appears that the auditory message volume remained the same. Naturally, it is to be expected that the correct auditory response rate will decrease when decibel levels increase. Both studies failed to take the Lombard effect into account, a well-recognized physiological phenomenon during which speakers increase their voice level and adapt their speech manner when in the presence of increasing background noise levels[41]. A non-randomized observational study performing an univariate analysis after dividing 20 surgical procedures of five surgeons to music versus no music observed a higher number of repeated requests when music was played[11]. However, we believe that multiple potential confounding factors were not adequately addressed. The use of music intraoperatively can theoretically act as a cue for creating awareness during specific situations in the OR, as lowering the music volume or turning off the music entirely during critical moments would draw the immediate attention of all surgical team members present. This would fit into the sterile cockpit concept employed by the aviation industry. During specific, critical, predefined moments, all attention should be diverted to the task at hand and irrelevant conversation and music are prohibited. As surgery involves a combined team effort of surgeons, residents, anesthetists, scrub nurses and circulating nurses, care should be taken to assess these specific phases with higher demands for each member involved in the entire surgical procedure, given the difference in specific task demand[10].

The aim of this systematic review was to assess the effect of noise in the OR. Although many studies have reported noise exceeding recommended decibel levels, its effect on both the patient and OR staff has only been investigated to a very modest degree. Our results were limited to only presenting the previously published data. Risk of bias according to standard assessment methods was considered high, but given that it is not possible to blind patients or members of the operation room to noise, we do not consider this to be of influence. Given the variety of outcome measures and the differences in study design, no meta-analysis could be performed. Drawing conclusions should be taken with caution, although several concepts on the negative effects of noise on both the patient and performer have been presented. Due to the use of a range of non-validated questionnaires, the varying ways in which the questions were posed, combined with the different survey methods used, it was not considered appropriate to calculate a single overall mean result regarding the attitudes of and perception towards music. Rather, we choose to present all study results individually. Nevertheless, the opinion of the health care staff seems to be in line with the view of the patient, namely that music during surgery is generally regarded to be a significant positive factor on all domains[13]. It should be noted that most surveys consisted of more general, non-specific questions, which could be interpreted in multiple ways. Furthermore, the same questions were often posed to different specialists and nurses with the answers presented jointly, although their specific situations and work demands differ greatly[10]. Especially in regards to communication and distraction, future studies should evaluate critical phases for each member involved in the surgical procedure during which care should be taken to minimize both noise and music in the OR.

It seems apparent that not all increases in noise levels have the same effects. Although the 'sterile cockpit concept' is often mentioned, a total sound-sterile work environment in the OR seems to be neither practically possible nor desirable. Some noise is unavoidable, given the fast-paced environment of the OR and high turnover, whilst proper communication is essential. Moreover, we believe that general conversation and music should be acceptable, as this increases work enjoyment in an already stressful environment and prohibiting it entirely would not be feasible. Future studies on noise in the OR should focus on patient outcome besides solely measuring decibel levels, ideally taking into account the physiological stress response or similar markers of stress. Furthermore, both reduction of specific noise sources as well as filtering out of noise during surgery should be further explored. Decreasing noise pollution levels caused by surgical instruments and alarms, which are the main noise sources in the operation room[4], can be achieved through innovative equipment design[61]. As intraoperative music has significant beneficial effects[12], implementing music through headphones for patients during surgery would both reduce unwanted noise pollution as well as provide music. Moreover, several studies have explored the use of intraoperative microphones and headphones for the OR team as well[24,62], especially in regards to robotic surgery during which the surgeon is often placed at a considerable distance away from the operation table. As more attention and scientific interest is increasingly payed in recent years to the health care work environment, attenuating noise pollution should also be included.

Conclusion

High noise levels in the OR seem to negatively affect both patient outcome and the surgical team. Future studies should assess whether this knowledge can be applied to benefit patient outcome and performance by the OR staff. Even though music significantly increases decibel levels in the OR, perception and attitude towards playing music during surgeon is favorably regarded by the majority of OR staff, irrespective of specialty.

Author Disclosure Statement

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

The authors would like to thank the Medical Library of the Erasmus MC University Medical Centre Rotterdam for their assistance with the literature search.

Appendix A. Literature search

Database	Years of Coverage	Before deduplication	After deduplication
Embase.com	1971 – October 16th, 2020	3010	2965
Medline Ovid	1971 – October 16th, 2020	1383	418
Cochrane Central	1971 – October 16th, 2020	165	93
Google Scholar	Not applicable	200	155
Total		**4758**	**3631**

Embase.com
(music/de OR 'music therapy'/de OR 'noise'/de OR 'noise pollution'/de OR (music OR musical OR musicotherap* OR ((auditor*) NEAR/3 (process* OR information*)) OR melod* OR ((acoustic*) NEAR/3 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise*):ab,ti,kw) AND (surgery/exp OR surgery:lnk OR 'obstetric operation'/exp OR 'postoperative complication'/exp OR 'anesthesiological procedure'/exp OR 'anesthesist'/exp OR 'anesthesiologist'/de OR 'surgeon'/de OR 'perioperative nursing'/de OR 'postanesthesia nursing'/de OR 'nurse'/exp OR 'operating room'/de OR 'recovery room'/de OR 'operating room personnel'/de OR 'surgical stress'/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,kw) AND ('interpersonal communication'/exp OR 'safety'/de OR 'patient safety'/exp OR 'safety culture'/de OR 'safety climate'/de OR 'nurse attitude'/de OR 'physician attitude'/de OR (communicat* OR safety OR safe OR ((attitude*) NEAR/3 (nurse* OR personnel* OR physician* OR surg* OR anaesthe* OR anesthe*))):ab,ti,kw) NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) NOT ([Conference Abstract]/lim AND [1800-2017]/py) AND [English]/lim

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(music/ OR music therapy/ OR noise/ OR (music OR musical OR musicotherap* OR ((auditor*) ADJ3 (process* OR information*)) OR melod* OR ((acoustic*) ADJ3 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise*).ab,ti,kf.) AND (General Surgery/ OR surgery.fx. OR exp Surgical Procedures, Operative/ OR exp Postoperative Complications/ OR exp Anesthesiology/ OR exp Perioperative Care/ OR exp Perioperative Nursing/ OR Operating Rooms/ OR Recovery Room/ OR exp Nurses/ OR exp Anesthetists/ OR exp Surgeons/ OR Operating Room Technicians/ 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,kf.) AND (Verbal Behavior/ OR Safety/ OR Patient Safety/ OR Attitude of Health Personnel/ OR (communicat* OR safety OR safe OR ((attitude*) ADJ3 (nurse* OR personnel* OR physician* OR surg* OR anaesthe* OR anesthe*))).ab,ti,kf.) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND english.lg.

Cochrane Central
((music OR musical OR musicotherap* OR ((auditor*) NEAR/3 (process* OR information*)) OR melod* OR ((acoustic*) NEAR/3 (distract* OR condition* OR stress* OR relax* OR stimulat*)) OR noise*):ab,ti,kw) 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,kw) AND ((communicat* OR safety OR safe OR ((attitude*) NEAR/3 (nurse* OR personnel* OR physician* OR surg* OR anaesthe* OR anesthe*))):ab,ti,kw)

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music|noise urgery|peroperative|perioperative|preoperative|postoperative|operative|operation|interoperative|intraoperative safety|safe|“attitudenurse|personnel|physician|surgeon|anaesthetist|anesthetist|anaesthesiologist|anesthesiologist”

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Part III

General discussion, Summary and Acknowledgements

Chapter 12

Discussion

"Plaudite, amici, comedia finita est."

Ludwig van Beethoven, Composer and Pianist, March 26, 1827.

Perioperative music and patient outcome

Music and medicine have been intertwined throughout history. In the last decade, an increasing number of scientific research regarding perioperative music and patients undergoing surgery has been performed and published. Recently, three systematic reviews and meta-analyses regarding the effects of perioperative music have been published[1-3], with perioperative music having a statistically significant beneficial effect on postoperative pain and anxiety. In the first part of this thesis, the effect of perioperative music on patient outcome and recovery was evaluated further.

Perioperative music and the physiological stress response to surgery

Music is universally known to reduce stress, with increasing scientific evidence revealing that music has beneficial effects on physiological stress-related outcome measures. In **Chapter 2**, the effect of perioperative music on the physiological stress response to surgery was evaluated. A more vigorous response disturbs the physiological homeostasis, due to the increased release of stress hormones and inflammatory cytokines[4-6]. The severity of the resulting organ response plays a vital role in the occurrence of postoperative complications[6,7]. The stress hormone cortisol plays a central role in the neuroendocrine metabolic stress response. It increases insulin resistance, thereby preventing glucose storage and favoring immediate glucose use during periods of stress[8]. Although this was useful in a historical perspective during a time when the fight or flight response was needed for survival, increased insulin resistance has been associated with higher postoperative complications and length of stay in surgical patients[4,5].

Perioperative music can significantly attenuate the physiological stress response to surgery, with mean postoperative cortisol levels being significantly lower in patients listening to music compared to patients who did not[6]. This implies that music can reduce postoperative complications, although this has not been assessed prior to this thesis[6,1]. The mechanism in which music reduces stress has been the subject of scientific research for decades. Different theories have been proposed. Clearly, the 'masking and distracting' effect plays a role[9]. Music masks unwanted environmental auditory stimuli like background noise, which has been identified as a stressor in the hospital and in particular the operation room for patient and staff alike[10]. However, music itself seems to have an additional beneficial effect. Several previously conducted studies employed headphones intraoperatively in the control group[6], whilst positive therapeutic suggestions intraoperatively do not seem to have the same beneficial effects[11]. Acting as a competing stimulus for other nerve impulses, music might influence perception by the brain as is simplified in the gate control theory[9]. Finally, music interacts with the autonomic nervous system, the limbic system, and affects its subsequent hormone release[12]. This is evident through the stress response of patients undergoing surgery[6], but also by brain area activation observed via functional brain imaging and the release of the reward-related hormone dopamine after listening to music[13,14].

Perioperative Music and Medication Requirement

In **Chapter 3**, the effect of perioperative music on intraoperative and postoperative medication requirement was assessed. In the last two decades, physicians are paying increased attention to perioperative medication requirement. This is particularly the case for opioids, due to their high risk of adverse side effects. Moreover, it is estimated that approximately six percent of opioid-naïve, surgical patients still persistently use opioid medication 90 days after surgery[15]. This seems to be irrespective of surgical severity. As surgery is the second most common reason to prescribe opioid medication, combined with the increasing number of surgical procedures performed each year[16], the prevalent use of postoperative opioids likely contributes to the global opioid pandemic.

Whilst a shift to opioid sparing analgesia has occurred, the balance between adequate analgesia and reduction of opioid use is a delicate one. Perioperative music can be beneficial for both[17,3], even after a relatively short-term exposure or when provided only during general anesthesia as described in **Chapter 4**[11,17]. These beneficial effects can have a number of potential implications for clinical practice. Music can offer additional pain relief in patients that only have opioid medication as an alternative analgesic, when paracetamol alone is insufficient. Non-opioid analgesics like non-steroidal anti-inflammatory drugs are generally avoided in the majority of gastrointestinal procedures, patients with an increased risk of peptic ulcer disease, patients with renal impairment, and elderly surgical patients. The use of locoregional nerve blocks in surgical patients can sometimes be limited due to use of anticoagulant medications. Furthermore, the amount of postoperative opioid requirement is related to the occurrence of adverse side effects and complications, possibly affecting postoperative patient recovery[16,18]. Whilst future studies should assess whether perioperative music can impact the opioid crisis as well, it should be noted that the risk of opioid dependence is related to a higher opioid requirement during hospital stay[16]. Finally, the associated costs of the postoperative opioid requirement itself and associated side effects, complications, and opioid crisis related costs should be taken into account as well, as even relatively small reductions in opioid requirement seem to have a relatively high impact[18].

Perioperative music can also significantly reduce intraoperative sedative medication requirement[17], possibly due to decreased anxiety and stress levels in patients about to undergo surgery. The clinical implications in regard to propofol for postoperative recovery are less clear, as it has attractive pharmacokinetic dynamics and seems to have limited adverse effects. However, benzodiazepines increase the risk of delirium, especially when combined with opioids. The concomitant use of benzodiazepines and opioids has also been identified as a risk factor for chronic opioid abuse[19]. Also, it seems logical to assume that less intraoperative sedative requirement will lead to surgical patients being awake and conscious earlier after surgery. Therefore, the effects of perioperative music on perioperative medication requirement fit seamlessly into current standard surgical patient care.

The effects of intraoperative music during general anesthesia

For decades, studies primarily performed in the anesthesiological field reported about a phenomenon known as implicit awareness or implicit memory formation of auditory stimuli during general anesthesia. An above chance recognition statistically of intraoperatively presented auditory stimuli seemed to be present when using priming and recall tasks in patient undergoing surgery with general anesthesia, even though sedation levels were deemed adequate and explicit recall was lacking. In **Chapter 4**, as recent functional imaging studies of the brain revealed the auditory cortex to be receptive and reactive to auditory stimuli even during deep sedation, the concept of implicit memory formation and its clinical relevance in regard to postoperative patient recovery was evaluated[11].

Intraoperative music played solely during general anesthesia significantly reduced postoperative pain in surgical patients, mirroring earlier meta-analysis who in contrast to Chapter 4 did not take high heterogeneity levels into account[1,3]. Furthermore, intraoperative music also significantly reduced postoperative opioid requirement[11]. Although these findings were not observed in Chapter 3, this discrepancy in results can be fully explained due to the data analysis method. In Chapter 3, the effects of perioperative music on medication requirement was assessed. As stated in the meta-analysis PROSPERO protocol, data of studies containing multiple music intervention groups were pooled. As two studies by Nilsson *et al.* contained both an intraoperative and postoperative music intervention group, these were pooled and not included in the sub-analysis of blinded studies in the meta-analysis in Chapter 3. However, the intraoperative music groups during general anesthesia in these two aforementioned studies are considered adequately blinded when compared to the control group, as all patients receive general anesthesia and wear headphones. Therefore, the study groups of these additional two studies were included in the intraoperative music meta-analysis of Chapter 4, yielding a significant beneficial effect of intraoperative music on postoperative opioid requirement. Interestingly, intraoperatively presented personalized therapeutic suggestions during general anesthesia in contrast to impersonalized music preselected by the research team did not yield beneficial effects on postoperative pain. This was also the case in a meta-analysis of 32 randomized controlled trials of therapeutic suggestions during general anesthesia, in which not double-blinded studies were also included[20]. Although they observed a beneficial effect on postoperative medication requirement of all analgesic taken together including studies dating back to the early sixties, this effect was relatively small (Standardized Mean Difference 0.169, 95% CI 0.079 to 0.260, $p = 0.000$). Several possibilities have been discussed for the difference in effect between intraoperative music and positive therapeutic suggestions, ranging from the use of benzodiazepine premedication to difference in brain area activation by different auditory stimuli[11].

In **Chapter 5,** the IMPROMPTU study aimed to further evaluate the relationship between intraoperative music, it's intraoperative perception during general anesthesia in patients undergoing surgery, the physiological stress response to surgery, and the occurrence of postoperative complications[7]. However, no significant beneficial effects by intraoperative, research-selected, classical instrumental music were observed in 70 esophageal and gastric cancer surgery resection patients. A variety of theoretical explanations for this lack of effect have been presented. Postoperative pain scores were generally low, with mean numeric rating scales being 2.5 points or less. Moreover, the majority of the surgical procedures involved might mean that a relatively small effect is not observed with the small sample size involved. Furthermore, over 20 percent of participants received benzodiazepines preoperatively, which could possibly influence implicit memory formation as discussed in Chapter 4. The lack of operation room noise due to the noise-cancelling headphones employed by the control group and the soft classical instrumental music which did not rank among the top three favorite music genres of the intervention group might also have lowered the beneficial effects of music. Finally, it could be possible that no effect exists, although this is contradicted by several studies included in the meta-analysis in Chapter 4 which observed both a beneficial effect of intraoperative music on postoperative pain and opioid requirement[11].

Practical recommendations in regards to the surgical patient

Given the observed beneficial effects of music discussed in this thesis, it is possible that perioperative music can also reduce postoperative complications and hospital length of stay. To date, studies are limited[6,17]. Taking into account the calculated standardized mean differences of approximately 0.30 in Chapters 2, 3 and 4 on the physiological stress response to surgery, postoperative pain, and postoperative opioid requirement, studies investigating perioperative music to date were not adequately powered to reveal such effects on complications and length of stay. Two tailed testing taking into account an effect size of 0.30 as observed, alpha of 0.05, with a power of 80%, requires a total of 352 participants. As the relation between pain, opioid requirement, and stress are not in a one-to-one ratio to the occurrence of complications and length of stay, even more participants will be needed to properly investigate the effect of music on the latter. Theoretically, perioperative music could especially benefit the elderly surgical patients, as they have an increased risk of opioid-related adverse effects, polypharmacy interaction, and limited options for non-opioid analgesia like non-steroidal anti-inflammatory drugs. Therefore, the MCHOPIN study described in **Chapter 6** will aim to assess the effects of perioperative music in a large, multicenter, randomized controlled trial of 452 elderly hip fracture patients undergoing surgery.

An universal high patients satisfaction with a high willingness to listen to music again in the future was present[17,21], which is crucial in an era of health care where patient satisfaction and patient-reported outcome measures take center stage. Even more important is the fact that patient experience measures are indicators of health care quality[22]. Given the previously mentioned beneficial effects and the observations that perioperative music is safe and seemingly has no adverse side effects[17], implementation as part of standard perioperative patient care seems to be the logical next step. A relative short term exposure appears to have a rather fast stress reducing and medication lowering effect, as the majority of studies investigating perioperative music exposed patients to less than 120 minutes of music and observed results within hours[6,17]. In **Chapter 7**, implementation of perioperative music was investigated. It was observed to be relatively easy, not time consuming, and successfully achievable in under six months in day care surgery at moderately-sized non-academic teaching hospitals[21]. Whilst perhaps scientifically interesting, the type of music and components within the musical pieces are of lesser value for clinical practice, as it is unlikely that patients will listen to music that they do not prefer. In general, patients were satisfied with preselected, provided music in the IMAGINE study, but further attention should be devoted to the way music can be provided to the patients taking both the music devices and music player applications into account. Future studies should evaluate implementation in regards to different surgical procedures and specialties, as the effects of interventions are related to the success of implementation[21].

Perioperative music and surgical performance

A vital component of the physician's Hippocratic Oath is to ensure patient safety. Identified factors that contribute to adverse patient outcomes in the operation room are lack of experience and technical skill, excessive workload, and communication issues[23,24]. The first factor is nowadays combated through supervision and rigorous training, which include simulation training programs to improve surgical task performance like the Fundamentals of Laparoscopic Surgery program[25]. Attention is nowadays also paid to mental and physical workload, by quantifying workload and placing restrictions on the maximum amount of working hours. Finally, time-out and sign-out procedures have been implemented as critical communication moments to increase patient safety. Surgical performance, and therefore surgical patient outcome, is a result of all aforementioned factors and a combined effort of the entire perioperative care team. As music is played during the majority of surgical procedures worldwide[10], the effect of music on surgical performance was evaluated in the second part of this thesis.

Perioperative Music and Surgical Task Performance

Chapter 8 consists of a systematic review of the effect of music on surgical task performance. Previously conducted studies evaluating this effect have all been restricted to a simulated setting[26]. Positive beneficial effects during surgical task performance were observed in all four studies that evaluated tasks performed with natural hand motions, like open wound closure, microsurgery, and robot-assisted surgery[26]. Varying results were observed during laparoscopic task performance (Table 1)[26], which is considered to be more strenuous on mental workload. In two studies by the same lead author that employed a similar study design, laparoscopic task accuracy was improved by classical piano music in expert surgeons[27], but not in novices to laparoscopy[28]. These tasks have previously been perceived to be relatively stressful for junior surgeons[29]. Preselected music did not improve task performance of 12 surgeons with variable experience levels during laparoscopic suturing[30], one of the most difficult laparoscopic skills to master[31,32]. No beneficial effect of preselected music was observed in 45 junior surgeons with no previous laparoscopy experience during a simulated laparoscopic cholecystectomy[33]. Only three studies included more than 30 participants[28,33]. Due to the varying study designs, different outcome measures, and limited number of included participants, no definitive conclusion could be drawn regarding the effects of music on laparoscopic task performance[26]. Hypothetically, the factors task complexity, mental workload and surgical experience could have played a role.

Table 1. Studies evaluating music and laparoscopic task performance

Study ID	Study population	Music intervention	Surgical task	Device used	Study outcome
Conrad 2010	8 expert surgeons	Classical piano sonatas by Mozart versus silence	Four simple laparoscopic tasks	SurgicalSIM VR laparoscopic simulator	Music variable effect on task completion time, improves accuracy, did not affect procedure recall.
Conrad 2012	31 junior surgeons, novices to laparoscopy	Classical piano sonatas by Mozart versus silence	Lifting and cutting, targeting object, feeding a rope, aligning object task	SurgicalSIM VR laparoscopic simulator	No significant difference is accuracy, but higher procedure recall during music
Fu 2020 (OPTIMISE study)	107 medical students, novices to laparoscopy	Participant-preferred music versus operation room noise	Ten alternating peg transfer tasks with dominant and non-dominant hand	Custom-made laparoscopic box trainer	Whilst music did not affect task performance, mental workload was significantly reduced. No relevant difference in heart rate and heart rate variability.
Miskovic 2008	45 junior surgeons, novices to laparoscopy	Preselected activating versus deactivating music versus silence	Clipping and cutting cystic duct and artery as part of laparoscopic cholecystectomy	LS500 (Xitact) VR laparoscopic simulator	No significant difference between groups in task performance. Higher heart rate during activating music.
Moorthy 2004	12 moderately and highly experienced surgeons	Classical music versus noise 80-85 dB versus silence	Three laparoscopic sutures on suture pad	Pelvi-trainer laparoscopic simulator	Neither noise nor music had a significant effect on dexterity measures of task performance
Oomens 2019 (ENSEMBLE study)	60 medical students, novices to laparoscopy	Participant-preferred music versus silence	Five peg transfer tasks with the dominant hand	Custom-made laparoscopic box trainer	Music improved task performance and reduced mental workload. No difference in heart rate or blood pressure.
Wiseman 2012	55 male volunteers, novices to surgery	Metal versus Mozart versus silence, played before surgical task performance	10 consecutive iterations of the ring and rope task	Custom-made box trainer, direct field view without 2D screen	Music exposure prior to the task can improve task performance, but affect tasks differently

Table 2. Comparison of ENSEMBLE and OPTIMISE study demographic characteristics

Demographic characteristics		ENSEMBLE study (n = 60)	OPTIMISE study (n = 97)	*p*-value
Age (years)		19 (18 – 21)	20 (18 – 21)	0.12
Study year		1 (1 – 3)	2 (1 – 3)	0.077
Sex	Male	19 (32%)	42 (43%)	0.17
	Female	41 (68%)	55 (57%)	
Dexterity	Right-handed	57 (95%)	82 (85%)	0.11
Importance of music (NRS)		8 (7 – 9)	8 (7 – 8)	0.010*
Listens to music while studying	Yes	48 (80%)	68 (70%)	0.19
	No	12 (20%)	29 (30%)	
Plays a musical instrument	Yes or used to	42 (70%)	52 (54%)	0.082
	No	18 (30%)	45 (46%)	
Top three favourite music genres when studying		Pop, classical, instrumental	Classical, other, pop	-
Top three chosen genres for study experiment		Pop, classical, rock	Pop, classical, hip hop	-

Somewhat surprising was the fact that these studies employed music selected by the research team. A positive trend between the perceived pleasantness of the preselected music by the participant and a beneficial effect was noted[26,33]. This mimics previously observed reduced autonomic reactivity and improved performance by surgeon-selected instead of researcher-selected music[34]. In **Chapters 9** and **10**, participant-preferred music was employed in the prospective ENSEMBLE and OPTIMISE studies in order to further evaluate the effect on laparoscopic task performance, as the surgeon was observed to most often select the music during surgery in daily clinical practice[10]. The main difference between these two studies was the laparoscopic task complexity[35]. The peg transfer task in the latter study was performed for a total of ten transfers, alternating between the dominant and non-dominant hand, compared to only five transfers solely with the dominant hand in the ENSEMBLE study. Demographic study characteristics between both studies did not differ statistically significantly, although a trend towards more participants playing a musical instrument in the ENSEMBLE study should be noted (Table 2). Also, importance of music in daily life was rated higher in the ENSEMBLE compared to the OPTIMISE study, although the exact clinical relevance is unclear as median levels were comparable (median NRS 8 (range 7 to 9) versus 8 (range 7 to 8), $p = 0.010$). Surgical experience did not differ, as all participants were laparoscopy novices. Based on task performance results in these studies, it seems that the beneficial effect of music on laparoscopic task performance disappears when task complexity is increased. This was also apparent through a higher mental workload in the OPTIMISE study, even though music still significantly lowered mental workload in both studies. Taking the aforementioned previously conducted studies into account which were reviewed in Chapter 8, it seems that the determinative factors task complexity and surgical experience dictate whether or not music is beneficial for surgical task performance.

Another difference between the ENSEMBLE and OPTIMISE studies was the control group, with operation room noise instead of silence introduced as an auditory control factor in the latter. The use of silence as a control factor does not reflect a real-life situation, given that it can never be totally silent in the operation room. The recorded operation room noise used contained consistent noise of a heart rate monitor and mechanical ventilator, lacking sudden loud sound peaks. Moreover, sound levels were similar as the participant-preferred music intervention. Noise pollution in the operation room can induce a more severe stress response in surgeons, act as a distracting and disturbing stressor, and negatively impact clinical reasoning[10]. However, it should be noted that these results were observed when comparing higher noise levels to lower noise levels, and not to silence. Whether the incorporation of operation room noise explains the difference in observed results of the ENSEMBLE and OPTIMISE study remains unclear. Future studies evaluating the effect of music on laparoscopic task performance should evaluate the aforementioned factors like surgical experience and task complexity further, as well as incorporate operation room noise in the study design to more realistically resemble clinical practice[35].

Perioperative music and surgical mental and physical workload

Playing music during surgery is common worldwide and well perceived irrespective of operation room profession[10]. The concept of stress and mental workload has gained attention in surgical research during the last two decades, as it seems apparent that mental workload is related to performance[24]. In **Chapter 11**, the effect of music and noise on the surgical staff was evaluated. The majority of staff surveyed worldwide involved in surgical patient care reported that music during surgery reduced stress of those working in the operation room[10]. These results were confirmed in the ENSEMBLE and OPTIMISE study, as mental workload was significantly reduced by music, with the dimension situational stress being also lower in both studies[35,36]. This beneficial effect seems to be increased, when mental workload is higher[35]. The multidimensional Surgery Task Load Index was chosen to evaluate mental workload, as this validated self-report instrument of the most commonly used mental workload questionnaire was designed specifically for surgery. Furthermore, it evaluates dimensions that have been recognized as key surgical stressors, which include laparoscopic surgery, task complexity, distraction, and time pressure[24]. Music lowered perceived task complexity in the ENSEMBLE study, but did not achieve a similar effect during the more demanding task in the OPTIMISE study. Although critics might argue that music during surgery can be distracting and impair communication[37], this does not seem to be apparent in our studies. A total of 1020 surveyed surgeons, anesthetists, and nurses worldwide did not believe music to be distracting in general, although this could be different in a critical situation[10]. Compared to silence in the ENSEMBLE study, music was not considered to be distracting during laparoscopic task performance[36]. Furthermore, music was considered significantly less distracting compared to operation room noise in the OPTIMISE study[35]. Music in the operation room was also believed to improve or at least not negatively affect concentration or communication by staff in the operation room[10]. Furthermore, playing music in the operation room was also regarded as positively influencing work enjoyment and improving team work[10]. Finally, temporal demands were also reduced when listening to music, with time pressure being applied through a running timer on the visual screen during laparoscopic task performance[35,36].

The effect of music on the autonomic nervous response as a measure for mental workload and stress during simulated surgical task performance has only been investigated in one published study prior to the ENSEMBLE and OPTIMISE studies[26,33]. A significant higher heart rate was observed during laparoscopic task performance when participants were exposed to music deemed 'activating' by the research team when compared to silence. This effect was not apparent in the 'deactivating' music group, but it was unclear whether the novice laparoscopists in this study also considered the music to be activating and deactivating. It does not seem to carry a clinically relevant difference when the music groups were viewed together (pooled mean heart rate 93 (pooled standard deviation 14) versus 89 (15) during silence). Similarly in the ENSEMBLE and OPTIMISE studies, no clinically relevant differences were observed in heart rate, blood pressure and heart rate variability due to music during laparoscopic task performance. However, given the short surgical task duration and therefore brief measurement moment, these outcome measures should not be disregarded in future studies yet. Other physiological markers of sympathetic activity and the stress response of interest, like galvanic skin conductance, eye-tracking devices, and non-invasive stress hormones measurement like salivary cortisol, have to date not been included when evaluating music, mental workload and surgical task performance.

Physical demands were reduced by participant-preferred music in both the ENSEMBLE and OPTIMISE study. This coincides with the decreased muscle effort and fatigue observed by music measured using electromyography during surgical task performance[26,38]. Muscle fatigue can negatively impact psychomotor performance and increase the risk of musculoskeletal disorders, which are nowadays prevalent among surgeons[39,40]. Possibly aggravated due to the advancement of laparoscopic surgery[39], up to 35.6% of surgeons reported 'working through the pain'[41]. Moreover, an estimated 12% of physicians were disabled due to musculoskeletal impairment, requiring a leave of absence and even early retirement[40]. Besides the association between work environment satisfaction and burn out[10], musculoskeletal pain is an important risk factor for burnout among care providers as well[42]. It would be interesting to evaluate whether the observed beneficial effects of music on postoperative pain in surgical patients can be mimicked to benefit the surgeon in that regard as well.

Applicability of music in clinical practice and during surgical training

Nowadays, there is increased attention to surgical training with simulation-based box trainers or virtual reality, as acquired skill during simulation training seems to be transferable to real-life surgery[43,44]. Furthermore, improved skill is associated with reduced postoperative complication and mortality rate, thereby improving patient outcome[45]. To date, all studies evaluating music and surgical performance have been restricted to a simulated setting. Music can improve surgical task performance in a simulated setting[26,36,35]. This beneficial effect seems to depend on mental workload, with task complexity and surgical experience being important determinative factors. Also, likeability of the music by the one performing the surgical task may play a role[34]. Several studies observed a reduction in time to task completion, including during wound closure[26]. Even a small reduction through music can be clinically relevant, as 1 minute of operation time is estimated to cost approximately $37[46]. Moreover, there seems to be an association between prolonged surgery duration and the occurrence of postoperative complications[47], although to what effect a reduction in surgery time also reduces complication rate is not yet clear. As lack of free time was the greatest barrier identified for surgical simulation training attendance, a reduction in task completion can be useful in training as well. Moreover, in order to combat boredom and lack of realism[48], the use of music, operation room noise, and auditory distractions should be incorporated in simulation based surgical training in order to resemble daily clinical practice more lifelike[48,49].

Music and medicine, final thoughts and the future

Perioperative music has significant beneficial effects on patient outcome, surgical task performance and mental workload. This is in line with previous systematic reviews and meta-analyses as mentioned on postoperative pain and anxiety[1-3], although high heterogeneity levels were observed due to clinical heterogeneity in regards to the patient population and surgical procedure. Inherently, the music intervention also had a number of variable factors. These included the different delivery methods, like the kind of music player and the use or disuse of headphones, whether music was played before, during, or after surgery, or a combination of these moments, the duration the music was played, and the characteristics of the music intervention[50]. Whilst the issue of heterogeneity was statistically dealt with in this thesis, some conflicting results remain present, especially in regards to music provided intraoperatively solely during general anesthesia. Research on postoperative complications and length of stay is limited, with most studies only including a relatively short follow-up period. Still, since perioperative music is well liked by patient and surgeon alike and no adverse side effects have been reported to date, it seems that it is now time for implementation in daily perioperative patient care. Not only would this allow for a true estimate of the effects of perioperative music, it would also evaluate practical barriers which have not been identified yet when investigating music in a controlled research setting during randomized controlled trials.

Like the implementation of fast track recovery protocols, which are now part of standard perioperative patient care, multidisciplinary cooperation will be required. Surgeons, anesthesiologists, and nurses in the operation room and on the ward will all have an important role to play. Patients themselves should also be actively involved, as it is unlikely that they will listen to music that they do not like. Furthermore, the information technology (IT) department as well as audio streaming services should be engaged in order to facilitate the use of perioperative music hospital-wide. Finally, attention to copyright should be paid, as music licensing contracts will be required if hospitals want to actively offer perioperative music to patients[51]. Future studies regarding music, surgical task performance, mental workload and patient outcome should incorporate elements from previous conducted studies, which have been systematically collected and reviewed in this thesis. Whatever the future of research regarding music will reveal, music in the operation room is here to stay.

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Chapter 13

Summary

Perioperative music and patient outcome

In **Chapter 2**, a meta-analysis of 18 randomized controlled trials with 1301 adult surgical patients investigating the effect of perioperative music on the physiological stress response to surgery and postoperative complications is presented. A significant, moderate, beneficial attenuating effect on the neurohormonal physiological stress response to surgery was observed, with postoperative cortisol values being less high when patients were exposed to music compared to those that were not exposed to music[1]. Previous studies reported that a more vigorous stress response was associated with a higher postoperative complication rate and worse patient outcome[2]. This insinuates that perioperative music can potentially reduce postoperative complications, although none of the included studies in this systematic review and meta-analysis assessed this.

In **Chapter 3**, a meta-analysis of 55 randomized controlled trials with 4968 adult surgical patients investigating the effect of perioperative music on postoperative opioid medication requirement, intraoperative sedative medication requirement, and hospital length of stay is presented. Perioperative music significantly reduced postoperative opioid requirement[3], with surgery being the second most common reason to prescribe opioids during the worldwide opioid crisis and opioid-related adverse events being prevalent and dose-dependent[4,5]. Music also significantly reduced intraoperative propofol and midazolam requirement, possibly due to its previously observed anxiolytic effect[6]. Anesthesia depth level remained similar in patients listening to music and needing less intraoperative sedatives compared to the control group. Therefore, perioperative music seems to contribute to improved patient outcome. Although no significant effect on length of stay was observed, only a limited number of studies with many investigating minor surgery assessed this outcome. Finally, patient satisfaction was markedly high in the included studies, with the majority of patients willing to listen to music again if operated on in the future once more.

In **Chapter 4**, a meta-analysis of 53 randomized controlled trials with 4200 adult surgical patients investigating the perception and effect of intraoperative presented auditory stimuli during general anesthesia on explicit memory formation, implicit memory formation, and patient outcome is presented. It has been previously reported that the auditory cortex remains reactive and receptive during general anesthesia[7]. Among the different auditory stimuli assessed, which included positive therapeutic suggestions, only music significantly reduced postoperative pain and opioid requirement[8]. A possibly theoretical explanation for this finding is that music activates different parts of the brain in comparison to words[9]. The effect of implicit awareness of music was further evaluated in **Chapter 5**. The IMPROMPTU study was a double-blinded, randomized controlled, multicenter trial investigating the effect of intraoperative music on postoperative pain, medication requirement, the physiological stress response to surgery, postoperative complications, and hospital length of stay in 70 esophageal and stomach cancer patients undergoing surgery. Although the previously reported effects were not reproduced, more insight was gained in perioperative factors potentially influencing implicit memory formation and several explanations regarding the contradictory results are presented[10].

Chapter 6 present the study protocol of the MCHOPIN study. The aim of this multicenter, randomized controlled trial is to investigate the effect of perioperative music on the clinical outcome in elderly hip fracture patients undergoing surgery[11]. Delirium, the most common complication in this delicate patient group, will be primarily assessed, as it has serious implications for the postoperative outcome, recovery and long term independence in daily living activities.

Chapter 7 consists of the results of the IMAGINE implementation study, in which the implementation success and effects in day care surgery procedures were evaluated. The perioperative music intervention was well liked by patients, easily applicable and not time consuming, leading to high patient satisfaction levels[12]. Further attention should be devoted to the optimal music delivery equipment.

Perioperative Music and Surgical Performance

Chapter 8 contains a systematic review of nine prospective studies with 212 participants assessing the effects of music on surgical performance. This beneficial so-called 'Mozart Effect' of music on spatial task performance was first described in the early nineties[13], and improved surgical performance has been associated with improved patient outcome[14]. Due to the limited number of participants, the difference in study design, and differing evaluated outcome measures, no meta-analysis could be performed and no definitive conclusion drawn[15]. Still, there appeared to be a tendency of significant improved surgical task performance in studies when the music was deemed pleasant by the participants. Also, the effect on stress by the performer of the surgical task was only very sparingly investigated.

The effect of music on surgical performance was therefore further explored in two prospective, randomized crossover trials of respectively 60 and 107 laparoscopic novices. As described in **Chapters 9** and **10**, the ENSEMBLE and OPTIMISE studies assessed the effect of participant-preferred music on surgical task performance and mental workload. The beneficial effect on surgical performance seemed to depend on mental workload and task demand, with participant-preferred music having a significantly beneficial effect on mental workload and key stressor domains in both studies[16,17]. Additional future research regarding music and surgical performance should assess the role of task demand and surgical experience.

Chapter 11 consists of a systematic review of 22 prospective studies with 3507 participants on the effect of noise in the operation room, as well as the predisposition of the members of the operation room towards music[18]. Higher noise levels seem to have a negative effect on patient outcome and adversely affect performance in the operation room. In contrast, music was generally enjoyed by the majority in the operation room, with reported beneficial subjective effects on individual performance or concentration, team performance and team work, and stress reduction. Music during surgery was not deemed to be distracting in general or negatively affecting communication, although this could vary depending on the specific clinical situation.

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Chapter 14

Samenvatting

In dit proefschrift werden de effecten van perioperatieve muziek op patiëntenuitkomsten en chirurgische prestaties onderzocht. In het eerste deel, bestaande uit zes hoofdstukken, werd op de heilzame effecten van muziek op de patiënt geconcentreerd, mede met betrekking tot focuspunten van de huidige chirurgische standaard patiëntenzorg. In het tweede deel, bestaande uit vier hoofdstukken, werden de effecten van muziek op de chirurg geëvalueerd.

Perioperatieve muziek en de uitkomst van de patiënt

In **Hoofdstuk 2** wordt een meta-analyse van 18 gerandomiseerde, gecontroleerde studies met 1301 volwassen chirurgische patiënten beschreven, waarin het effect van perioperatieve muziek op de fysiologische stressrespons van een operatie wordt gepresenteerd. Een significant gunstig effect werd geobserveerd, waarbij de postoperatieve cortisol waarden minder hoog waren wanneer patiënten blootgesteld waren aan muziek vergeleken met patiënten die niet blootgesteld waren aan muziek[1]. Omdat een meer krachtige stressrespons geassocieerd is een hoger aantal postoperatieve complicaties en een slechtere patiëntenuitkomst, impliceert dit dat perioperatieve muziek potentieel het aantal postoperatieve complicaties kan verminderen[2]. Echter werd dit in geen van de geïncludeerde studies in deze systematische review en meta-analyse geëvalueerd.

Hoofdstuk 3 betreft een meta-analyse van 55 gerandomiseerde, gecontroleerde studies met 4968 volwassen chirurgische patiënten, waarin het effect van perioperatieve muziek op het postoperatieve opioïdengebruik, de intraoperatieve sedatiebehoefte en de opnameduur in het ziekenhuis wordt gepresenteerd. Door perioperatieve muziek werd het postoperatieve opioïdengebruik significant verlaagd[3]. Tijdens de huidige wereldwijde opioïdencrisis is gebleken dat het ondergaan van een operatie de tweede meest frequente reden is om opioïden voor te schrijven. Daarnaast is het optreden van opioïden-gerelateerde bijwerkingen afhankelijk van de dosis[4,5]. Door muziek werden de intraoperatieve sedatiebehoefte middels propofol en midazolam eveneens significant verlaagd, mogelijk door het al eerder waargenomen angst reducerende effect in een eerdere meta-analyse[6]. De anesthesiediepte bleef hetzelfde van patiënten die luisterden naar muziek en minder intraoperatieve sedativa nodig hadden vergeleken met de controle groep. Zodoende lijkt perioperatieve muziek bij te dragen aan een betere patiëntenuitkomst. Alhoewel geen effect op opnameduur werd geobserveerd, werd deze uitkomstmaat slechts in een beperkt aantal studies met vaak kleinere operaties onderzocht. Tenslotte was het opvallend dat de patiënttevredenheid in de geïncludeerde studies hoog was, waarbij een meerderheid van de patiënten opnieuw naar muziek zou willen luisteren indien ze in de toekomst nogmaals geopereerd zouden worden.

In **Hoofdstuk 4** wordt een meta-analyse van 53 gerandomiseerde, gecontroleerde studies met 4200 volwassen chirurgische patiënten beschreven, waarin de perceptie en het effect van intraoperatief gepresenteerde auditieve stimuli tijdens algehele narcose op expliciete geheugenvorming, impliciete geheugenvorming en de patiëntenuitkomst werd onderzocht. Eerder werd gerapporteerd dat de auditieve cortex tijdens algehele narcose reactief en receptief blijft[7]. Van de verschillende auditieve stimuli die waren onderzocht leidde alleen muziek tot een significante reductie wat betreft postoperatieve pijn en opioïdengebruik[8]. Een mogelijke theoretische verklaring voor deze bevinding is dat muziek in tegenstelling tot woorden andere hersengebieden activeert[9].

In **Hoofdstuk 5** werd het effect van impliciet bewustzijn van muziek verder onderzocht. De IMPROMPTU studie is een dubbelblinde, gerandomiseerde, gecontroleerde, multicenter studie waarin het effect van intraoperatieve muziek werd onderzocht op postoperatieve pijn, medicatiegebruik, de fysiologische stressrespons van een operatie, postoperatieve complicaties en opnameduur in het ziekenhuis bij 70 slokdarm- en maagcarcinoom patiënten die een operatie hebben ondergaan. Alhoewel de eerder gerapporteerde effecten niet konden worden gereproduceerd, werd meer inzicht verkregen in perioperatieve factoren die mogelijk van invloed kunnen zijn op impliciete geheugenvorming. Verschillende verklaringen voor de tegenstrijdige resultaten werden gepresenteerd[10].

In **Hoofdstuk 6** wordt het studieprotocol van de MCHOPIN studie gepresenteerd. Het doel van deze multicenter gerandomiseerde, gecontroleerde studie is om de effecten van perioperatieve muziek op de klinische uitkomst van oudere patiënten met een heupfractuur die worden geopereerd te onderzoeken[11]. Het delier, de meest voorkomende complicatie in deze groep van kwetsbare patiënten, zal primair worden onderzocht, aangezien dit serieuze implicaties voor de postoperatieve uitkomst, het herstel en de zelfredzaamheid van dagelijkse activiteiten heeft.

In **Hoofdstuk 7** worden de resultaten van de IMAGINE implementatiestudie gepresenteerd, waarbij het implementatiesucces en de effecten bij operaties in dagbehandeling werden geëvalueerd. De perioperatieve muziekinterventie werd door de patiënten zeer gewaardeerd, was makkelijk toepasbaar en niet tijdrovend en leidde tot een hoge patiënttevredenheid. Bijzondere aandacht moet aan de meest optimale muziekapparatuur besteed worden.

Perioperatieve muziek en de chirurgische prestaties

Hoofdstuk 8 bevat een systematische review van negen prospectieve studies met 212 participanten omtrent de effecten van muziek op chirurgische prestaties. Het gunstige zo geheten 'Mozart Effect' van muziek op het uitvoeren van ruimtelijke inzichtstesten werd voor het eerst in de vroege negentiger jaren beschreven[12]. Verbeterde chirurgische prestaties zijn geassocieerd met een betere patiëntenuitkomst[13]. Door het beperkte aantal participanten, verschillen in studieopzet en de verschillende geëvalueerde uitkomstmaten kon geen meta-analyse worden uitgevoerd en geen definitieve conclusie getrokken worden[14]. Wel leek er een tendens te bestaan van significante verbetering in chirurgische prestaties als de muziek door de participanten als aangenaam werd beschouwd. Het effect van muziek op stress van de uitvoerder van de chirurgische taak bleek slechts zeer beperkt onderzocht.

Het effect van muziek op de chirurgische prestaties werd zodoende verder onderzocht in twee prospectieve, gerandomiseerde, crossover studies van respectievelijk 60 en 107 proefpersonen zonder laparoscopische ervaring. Zoals beschreven in **Hoofdstuk 9** en **10** werd in de ENSEMBLE en OPTIMISE studies het effect van voorkeursmuziek op de laparoscopische chirurgische taakuitvoering en mentale werkbelasting onderzocht. De aanwezigheid van het gustige effect door muziek leek af te hangen van de mate van mentale werkbelasting en de complexiteit van de uit te voeren chirurgische taak. In beide studies had voorkeursmuziek wel een significant gunstig effect op de mentale werkbelasting en sleuteldomeinen van stress had[15,16]. Toekomstig onderzoek met betrekking tot muziek en chirurgische prestatie zou zich moeten richten op de rol van taakbelasting en chirurgische ervaring.

Hoofdstuk 11 bestaat uit een systematisch review van 22 prospectieve studies met 3507 participanten over het effect van lawaai in de operatiekamer, alsmede de predispositie van leden van het operatieteam tegenover muziek[17]. Hogere lawaaigehaltes lijken een negatief effect op de patiëntenuitkomst te hebben en prestaties in de operatiekamer negatief te beïnvloeden. Daarentegen werd muziek in de operatiekamer in het algemeen door de meerderheid gewaardeerd, waarbij gunstige subjectieve effecten over individuele prestatie of concentratie, teamprestatie en teamwork, en stressreductie werden beschreven. Peroperatieve muziek werd in het algemeen gezien niet als afleidend, noch werd hierdoor de communicatie negatief beïnvloed alhoewel dit kon variëren afhankelijk van de specifieke klinische situatie.

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Chapter 15

Acknowledgments
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Acknowledgments

Tijdens dit promotietraject heb ik het privilege gehad om mijn passie voor muziek en chirurgie te mogen combineren. Dit proefschrift is hiervan het resultaat, mede door een samenwerkingsproces waaraan artsen, verpleegkundigen, paramedici en diverse niet-medici hebben bijgedragen. Allen ben ik zeer veel dank verschuldigd, met name alle patiënten en medisch studenten die hebben deelgenomen aan de onderzoeken. In het bijzonder wil ik enkele personen uitlichten die een speciale rol in het tot stand komen van dit proefschrift en de levensperiode hier rondom hebben gehad.

Prof. Verhofstad, beste Michael, in ons eerste gesprek benoemde u de gouden leidraad van mijn cq. een promotietraject, ‘drie stappen vooruit, twee stappen terug’. Hier heb ik me aan vastgehouden met de gedachte dat de stip op de horizon eens tastbaar zal worden. In tijden van onzekerheid heeft u mij gesteund om steeds die derde stap voorwaarts te zetten.

Prof. Lange, beste Johan, mijn eerste kennismaking met de wonderlijke wereld van medisch chirurgisch onderzoek begon tijdens de studie bij u. De productieve samenwerking met de Muziek als Medicijn werkgroep en prof. Jeekel is door uw verwijzing tot stand gekomen. Ondanks dat onze muziek statistisch significant verschillen, heeft u mij de mogelijkheid gegeven om als onderzoeker te floreren.

Prof. Wijnhoven, beste Bas, mijn dank gaat uit naar zowel de wetenschappelijke begeleiding, als de aandacht voor de praktische uitvoerbaarheid en het welzijn van de onderzoeker. Mede door uw inzet en interventie hebben we de IMPROMPTU studie en daarmee mijn proefschrift kunnen voltooien. Aanwezigheid bij de operaties heeft mede geleid tot mijn motivatie om chirurg te worden.

Dr. Klimek, beste Markus, sinds de studietijd en minor een fijne samenwerking op zowel onderzoeksgebied alsmede het extra-curriculaire MINDZ project.

Prof. Jeekel, beste Hans, als voornaamste begeleider en mentor bent u de primaire drijfkracht geweest achter dit promotietraject. Samen hebben we talloze malen het podium gedeeld, al dan niet met muzikaal samenspel, uit liefde voor de muziek en chirurgie. Uw eeuwige enthousiasme zal mij altijd bijblijven en inspireren in zowel mijn professionele carrière als persoonlijke leven.

Prof. Kleinrensink, beste Gert-Jan, ook hier begon de samenwerking vele jaren voorafgaand aan de ‘VINCE’ studies, waarbij dit proefschrift niet compleet zou zijn zonder deze hoofdstukken. Prof. Bouvy en prof. Boer, dank voor het kritisch evalueren van dit proefschrift. Prof. de Zeeuw, dank voor de mogelijkheid om dit onderzoek mede gesteund door de afdeling Neuroscience uit te kunnen voeren.

Collega onderzoekers van de MAM en de REPAIR, dank voor de samenwerking, gezelligheid, het koffiedrinken, en adviezen omtrent de opzet en uitvoering van alle onderzoeksprojecten. In het bijzonder Rosalie Kühlmann en Marianne van der Heijden voor het mij wegwijs maken bij de start van mijn onderzoeksperiode, Vincent Kleinrensink voor de samenwerking met betrekking tot de studies die in de volksmond door de supervisoren naar jou zijn vernoemd, en Dimitri Snijders voor de kritische feedback en statistische ondersteuning.

Studentonderzoekers die ik door de jaren heen heb mogen superviseren. Veerle Elbers, Jolien Bartho, Dino Gačević, Anita Pols, Pascale Wessels, Willemijn Borst, Joséphine Janssen, Karel Sleurink, Niek Merkus en Kwint Mackenbach. Mijn dank voor eenieders bijdrage aan dit proefschrift.

De chirurgen, anesthesisten, assistenten, verpleegkundigen, operatiemedewerkers van het Erasmus MC, Elisabeth-Tweesteden Ziekenhuis Tilburg, Maasstad Ziekenhuis Rotterdam, St. Antonius Ziekenhuis, en OLVG Amsterdam. Dank voor de gezelligheid en het meeopereren. Speciale dank aan de directe aanspreekpunten van de chirurgie en anesthesie, te weten Sjoerd Lagarde, Christian Favoccia, Joos Heisterkamp, Annemarie van Oers, Peter-Paul Coene, Seppe Koopman, Detlef van der Velde, Leonie Slegers, Robert Haverlag, Johan Haumann en Anand Menon.

Mijn oprechte dank aan Eline Vrijenhoef, Elsbeth Dankelman, Linda Alonso, Annelies Bijl, en Antoinette van Lith voor het faciliteren van talloze besprekingen die benodigd waren om dit proefschrift tot een succes te leiden. Antoinette, doe de groeten aan Belle en Beau.

Waarde collega's van het Franciscus Gasthuis & Vlietland en het Zuyderland MC waar ik mijn vervolgstappen in de kliniek bij de chirurgie mocht zetten met welkome steun en interesse.

Meindert Sosef en Guy Vijgen, dank voor de hernieuwde motivatie en ontvangst in het Zuiden.

De Stuurgroep Muziek als Medicijn wil ik bedanken voor de ondersteuning gedurende deze jaren. In het bijzonder Fryke Wouda Kuipers, voor de koppen koffie die we hebben gedronken, alle subsidieaanvragen die we samen hebben gedaan, alsmede alle (levens) adviezen.

Vrienden en collega musici waarmee ik in recente jaren het podium heb gedeeld.

Esther Ida van Althuis, luisterend oor en confidante. Sinds de Rotterdamse Eurekaweek zijn we talloze avonturen verder, met als hoogtepunt oud en nieuw vieringen op de zonnige stranden van de Canarische Eilanden om een dubbele defenestratie af te wenden.

Pim Oomens, waarde collega, mede-onderzoeker, bovenal goede vriend. Na ruim twee jaar de werkvloer te hebben gedeeld in Tilburg en het Erasmus MC kwam er helaas een einde aan de dagelijkse samenwerking. De vriendschap is gebleven waarbij we nog meerdere projecten samen hebben afgerond. Dit boekje is ook een beetje van jou!

Mijn ouders, voor de steun niet alleen gedurende dit promotietraject maar ook ver daarbuiten.

Edouard Fu, mijn allerliefste broeder, voor het eerst hebben wij tegelijkertijd hetzelfde pad in ons leven belopen, wat ons nog dichter bij elkaar heeft gebracht. Jij bent mijn grootste steun geweest. Ik ben uitermate trots op het feit dat wij beide zijn gepromoveerd.

List of Publications

This Thesis

V.X. Fu, S.M. Lagarde, C.T. Favoccia, J. Heisterkamp, A.E. van Oers, P.P.L.O. Coene, J.S.H.A. Koopman, W.A. Dik, S.A.A. van den Berg, R.A. Feelders, J. Jeekel, B.P.L. Wijnhoven. Intraoperative Music to PROMote PaTient oUtcome (IMPROMPTU): a double-blind, placebo-controlled, randomized multicenter trial. *Submitted, 2021.*

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V.X. Fu, P. Oomens, D. Sneiders, S.A.A. van den Berg, R.A. Feelders, B.P.L. Wijnhoven, J. Jeekel. The Effect of Perioperative Music on the Stress Response to Surgery: A Meta-analysis. J Surg Res. 2019; 244: 444-455. doi.org/10.1016/j.jss.2019.06.052.

P. Oomens*, **V.X. Fu***, G.J. Kleinrensink, J. Jeekel. The effect of music on surgical performance: a systematic review. Surg Endosc. 2019; 33(9): 2774-2784. doi.org/10.1007/s00464-019-06868-x.

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V.X. Fu, M.J.P.V. Macco, G.H.E.J. Vijgen. Een 9-jarige jongen met lucht in de buik. Diagnose in Beeld. *Submitted*, 2021.

V.X. Fu, H.B. Verheul, G.N. Beute, S. Leenstra S, H.P.M. Kunst, J.J.S. Mulder, P.E.J. Hanssens. Retreatment of Vestibular Schwannoma with Gamma Knife Radiosurgery: clinical outcome, tumor control and review of literature. J Neurosurg. 2018;129(1):137-145. doi.org/10.3171/2017.3.JNS162033.

* Denounces shared first authorship

PhD Portfolio

Name:	Victor Xing Fu
Date and Place of Birth:	17 January 1990, Montreal, Canada
Erasmus MC Department:	Neuroscience, Surgery
PhD Period:	01-06-2017 – 01-04-2020
Thesis Title:	Music and Surgery - The Effect of Perioperative Music on Patient Outcome and Surgical Performance
Promotores:	Prof. dr. M.H.J. Verhofstad and Prof. dr. J.F. Lange
Copromotores:	Prof. dr. B.P.L. Wijnhoven and Dr. M. Klimek
PhD Defense:	April 13, 2022

PhD Portfolio		Year	ECTS
General Courses	Research Integrity	2019	0.3
	BROK (Good Clinical Practice) (Score 97 / 100)	2018	1.0
Teaching and Supervision	Supervision of master thesis students (1.5 ECTs per student)	2017 – 2020	12.0
	Supervision of research students (0.5 ECT per student)	2017 – 2020	1.0
	Muziek in de Zorg (MiNDZ)	2019	1.0
Conferences and Lectures (selected)	Oral Presentation, Themater Lezingen Isala Theater, Capelle a/d IJssel, The Netherlands	2020	1.0
	Invited Lecture, Symposium Chirurgie en Anesthesie Maxima Medisch Centrum, Veldhoven, The Netherlands	2020	1.0
	Invited Lecture, VCMS Rotterdam Erasmus MC, Rotterdam, The Netherlands	2020	0.5
	Invited Lecture, Music as Medicine Rijksmonument Kasteel Keppe, Laag-Keppel, The Netherlands	2019	1.0
	Invited Lecture, Miracles of Music congress Gooiland Theater, Hilversum, The Netherlands	2019	1.0
	Invited Keynote Lecture, Symposium Infectiepreventie en Wondzorg Alrijne Ziekenhuis, Zoetermeer, The Netherlands	2019	1.0
	Invited Lecture, Viecuri Doctor's Dinner Scelta, Venlo, The Netherlands	2018	1.0
	Oral Presentation, SEOHS 2019 De Nieuwe Liefde, Amsterdam, The Netherlands	2019	0.5
	Oral Presentation, NVvH Chirurgendagen 2019 Conference Centre Koningshof, Veldhoven, The Netherlands	2019	1.0
	Invited Lecture, Music-CHOPIN, EMSOC benefit concert Stadsgehoorzaal, Leiden, The Netherlands	2018	0.5

Conferences and Lectures (selected)	Oral Presentation, Albert Schweitzer Hospital Symposium Trinitis Kapel, Dordrecht, The Netherlands	2018	1.0
	Invited Keynote Lecture, Nacht van de Wetenschap Centrale Bibliotheek, Den Haag, The Netherlands	2017	1.0
	Invited Lecture, Opening Academisch Jaar Erasmus Universiteit Faculty Club Erasmus, Rotterdam, The Netherlands	2017	1.0
	Invited Keynote Lecture, 52th International Meeting ESSR Beurs van Berlage, Amsterdam, The Netherlands	2017	1.0
	Invited Lecture, Art and Music in Surgery (VCMS Amsterdam) Theatrum anatomicum de Waag, Amsterdam, The Netherlands	2017	1.0
	Oral Presentation, Wetenschapsdag ETZ, Elisabeth-Tweesteden Ziekenhuis, Tilburg, The Netherlands	2017	0.5
Attendance	RICH Congress 2.0, Erasmus MC, Rotterdam, The Netherlands	2019	0.3
Television and Multimedia	Nationale Wetenschapsagenda live session, Muziek als Medicijn	2021	0.2
	De Jonge Specialist (coverstory), Jaargang 7 – Juni 2020	2020	0.1
	Zomer met Art, RTL4 (live late night talkshow)	2019	0.2
	Amazing Erasmus ‘De Visie van Victor Fu’ (coverstory)	2019	0.2
	Erasmus MC: de passage, RTL4 (documentary, yet unaired)	2018	0.2
	Nieuwsuur, NPO2 ‘Het Ziekenhuis van de Toekomst’ (documentary)	2018	0.2
		Total ECTS	30.7

Curriculum Vitae

Victor Xing Fu was born on 17 January 1990 in Montreal, Canada. He attended secondary education at the Stedelijk Gymnasium Leiden. From an early age, he developed a significant interest in music. As a proficient classical pianist, he has performed in several national concert halls in the Netherlands and received several awards at locoregional piano competitions.

After starting medical school in 2008 at the Erasmus MC, University Medical Center Rotterdam, he continued to combine music and medicine together, culminating in an invited recital performance in De Doelen in 2009 and twice at the NVvH Chirurgendagen. During his internships, scientific curiosity was cultivated as well, after working at the REPAIR research group under guidance of Prof. dr. J.F. Lange and neurosurgery department in Tilburg through Dr. H.B. Verheul and G.N. Beute.

After graduating in 2015, he started as a resident not in training at the Department of Surgery of the Elisabeth-Tweesteden Hospital in Tilburg under Dr. P.W.H.E. Vriens and Dr. M.S. Ibelings. In 2017, he started his PhD Music as Medicine under guidance of Prof. J. Jeekel. During this time, his musical performance background aided in him becoming a prolific speaker leading to several cover stories, including Amazing Erasmus and De Jonge Specialist, and national media coverage, including Nacht van de Wetenschap, Nieuwsuur, and RTL late night. In May 2020, he continued as a resident not in training at the Department of Surgery of the Franciscus Gasthuis & Vlietland, Rotterdam, under Dr. T.M.A.L. Klem. In July 2021, he moved to the Department of Surgery of the Zuyderland Medical Center in Heerlen and Sittard-Geleen, under Dr. M.N. Sosef. Finishing his Thesis in January 2021, he aims to continue to combine music and surgery together in order to improve perioperative patient care by launching several implementation projects.