Perception of auditory stimuli during general anesthesia and its effects on patient outcomes: a systematic review and meta-analysis

Perception de stimuli auditifs pendant l’anesthésie générale et ses effets sur les devenirs des patients : revue systématique et méta-analyse

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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, Ovid Medline, and Cochrane Central from inception date until 15 October 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 of 5,859 identified articles (4,200 patients) were included. There was evidence of implicit memory formation in seven out of 17 studies (41%) when assessed using perceptual priming tasks. Mixed results were observed on postoperative behavioural 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; \( P = 0.039 \); \( I^2 = 36 \); \( n = 336 \)), while 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.
Résumé

**Objectif** L’intérêt pour la création de mémoire implicite et la perception inconsciente de stimuli auditifs pendant l’anesthésie générale a refait surface depuis qu’il a été rapporté que l’audition de musique périopératoire produisait des effets bénéfiques. Nous avons mené une revue systématique et une méta-analyse des études randomisées contrôlées (ERC) évaluant la création de mémoire explicite et implicite pendant l’anesthésie générale et ses effets sur les devenirs postopératoires et le rétablissement des patients.

**Sources** Nous avons effectué une recherche documentaire systématique dans les bases de données Embase, Ovid Medline et Cochrane Central depuis leur date de création jusqu’au 15 octobre 2020. Étaient admissibles à l’inclusion les ERC évaluant la stimulation auditive peropératoire chez les patients chirurgicaux adultes sous anesthésie générale, dans lesquelles les patients, le personnel de soins de santé et les évaluateurs des devenirs étaient tous en aveugle. Nous avons utilisé des modèles à effets aléatoires pour les méta-analyses. Cette étude a respecté les lignes directrices PRISMA et a été enregistrée dans le registre PROSPERO (CRD42020178087).

**Constatations principales** Cinquante-trois des 5859 articles identifiés (4200 patients) ont été inclus. Sept études sur 17 (41 %) comportaient des données probantes concernant la création de mémoire implicite lorsqu’elle était évaluée à l’aide de tâches d’amorçage perceptif. Des résultats mitigés ont été observés sur la réponse comportementale et motrice postopératoire après des suggestions peropératoires. La musique peropératoire a considérablement réduit la douleur postopératoire (différence moyenne standardisée [DMS] -0.84; intervalle de confiance [IC] de 95 %, -1.1 à -0.57; P < 0.001; I² = 0; n = 226) et les besoins en opioïdes (DMS, -0.29; IC 95 %, -0.57 à -0.015; P = 0.039; I² = 36; n = 336), mais pas les suggestions thérapeutiques positives.

**Conclusion** Les résultats de cette revue systématique et méta-analyse montrent que les stimuli auditifs peropératoires peuvent être perçus et traités pendant une anesthésie générale cliniquement adéquate, indépendamment de la gravité de l’intervention chirurgicale, menant à la création de mémoire implicite sans conscience explicite. La musique peropératoire peut avoir des effets bénéfiques significatifs sur la douleur postopératoire et les besoins en opioïdes. Il n’est pas encore possible de déterminer si le type d’anesthésie peropératoire utilisé a une influence.

**Keywords** explicit recall · implicit awareness · memory formation · music · positive suggestions

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%, but have been observed to be as high as 2% in selected populations. Nevertheless, 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. This would allow for implicit awareness, defined as intraoperative unconscious perception without explicit recall.

In the early 1990s and 2000s, there was a strong interest in this phenomenon, and it was investigated 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”. 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 (RCT). Nevertheless, no definitive conclusions were drawn at that time.

Recently, a new interest in auditory perception has arisen as perioperative music has been reported to have beneficial effects. Two recent meta-analyses evaluated the effects of perioperative music before, during and after surgery. The effects of intraoperative music—applied only while the patients were under general anesthesia—were only briefly assessed in a sub-analysis. Although intraoperative music can seemingly reduce postoperative pain, this conclusion was based on a limited number of studies with high heterogeneity that was not further addressed. 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. Whether other auditory stimuli can achieve the same effects and to which extent different perioperative factors are of influence was also not evaluated. Consequently, by focusing solely on intraoperatively presented auditory stimuli during general anesthesia alone and not limiting assessment to music only, the mechanisms of intraoperative auditory processing and perception can be further explored. Moreover, a renewed systematic search and analysis with a larger number of studies is needed to address the issues of these previous studies and reach more definite conclusions.
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 needed 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 in 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 until 15 October 2020. We used an exhaustive literature search method that yields 44% more references and 20% more included studies than traditional literature search methods do,13 assisted by a biomedical information specialist (full search syntax available in Electronic Supplementary Material [ESM], eAppendix A). Peer-reviewed, published, full-text-available RCTs 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:

- Type of patients: Adult patients undergoing surgery with general anesthesia
- Type of studies: Peer-reviewed, published, full-text-available RCTs in the English language in which patients, perioperative staff, outcome assessors were all blinded
- Type of intervention and control: Intraoperative auditory stimuli (for example: music, positive suggestions, stories) compared with 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, 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 (V.F., K.S., J.C.J.) and the full text was assessed 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 for the aforementioned eligibility criteria, while 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 (V.F., K.S., J.C.J.) 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 physiologic stress response to surgery, which has been implicated in implicit memory formation, were also extracted.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. These factors can either influence the amount of perioperative medication administered or the duration of exposure to the intraoperative stimuli, and were prespecified in our previous meta-analysis.10 We assessed the risk of bias using the Cochrane Collaboration’s tool of assessing the risk of bias in RCTs.17 If the aforementioned baseline characteristics were not detailed per study group, the other risk of bias was considered unclear. A statistically 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. 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 (CIs) were calculated. An SMD of -0.2 or less can be considered a small beneficial effect, -0.5 a moderate beneficial effect, and -0.8 or higher a large beneficial effect. We assessed heterogeneity with the $I^2$ test. Data analysis was performed with OpenMeta-Analyst open source software, which uses R as the underlying basis and Python for graphical user interface implementation. 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

While our aim was to perform meta-analysis of all outcomes, this was not possible for implicit and explicit memory because of the way the data were presented as well as the lack of proper controls in several studies. Although the type of patients, studies, intervention, and control were specified for the Population, Intervention, Comparison, and Outcome framework, 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 vs positive therapeutic suggestions), type of anesthesia (i.e., intravenous vs inhalational), and additional influencing factors like surgical severity. Only the first analysis was possible because of the limited number of studies included in the quantitative synthesis. Likewise, meta-regression or publication bias assessment was not possible. Finally, some factors such as perioperative data extracted and the other risk of bias category were not registered in the protocol, but followed our previous meta-analysis.

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 RCTs (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) (Fig. 1). There was a high interreviewer agreeability throughout the screening and data extraction process of 92%, and all differences were solved through mutual discussion.

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 while it played continuously throughout the surgical procedure in 38 studies. Two studies did not state the exact auditory intervention duration. The mean patient age ranged from 21 to 40 yr in 15 studies (28%) and from 41 to 60 yr in 29 studies (55%), and was 61 yr or higher in six studies (11%). 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 ESM eAppendix B. In 31 studies, premedication was administered before general anesthesia induction; opioids in nine and benzodiazepines in 17 studies (Table 2). In most studies, anesthesia consisted 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. 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. Seven studies assessed patient outcome measures, three studies assessed explicit memory formation, and one study assessed implicit memory formation.

Explicit memory formation

Explicit memory formation or conscious recollection of auditory stimuli was assessed in 45 studies (3,528 patients) using three different assessment methods (Fig. 1, Table 3). Assessment was performed immediately postoperatively in four studies, within the first 24 hr postoperatively in 30 studies, and within the first and seventh postoperative day in hospital 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. Among 43 studies (3,320 patients) using the open-recall test, positive test results indicative of explicit memory formation were observed in three studies (7.0%; 0.54% of patients). Two studies reported positive open-recall test results in six (3.4%) and three patients (2.3%), though none remembered hearing any auditory stimuli. Nine of the 15 patients (60%) reported being aware of music being played during their total knee arthroplasty.

The recognition test, in which patients are asked whether or not they recognized the auditory stimuli that was played intraoperatively, was used in ten studies (798 patients).
| Study | Surgical procedure | Auditory intervention | Group 1 | N<sub>1</sub> | Group 2 | N<sub>2</sub> | Outcome parameters |
|-------|-------------------|-----------------------|---------|--------------|---------|--------------|-------------------|
| Aceto et al. 2003<sup>38</sup> | Elective laparoscopic cholecystectomy | Repetitive story-keywords using familiar Christian religious stories | Sevoflurane and air (FiO₂ 40%) | 10 | Sevoflurane and 60%N<sub>2</sub>O in 40%O<sub>2</sub> | 10 | Explicit memory (open-recall) |
| | | | Isoflurane and air (FiO₂ 40%) | 10 | Isoflurane and 60%N<sub>2</sub>O in 40%O<sub>2</sub> | 10 | Implicit memory (story-related free association) |
| | | | | | | | Mid-latency auditory evoked potential relationship with memory formation |
| Aceto et al. 2013<sup>36</sup> | 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 et al. 2015<sup>37</sup> | 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 et al. 1998<sup>35</sup> | 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) |
| | | | | | | | Implicit memory (word-stem completion test) |
| Bejjani et al. 2009<sup>28</sup> | 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) |
| Bennett et al. 1985<sup>46</sup> | 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) |
| Block et al. 1991<sup>82</sup> | Elective gastroplasty, cholecystectomy or gynecological surgery | Positive therapeutic suggestions 6-min tape, continuously played expect for the first 59 patients | Positive therapeutic suggestions | 109 | Headphones with blank tape | 100 | Patient outcome (pain, opioids, PONV, antiemetics, length of stay) |
| Boeke et al. 1988<sup>83</sup> | 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 |
| Bonebakker et al. 1993<sup>44</sup> | Elective surgery Category word pair tape 30 min, followed by bird sounds continuously | 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) |
| Bonke et al. 1986<sup>49</sup> | 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) |

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| Study                   | Surgical procedure                                      | Auditory intervention                                                                 | Group 1                                                                 | N₁         | Group 2                                                                 | N₂         | Outcome parameters                                                                                           |
|------------------------|---------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------|------------|------------------------------------------------------------------------|------------|-------------------------------------------------------------------------------------------------------------|
| Caseley-Rondi et al. 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) |
| Dawson et al. 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, antiemetics, length of stay)             |
| De Roode et al. 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 |
| Deeprase et al. 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 et al. 1996    | Arthroscopy day care surgery                              | Eight tapes with ten facts or names with filler sound continuously                     | Presented facts                                                         | 29         | Target names                                                           | 29         | Explicit memory (open-recall) Implicit memory (presented facts and target names)                            |
| Eberhart et al. 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, antiemetics, 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)                                |
| Ghoneim et al. 2000   | Elective general, gynecological, orthopedic, and plastic surgery | Repetitive story-keyword 30-min tape repeated four times                          | Opioid 7.5 µg kg⁻¹ fentanyl bolus                                        | 100        | N₂O-opioid infusion 1.5 µg kg⁻¹ min⁻¹ alfentanil                      | 40         | Explicit memory (open-recall, recognition test) Implicit memory (story-related free association) Mid-latency auditory evoked potential relationship with memory formation |
| Hughes et al. 1994    | Elective ear-nose-throat, urological, gynecological, orthopedic surgery | Behavioural suggestion tape on smoking cessation played continuously               | Smoking cessation message                                               | 50         | Control tape with counted numbers                                    | 50         | Explicit memory (open-recall) Implicit memory (postoperative behavioural response)                         |
| Study                | Surgical procedure                          | Auditory intervention                                                                 | Group 1                                                                 | N₁   | Group 2                                                                 | N₂   | Outcome parameters                                                                 |
|---------------------|---------------------------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------|------|--------------------------------------------------------------------------|------|-----------------------------------------------------------------------------------|
| Ikedo et al. 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)           |
| Jansen et al. 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)                                                     |
| Jayaraman et al. 2006 | Laparoscopic cholecystectomy                   | Positive therapeutic suggestions and calming music played continuously                  | Music                                                                 | 24   | Routine operating room sounds                                             | 34   | Explicit memory (open-recall)                                                     |
| Jelicic et al. 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)                                                     |
| Jelicic et al. 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)                                                     |
| Kahloul et al. 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)                                                |
| Kerssens et al. 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)                                   |
| Kerssens et al. 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)                                   |
| Kliempt et al. 1999 | General, non-cancer surgery                  | Classical music or hemisync played continuously                                       | Adagio Karajan                                                        | 25   | Headphones with blank tape                                                | 16   | Patient outcome (intraoperative fentanyl requirement)                             |
| Lebovits et al. 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)                                                     |
| Lequeux et al. 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)                     |
|                     |                                             |                                                                                        | Low-opioid remifentanil                                              | 39   |                                                                         |      | Implicit memory (word-stem completion test)                                       |
|                     |                                             |                                                                                        |                                                                       |      |                                                                         |      | Noxious stimuli and opioid effect on memory                                       |
| Study                  | Surgical procedure                                      | Auditory intervention                                      | Group 1              | Group 2                  | N<sub>1</sub> | N<sub>2</sub> | Outcome parameters                                                                 |
|-----------------------|--------------------------------------------------------|------------------------------------------------------------|----------------------|--------------------------|--------------|--------------|-------------------------------------------------------------------------------------|
| Lewis et al. 2004<sup>83</sup> | Laparoscopic bariatric or lumbar disk surgery          | Hemisync played continuously                              | Hemisync             | Headphones with blank tape | 30           | 30          | Patient outcome (intraoperative fentanyl requirement)                                |
| Liu et al. 1992<sup>52</sup>   | Total abdominal hysterectomy                            | Positive therapeutic suggestions 10 min tape or hospital story played continuously | Positive therapeutic suggestions | Headphones with blank tape | 24           | 25          | Explicit memory (open-recall)                                                       |
| Maroof et al. 1997<sup>84</sup> | Elective abdominal hysterectomy                        | Positive therapeutic suggestions 15 min tape played continuously | Positive therapeutic suggestions | Headphones with blank tape | 25           | 25          | Explicit memory (open-recall)                                                       |
| McLinton<sup>53</sup> et al. 1990 | Elective open abdominal hysterectomy                    | Positive therapeutic suggestions 15 min tape played continuously | Positive therapeutic suggestions | Headphones with blank tape | 25           | 25          | Explicit memory (open-recall)                                                       |
| Melzack et al. 1996<sup>52</sup> | Elective cholecystectomy or hysterectomy                | Positive therapeutic suggestions and motor instructions 4 min tape | Positive therapeutic and postoperative motor response suggestions | Headphones with blank tape | 10           | 10          | Explicit memory (recognition test)                                                  |
| Mignault et al. 2004<sup>61</sup> | Abdominal hysterectomy with (hystero)salpingo-oophorectomy | Classical, jazz, new-age, or popular piano music compact disc | Music                | Headphones without music       | 15           | 15          | Explicit memory (open-recall)                                                       |
| Millar and Watkinson 1983<sup>30</sup> | Upper-abdominal, gynecological surgery                  | Four ten-word lists 14-min tape                            | Word list            | Headphone with static radio noise | 27           | 26          | Explicit memory (open-recall, free recall, recognition test)                        |
| Myles et al. 1996<sup>49</sup>   | Elective or semi-selective surgery                      | Behavioural 3-min suggestion tape on smoking cessation played continuously | Positive suggestion for smoking cessation | Headphones with blank tape | 185          | 178         | Explicit memory (open-recall)                                                       |
| Nilsson et al. 2001<sup>54</sup> | Elective open abdominal hysterectomy                    | Positive therapeutic suggestions with or without music played continuously | Relaxing and calming music | Headphones with OR noise | 30           | 28          | Explicit memory (open-recall)                                                       |
| Nilsson et al. 2003<sup>55</sup> | Day care inguinal hernia repair or varicose vein surgery | Slow, flowing, new age 43-min music tape played continuously | Positive therapeutic suggestions with music Instrumental music | Headphones with blank CD | 51           | 49          | Explicit memory (open-recall)                                                       |
| Nilsson et al. 2005<sup>56</sup> | Open inguinal Lichtenstein hernia repair                | Slow, flowing, new age 43-min music tape played continuously | Instrumental music    | Headphones with blank CD | 25           | 25          | Patient outcome (pain, opioids)                                                     |
| Study            | Surgical procedure | Auditory intervention | Group 1                                      | N₁  | Group 2                                      | N₂  | Outcome parameters                                                                 |
|------------------|--------------------|-----------------------|---------------------------------------------|-----|---------------------------------------------|-----|-------------------------------------------------------------------------------------|
| Oddby-Muhrbeck et al. 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, antiemetics, length of stay) |
| Parker et al. 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)                                      |
| Kalyani et al. 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 et al. 2000‡ | Gynecological minor surgery | Positive suggestions and 8-word list played once before surgical stimuli start | Sevoflurane 1.2% Sevoflurane 1.5% | 15  | Sevoflurane 2.0% | 16  | Explicit memory (open-recall, recognition test) Implicit memory (postoperative behavioural response) |
| Reza et al. 2007‡ | Elective Cesarean section | Soft instrumental Spanish guitar music played continuously | Music | 50  | White noise | 50  | Patient outcome (pain, opioids, PONV, antiemetics)                                      |
| 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 et al. 2008‡ | Primary total knee arthroplasty | Music played continuously | Music | 15  | White noise | 15  | Explicit memory (open-recall) Patient outcome (pain, patient satisfaction) |
| Szmuk et al. 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)                                      |
| Tsuchiya et al. 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) |
| Westmoreland et al. 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 et al. 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, antiemetics) |
In four studies, an above chance probability was observed with regard to correctly recognizing the auditory stimuli compared with the control group, indicating potential explicit memory formation. Except for one patient who correctly remembered a single test word, no explicit memory formation through the open-recall test was found, and patients undergoing the recognition test were generally 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 of explicit memory formation.

Implicit memory formation

Implicit memory formation was assessed in 23 studies (1,864 patients) (Fig. 1, Table 3), with 17 using a perceptual learning or priming test and six assessing change in postoperative behavioural patient response. In total, nine studies (39%) reported evidence for implicit memory formation. Two studies used multiple tests.

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 hr postoperatively. 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 test results occurred during the postoperative interview than did in the control group, while 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. 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. 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. who used a comparable anesthesia maintenance regimen in elective surgical patients, and Russel and Wang, who evaluated major gynecological surgery patients undergoing TIVA propofol-alfentanil anesthesia—did not observe evidence of implicit memory formation. In both 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. Only Deeprose et al. reported implicit memory formation in propofol-nitrous oxide (N₂O) day care orthopedic surgery patients, but the two TIVA propofol studies with benzodiazepine premedication did not. The presented facts and target names test was used in four studies (15%), which consisted of asking patients questions relating to intraoperatively presented statements and fictitious names. Jelicic et al. (1992) observed implicit memory formation in strabismus surgery patients undergoing opioid-N₂O 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

| Study                | Surgical procedure                          | Auditory intervention                      | Group 1 | N₁ | Group 2 | N₂ | Outcome parameters                                |
|----------------------|---------------------------------------------|--------------------------------------------|---------|----|---------|----|--------------------------------------------------|
| 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)            |

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; MAC = minimum alveolar concentration; N1 = number of patients in group 1; N2 = number of patients in group 2; N₂O = Nitrous oxide; O₂ = oxygen; OR = operating room; PACU = postoperative anesthesia care unit; PONV = postoperative nausea and vomiting.
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, nor using the preference task evaluating preference of intraoperatively presented melodies.

Six studies (643 patients) assessed implicit memory formation through changes in postoperative behavioural patient responses after being 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, as did two studies that evaluated smoking cessation after intraoperatively played taped instructions. Finally, two studies did not find any differences in answers to questions or use of keywords postoperatively while filling out a questionnaire, indicating no implicit memory formation.

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. Intraoperative music significantly reduced postoperative pain when assessed within the first three hr after surgery (pooled SMD, \(-0.51\); 95% CI, \(-0.81\) to \(-0.22\); \(P < 0.001\); \(I^2 = 38\); \(n = 320\) patients in five studies) and 24

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**TABLE 2** Baseline study characteristics

| Baseline study characteristics | Overall | Explicit memory | Implicit memory | Patient outcome |
|-------------------------------|---------|-----------------|----------------|----------------|
| **Number of studies (patients)** | 53 (4,200) | 45 (3,528) | 23 (1,864) | 29 (2,249) |
| **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 |

Overview of baseline characteristics of the included studies. Jayaraman (2006), Lebovits (1999), Liu (1992), Melzack (1996), Nilsson (2001) employed multiple auditory intervention groups, whilst Rema (2005), Russel and Wang (2001) employed an auditory intervention consisting of both suggestions with a word list. Not all studies specified the administered premedication.
| Study               | Intervention                                                                 | ANA                           | Explicit recall | Implicit memory formation                                                                 | Time   | Comments                                                                 |
|---------------------|-------------------------------------------------------------------------------|-------------------------------|----------------|------------------------------------------------------------------------------------------|--------|--------------------------------------------------------------------------|
| Aceto et al.        | Repetitive Christian story-keyword sequence                                   | Balanced                      | Open-recall test (0%)                                  | Story-related free association test (1/40, 2.5%)                                              | 24 h   | MLAER Pa latency increase related to implicit memory formation          |
| Aceto et al.        | Repetitive fairy story-keyword sequence                                       | Balanced                      | Open-recall test (0%)                                  | Story-related free association test (3/54, 5.5%)                                              | End, 24 h | Auditory stimulation associated with lower prolactin concentrations    |
| Aceto et al.        | Repetitive fairy story-keyword sequence                                       | Balanced                      | Open-recall test (0%)                                  | Story-related free association test (8/127, 6.3%)                                              | End, 24 h | 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 et al.        | Repetitive word list                                                          | Balanced                      | Open-recall test (0%)                                  | Word pair free association test (evidence of preserved implicit memory)                         | POD 3–6 | 23 of 25 patients showed higher rate of correct word pair associations of intraoperatively presented word list      |
| Bejjani et al.      | Repetitive word list                                                          | TIVA                          | Open-recall test (0%)                                  | Word-stem completion test (no evidence of implicit memory formation)                           | POD 1   | Correct answer rate between word list that was played and was not played not different |
| Bennett et al.      | 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 et al.        | Positive therapeutic and nonsense suggestions, seaside sounds                 | Balanced                      | Open-recall test (0%)                                  | Not assessed                                                                                 | POD 6 or 7 | No explicit memory formation                                          |
| Bonebakker et al.   | 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 et al.        | Positive therapeutic suggestions                                              | Balanced                      | Open-recall test (0%)                                  | Not assessed                                                                                 | POD 6 or 7 | No explicit memory formation                                          |
| Caseley-Rondi et al.| Personalized positive suggestions with music                                  | Balanced                      | Open-recall test (0%)                                  | Preference task (no evidence of implicit memory formation)                                     | 24 h, POD 3 | Above chance accuracy on patient’s guesses who correctly assessed that suggestions were played |
| Dawson et al.       | Positive therapeutic suggestions                                              | Balanced                      | Open-recall test (0%)                                  | Not assessed                                                                                 | POD 5   | No explicit memory formation                                          |
| De Roode et al.     | 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 |
| Dee prose et al.    | Repetitive word list                                                          | Balanced                      | Open-recall test (0%)                                  | Word-stem completion test (implicit memory formation present both in fentanyl and no fentanyl group) | 1.5 h   | Slightly higher mean implicit memory formation score for no fentanyl group, but not statistically significant |

**Intraoperative auditory perception and patient outcome**
| Study                  | Intervention                                                                 | ANA     | Explicit recall          | Implicit memory formation                                                                 | Time       | Comments                                                                                       |
|-----------------------|------------------------------------------------------------------------------|---------|--------------------------|-------------------------------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------|
| Donker et al. 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                                                                            | 24 hr      | No explicit memory formation                                                                 |
| 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 et al. 2000† | Repetitive story-keyword sequence                                           | Balanced| Open-recall test (6/179; 3.4%) | Story-related free association test (implicit memory formation present in opioid bolus-70% N2O group) | POD 1 or POD 3-4 | Significant explicit and implicit memory formation in opioid bolus-70% N2O MLAER Nb amplitude increase related to explicit, while Na, Pa, and Nb latency decrease related to implicit recall |
| Hughes et al. 1994†   | Behavioural change message                                                   | Balanced| Open-recall test (0%)    | Postoperative behavioural response (significantly changed)                               | 4 weeks    | Significant more stopped or reduced smoking in intervention group                            |
| Jansen et al. 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 et al. 2006 | Music and positive therapeutic suggestions                                  | Balanced| Open-recall test (0%)    | Not assessed                                                                            | End        | No explicit memory formation                                                                 |
| Jelicic et al. 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 et al. 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)              | POD 1      | No implicit memory in spontaneously breathing patients, in contrast to N2O-opioid anesthesia in 1992 study |
| Kahloul et al. 2017   | Tunisian, Eastern, Western or instrumental music                             | Balanced| Not specified             | Not assessed                                                                            | 24 hr      | No significant difference in awareness between intervention and control group               |
| Kerssens et al. 2001  | Familiar word category exemplars with filler birds singing sound             | TIVA    | Open-recall test (0%)    | 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 et al. 2009  | 15-word list                                                                 | Balanced| Open-recall test (3/109; 2.3%) | Recognition test (above chance recognition in BIS-guided group)                          | 6 h        | 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. |
Intraoperative auditory perception and patient outcome

| Study | Intervention | ANA | Explicit recall | Implicit memory formation | Time | Comments |
|-------|--------------|-----|-----------------|--------------------------|------|----------|
| Lebovits et al. 1999<sup>63</sup> | Positive therapeutic suggestions, story | TIVA | Open-recall test (0%) | | End, 6hr, 24 hr | No explicit memory formation |
| Lequeux et al. 2014<sup>29</sup> | 2-word list | TIVA | Open-recall test (0%) | Free-recall test (NS) | Word-stem completion test (no evidence of implicit memory formation) | 2-3 hr | No implicit memory formation during BIS-guided propofol-remifentanil anesthesia with low remifentanil doses |
| Liu et al. 1992<sup>52</sup> | Positive therapeutic suggestions, story | Balanced | Open-recall test (0%) | Recognition test (NS) | | POD 1 | No explicit memory formation |
| Maroof et al. 1997<sup>64</sup> | Positive therapeutic suggestions | Balanced | Open-recall test (0%) | | Not assessed | 24 hr | No explicit memory formation |
| McTintock et al. 1990<sup>53</sup> | Positive therapeutic suggestions | Balanced | Open-recall test (0%) | | | Not assessed | 24 hr | No explicit memory formation |
| Melzack et al. 1996<sup>32</sup> | Personalized positive therapeutic and motor suggestions vs repetitive story keyword | Balanced | Free recall (NS) | | Postoperative behavioural response (no difference between groups, no trend in keywords chosen postoperatively) | POD 1-4 | Also did not observe a significant beneficial effect on postoperative pain levels and hospital length of stay |
| Migneault et al. 2004<sup>61</sup> | Classical, jazz, new-age, or popular piano music | Balanced | Open-recall test (0%) | | Not assessed | 24 hr | No explicit memory formation |
| Millar and Watkinson 1983<sup>30</sup> | 10-word list | Balanced | Open-recall test (0%) | Free-recall test (NS) Recognition test (higher recognition rate, but NS) | Not assessed | 24 hr | Although higher word recognition rate indicating explicit recall, no significant difference in hand movements for isolated forearm technique |
| Myles et al. 1996<sup>49</sup> | Behavioural change message | Balanced | Open-recall test (0%) | | VAS motivation to stop smoking Postoperative behavioural 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 et al. 2001<sup>54</sup> | Music with either sea wave sounds or positive therapeutic suggestions | Balanced | Open-recall test (0%) | | Not assessed | 24 hr | No explicit memory formation |
| Nilsson et al. 2003<sup>55</sup> | Instrumental new-age synthesizer music | Balanced | Open-recall test (0%) | | Not assessed | PACU release | No explicit memory formation |
| Oddby-Muhrbeck et al. 1995<sup>57</sup> | Positive therapeutic suggestions interspersed with soft music | Balanced | Open-recall test (0%) | | | 24 hr | No explicit memory formation |
| Parker et al. 1994<sup>31</sup> | 10-word list | Balanced | Free-recall test (0%) | Recognition test (NS) | | POD 1 | Almost all patients attributed the recognition test as guesswork |
| Kalyani et al. 2015<sup>36</sup> | Classical instrumental music | Balanced | Open-recall test (0%) | | | 24 hr | No explicit memory formation |
hr after surgery (pooled SMD, -0.84; 95% CI, -1.1 to -0.57; 
P < 0.001; I² = 0; n = 226 patients in three studies). 
Intraoperative positive therapeutic suggestions did not 
reduce postoperative pain (pooled SMD, 0.03; 95% CI, - 
0.34 to 0.40; P = 0.86; I² = 43; n = 202 patients in four 
studies) (Fig. 2). Postoperative opioid requirements were 
assessed in 12 studies, with nine included in the meta-
analysis.52-57,59-61 Intraoperative music significantly 
reduced postoperative opioid requirements (pooled SMD, 
-0.29; 95% CI, -0.57 to -0.02; P = 0.04; I² = 36; n = 336 
patients in five studies), whereas positive therapeutic 
suggestions did not (pooled SMD, -0.12; 95% CI, -0.40 
to 0.16; P = 0.41; I² = 39; n = 372 patients in five studies) 
(Fig. 3).

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

Length of stay was assessed in 12 studies, six of which qualified for inclusion in the meta-analysis. 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; \( R^2 = 73; n = 286 \) patients in four studies) or postoperative anesthesia care unit stay (pooled \( R^2 = 0.58; \ R^2 = 0; n = 141 \) patients in two studies) were observed. Patient satisfaction or subjective well-being was assessed in seven studies, of which three assessing intraoperative music qualified for inclusion in the meta-analysis.\(^{23,54,68}\) No significant difference was observed (pooled \( R^2 = 0.63; 95\% \; CI, -0.98 \; to \; 2.24; \ P = 0.44; \ R^2 = 96; n = 198 \) patients in three studies).

Risk of bias assessment

A risk of bias summary is presented in Fig. 4, with a detailed individual study level bias risk description in ESM eAppendix C, and Fig. 5. 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 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 to assess their effects on memory formation. Therefore, the anesthesiologist was not blinded to group allocation. Nevertheless, 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 in 20 studies (38%) because details of excluded patients were not specified. 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%). Because of 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.\(^{25,33,69}\) Publication bias was not assessed because of the limited number of studies included in quantitative synthesis, following the recommendations of the Cochrane Handbook.\(^{18}\)

Discussion

This systematic review and meta-analysis of 53 RCTs 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 are likely 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 physiologic 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

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Fig. 4 Risk of bias graph.
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. 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. 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. In all included studies with evidence of implicit memory formation and in the music intervention studies from 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 affect implicit memory formation, warranting further research. Because of 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 because of drug-induced amnesia. While sedation depth level plays a clear role in explicit recall, implicit memory formation was also observed in several studies that appeared to employ clinically adequate, ETAG- or BIS-guided anesthesia. 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 hr after surgery during which pain levels are generally the highest. The underlying mechanism could involve an attenuating effect on the physiologic stress response to surgery and stress hormone levels. 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 be because different brain regions are active during music vs speech. The variation in several potential implicit memory formation factors such as premedication use and longer measurement duration of patient outcome parameters compared with the “music medicine” studies should also be noted. 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 too 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 physiologic stress response to surgery has been implicated in implicit memory formation. In contrast to previous meta-analyses, we focused solely on the mechanisms and effects of auditory processing and perception during general anesthesia. We also included more studies that were not previously examined. This allowed us to deal with the issue of high heterogeneity levels while also taking into account the follow-up measurement moment and different type of auditory stimuli, strengthening our results. While clinical heterogeneity is still assumed to be present, we observed acceptable levels of heterogeneity ($I^2 < 40\%$). In contradiction to our previous meta-analysis, we also observed a significant beneficial effect of intraoperative music on postoperative opioid requirements. Because of 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. The number of included studies in the meta-analysis was limited, so additional subgroup analyses and assessment of publication bias were also not possible. A significant proportion of the included studies used $\text{N}_2\text{O}$, but its use is declining worldwide. 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 patient population, surgical procedures, perioperative anesthesia regimens, and outcome among the included studies 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 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 shows 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, while positive therapeutic suggestions had no apparent effects on patient recovery.

Author contributions 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.

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