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REVIEW ARTICLE/BRIEF REVIEW

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.*

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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; I^2 = 0; n = 226) et les besoins en opioïdes (DMS, -0,29; IC 95 %, -0,57 à -0,015; P = 0,039; I^2 = 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.[1-3] 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.[4,5] 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".[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 (RCT). Nevertheless, 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 while the patients were under general anesthesia—were only briefly assessed in a sub-analysis.[9,10] 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.[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 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.[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 (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.[18] 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.[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

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.[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 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 inter-reviewer 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.

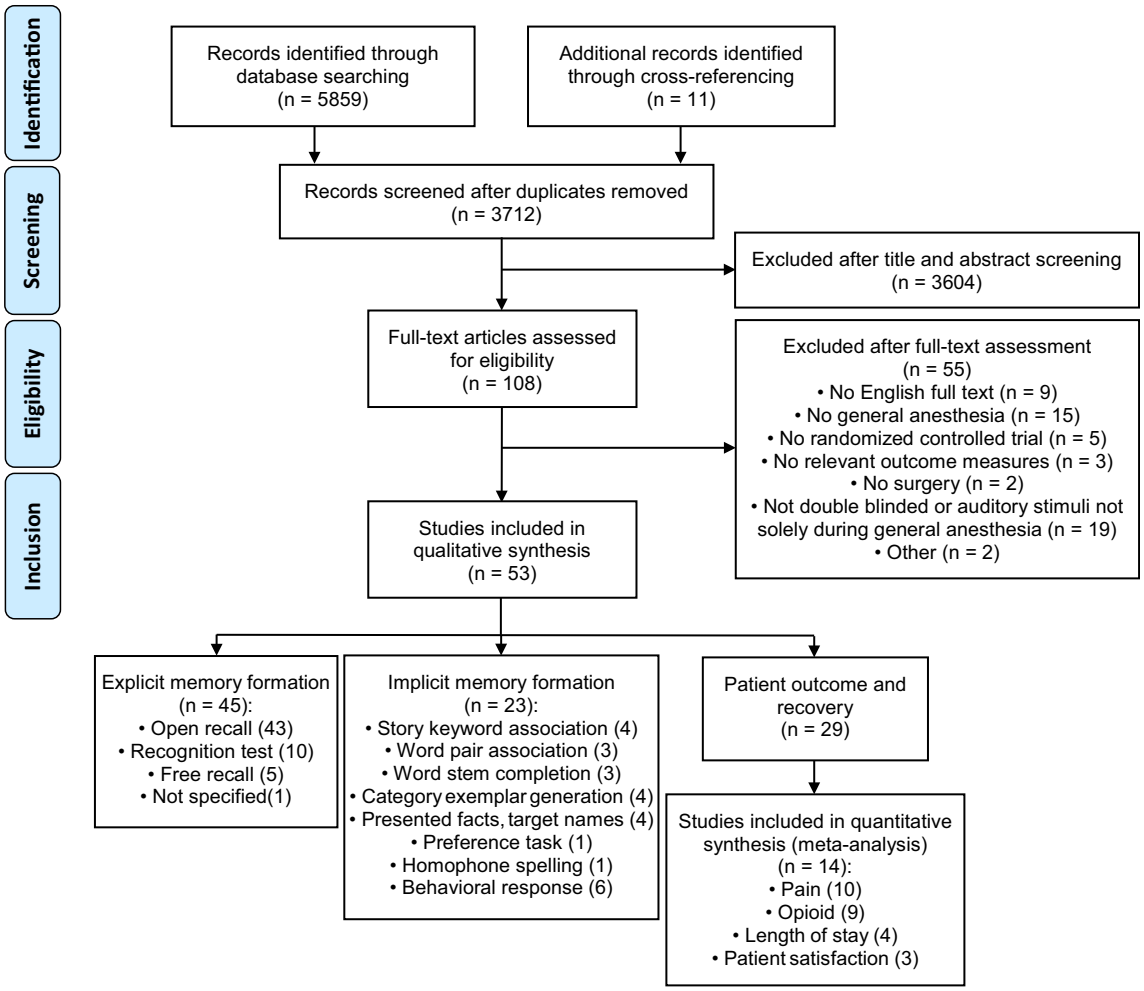


Fig. 1 PRISMA flow diagram. Two studies evaluated both patient outcome and recovery, as well as memory formation and behavioural change. n = number of studies.

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.[20] 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.[21,22] Nine of the 15 patients (60%) reported being aware of music being played during their total knee arthroplasty.[23]

The recognition test, in which patients are asked whether or not they recognized the auditory stimuli that was played intraoperatively,[24] was used in ten studies (798

TABLE 1 Overview of included studies

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Aceto *et al.* 2003[38]	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)
			Isoflurane and air (FiO_2 40%)	10	Isoflurane and 60%N_2O in 40%O_2	10	Implicit memory (story-related free association)
							Mid-latency auditory evoked potential relationship with memory formation
Aceto *et al.* 2013[36]	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[37]	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[35]	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 *et al.* 2009[28]	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 *et al.* 1985[46]	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[82]	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[83]	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 *et al.* 1993[44]	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)
					Headphones without words	15	Implicit memory (category exemplar generation task)
Bonke *et al.* 1986†[66]	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)
					Earphones with operation room sound	30	Patient outcome (pain, opioids, PONV, length of stay)

TABLE 1 continued

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Caseley-Rondi *et al.* 1994[25]	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†[59]	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[39]	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 *et al.* 2005[26]	Day care orthopedic surgery	Four 28-word list 14-min tapes played continuously	Propofol and N_2O anesthesia with 1.5mg/kg fentanyl induction	32	Propofol and N_2O 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[40]	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†[60]	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†[50]	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[21]	Elective general, gynecological, orthopedic, and plastic surgery	Repetitive story-keyword 30-min tape repeated four times	Opioid 7.5 $\mu g \cdot kg^{-1}$ fentanyl bolus	100	N_2O-opioid infusion 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ alfentanil	40	Explicit memory (open-recall, recognition test) Implicit memory (story-related free association)
			Isoflurane 0.3% - fentanyl 1 $\mu g \cdot kg^{-1}$	16	Isoflurane 0.7% - fentanyl 1 $\mu g \cdot kg^{-1}$	24	Mid-latency auditory evoked potential relationship with memory formation
Hughes *et al.* 1994[48]	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)

TABLE 1 continued

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Ikedo *et al.* 2007[69]	Coronary artery bypass graft and/or open valve heart surgery	Prayer or hemisync played continuously	Generic prayer Hemisync	24 27	Headphones with blank compact disc	27	Patient outcome (opioids, postoperative complications, length of stay)
Jansen *et al.* 1991[47]	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 *et al.* 2006[62]	Laparoscopic cholecystectomy	Positive therapeutic suggestions and calming music played continuously	Music Music with positive therapeutic suggestions	24 27	Routine operating room sounds	34	Explicit memory (open-recall) Patient outcome (pain, PONV, subjective well-being)
Jelicic *et al.* 1992[41]	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)
Jelicic *et al.* 1993[42]	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 *et al.* 2017†[51]	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 *et al.* 2001[45]	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 *et al.* 2009[22]	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 *et al.* 1999[84]	General, non-cancer surgery	Classical music or hemisync played continuously	Adagio Karajan Hemisync	25 25	Headphones with blank tape	16	Patient outcome (intraoperative fentanyl requirement)
Lebovits *et al.* 1999[63]	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)
Lequeux *et al.* 2014[29]	Unspecified ASA I–II surgery patients	Two 20-word lists with one played continuously	High-opioid remifentanil Low-opioid remifentanil	39 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

TABLE 1 continued

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Lewis *et al.* 2004[85]	Laparoscopic bariatric or lumbar disk surgery	Hemisync played continuously	Hemisync	30	Headphones with blank tape	30	Patient outcome (intraoperative fentanyl requirement)
Liu *et al.* 1992†[52]	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)
					Headphones with blank tape	24	Patient outcome (pain, analgesic requirement, PONV, length of stay)
Maroof *et al.* 1997[64]	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, antiemetics)
McLintock *et al.* 1990†[53]	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 *et al.* 1996[32]	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 behavioural response)
							Patient outcome (pain, length of stay)
Migneault *et al.* 2004†[61]	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[30]	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 *et al.* 1996[49]	Elective or semi-elective surgery	Behavioural 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 behavioural response)
Nilsson *et al.* 2001†[54]	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)
			Positive therapeutic suggestions with music	31			Patient outcome (pain, opioids, PONV, length of stay, subjective well-being)
Nilsson *et al.* 2003†[55]	Day care 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 *et al.* 2005†[56]	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)

TABLE 1 continued

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Oddby-Muhrbeck *et al.* 1995† [67]	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[31]	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[86]	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[27]	Gynecological minor surgery	Positive suggestions and 8-word list played once before surgical stimuli start	Sevoflurane 1.2% Sevoflurane 1.5%	15 16	Sevoflurane 2.0%	16	Explicit memory (open-recall, recognition test) Implicit memory (postoperative behavioural response)
Reza *et al.* 2007†[57]	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[33]	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†[23]	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†[58]	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[86]	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[34]	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[65]	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)

TABLE 1 continued

Study	Surgical procedure	Auditory intervention	Group 1	N_1	Group 2	N_2	Outcome parameters
Zhang 2005†[68]	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; F_iO_2 = 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; O_2 = oxygen; OR = operating room; PACU = postoperative anesthesia care unit; PONV = postoperative nausea and vomiting.

patients). In four studies,[22,25-27] 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,[22] 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.[28-32]

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.[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 hr 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 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.[21,36-38] 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.[33-35] 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.*,[34] who used a comparable anesthesia maintenance regimen in elective surgical patients, and Russel and Wang,[33] 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.[26,28,29] Only Deeprose *et al.*[26] 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 to intraoperatively presented statements and fictitious names.[43] Jelicic *et al.* (1992)[41] 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),[44] as well as the

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 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.

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,[33,34,44,45] nor using the preference task,[25] evaluating preference of intraoperatively presented melodies.[24]

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,[46,47] as did two studies that evaluated smoking cessation after intraoperatively played taped instructions.[48,49] 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.[27,32]

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.[23,50-58] 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

TABLE 3 Explicit and implicit memory assessment

Study	Intervention	ANA	Explicit recall	Implicit memory formation	Time	Comments
Aceto *et al.* 2003††[38]	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.* 2013††[36]	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.* 2015††[37]	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.* 1998††[35]	Repetitive word list	Balanced	Open-recall test (0%) Recognition test (NS)	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.* 2009[28]	Repetitive word list	TIVA	Open-recall test (0%) Free 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.* 1985††[46]	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.* 1988[83]	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.* 1993[44]	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.* 1986[66]	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	POD 6 or 7	No explicit memory formation
Caseley-Rondi *et al.* 1994†[25]	Personalized positive suggestions with music	Balanced	Open-recall test (0%) Recognition test (above chance recognition)	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 ak,* 2001[59]	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	POD 5	No explicit memory formation
De Roode *et al.* 1995[39]	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 *et al.* 2005† ††[26]	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)	1.5 h	Slightly higher mean implicit memory formation score for no fentanyl group, but not statistically significant

TABLE 3 continued

Study	Intervention	ANA	Explicit recall	Implicit memory formation	Time	Comments
Donker *et al.* 1996[40]	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[60]	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	24 hr	No explicit memory formation
Evans and Richardson 1988[50]	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† ††[21]	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)	POD 1 or POD 3-4	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 *et al.* 1994††[48]	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[47]	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[62]	Music and positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	End	No explicit memory formation
Jelicic *et al.* 1992††[41]	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[42]	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 N_2O-opioid anesthesia in 1992 study
Kahloul *et al.* 2017[51]	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[45]	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 *et al.* 2009†[22]	15-word list	Balanced	Open-recall test (3/109; 2.3%) Recognition test (above chance recognition in BIS-guided group)	Not assessed	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.

TABLE 3 continued

Study	Intervention	ANA	Explicit recall	Implicit memory formation	Time	Comments
Lebovits *et al.* 1999[63]	Positive therapeutic suggestions, story	TIVA	Open-recall test (0%)	Not assessed	End, 6hr, 24 hr	No explicit memory formation
Lequeux *et al.* 2014[29]	2- word list	TIVA	Open-recall test (0%) Free-recall test (NS) Recognition test (NS)	Word-stem completion test (no evidence of implicit memory formation)	2-3 hr	No implicit memory formation during BIS-guided propofol-remifentanil anesthesia with low remifentanil doses
Liu *et al.* 1992[52]	Positive therapeutic suggestions, story	Balanced	Open-recall test (0%)	Not assessed	POD 1	No explicit memory formation
Maroof *et al.* 1997[64]	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	24 hr	No explicit memory formation
McLintock *et al.* 1990[53]	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	24 hr	No explicit memory formation
Melzack *et al.* 1996[32]	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[61]	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[30]	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[49]	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[54]	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[55]	Instrumental new-age synthesizer music	Balanced	Open-recall test (0%)	Not assessed	PACU release	No explicit memory formation
Oddby-Muhrbeck *et al.* 1995[67]	Positive therapeutic suggestions interspersed with soft music	Balanced	Open-recall test (0%)	Not assessed	24 hr	No explicit memory formation
Parker *et al.* 1994[31]	10-word list	Balanced	Free-recall test (0%) Recognition test (NS)	Not assessed	POD 1	Almost all patients attributed the recognition test as guesswork
Kalyani *et al.* 2015[86]	Classical instrumental music	Balanced	Open-recall test (0%)	Not assessed	24 hr	No explicit memory formation

TABLE 3 continued

Study	Intervention	ANA	Explicit recall	Implicit memory formation	Time	Comments
Renna *et al.* 2000†[27]	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 behavioural response (no difference in subjective assessment postoperatively)	2–3 hr	Recognition test was classified as an implicit memory formation assessment instead of an explicit recall test
Russel and Wang 2001[33]	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 2 hr	Only one word pair was correctly chosen repeatedly during the word pair association test, but not significantly different in both groups
Simcock *et al.* 2008[23]	Choice of 3 music compact discs	TIVA	Open-recall test (60%)	Not assessed	24 hr	60% patients reported correctly that they were exposed to music
Tsuchiya *et al.* 2003[87]	Natural environmental sounds (ripple, stream, wind, and twitter)	TIVA	Open-recall test (0%)	Not assessed	24 hr	No explicit memory formation
Westmoreland *et al.* 1993[34]	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)	2 h and 48 hr	No implicit memory formation, therefore unclear whether premedication midazolam influences memory formation
Williams *et al.* 1994[65]	Positive therapeutic suggestions	Balanced	Open-recall test (0%)	Not assessed	24 hr	No explicit memory formation
Zhang *et al.* 2005[68]	Participant-selected music	Balanced	Open-recall test (0%)	Not assessed	24 hr	No explicit memory formation

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 behavioural 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; HP = hemodynamic parameters; IMM = inhalational induction and maintenance anesthesia; 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.

hr after surgery (pooled SMD, -0.84; 95% CI, -1.1 to -0.57; $P < 0.001$; $I^2 = 0$; $n = 226$ patients in three studies). Intraoperative positive therapeutic suggestions did not reduce postoperative pain (pooled SMD, 0.03; 95% CI, -0.34 to 0.40; $P = 0.86$; $I^2 = 43$; $n = 202$ 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; $P = 0.04$; $I^2 = 36$; $n = 336$ patients in five studies), whereas positive therapeutic suggestions did not (pooled SMD, -0.12; 95% CI, -0.40 to 0.16; $P = 0.41$; $I^2 = 39$; $n = 372$ 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

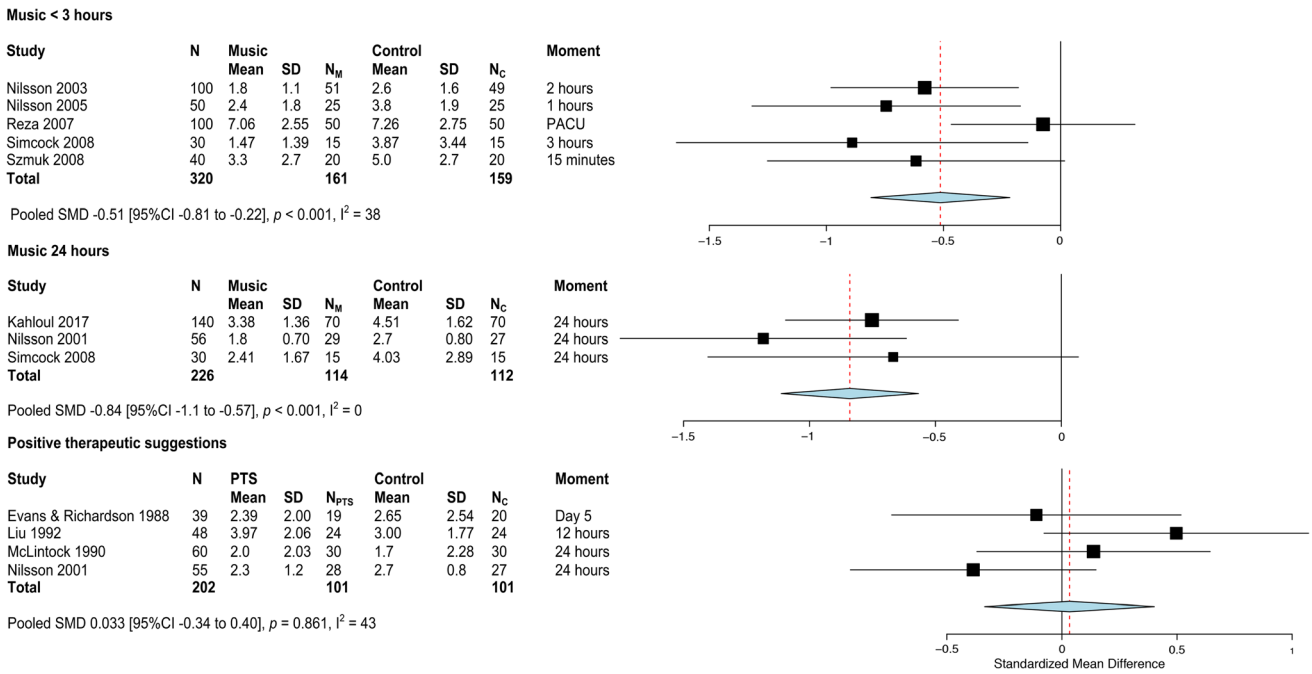


Fig. 2 Effects of music and positive therapeutic suggestions on pain. Forest plot presenting the effect of intraoperative music and positive therapeutic suggestions on postoperative pain. CI = confidence interval; Moment = moment of measurement; *n* = total number of patients per study; N_C = number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

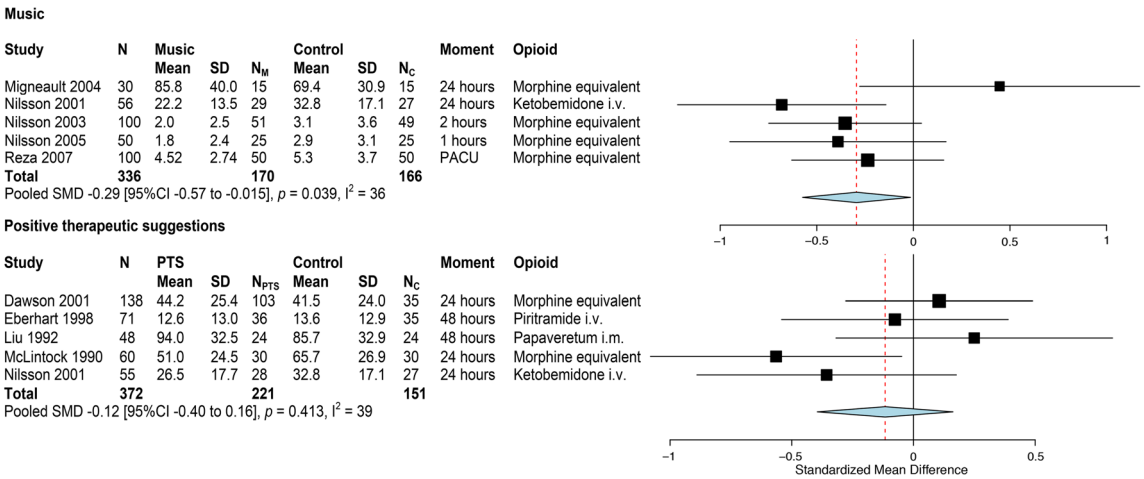


Fig. 3 Effects of music and positive therapeutic suggestions on opioid requirements. Forest plot presenting the effect of intraoperative music and positive therapeutic suggestions on postoperative opioid requirements (milligrams of morphine equivalents). CI = confidence interval; i.m. = intramuscular; 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 = postanesthesia care unit; PTS = positive therapeutic suggestions; SD = standard deviation; SMD = standardized mean difference.

therapeutic suggestions.[60,64,65] 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.[50,52,59,60,66,67] 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; $P = 0.52$; $I^2 = 73$; $n =$ 286 patients in four studies) or postoperative anesthesia care unit stay (pooled SMD, -0.09; 95% CI, -0.42 to 0.24; $P = 0.58$; $I^2 = 0$; $n = 141$ 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 SMD, 0.63; 95% CI, -0.98 to 2.24; $P = 0.44$; $I^2 =$ 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

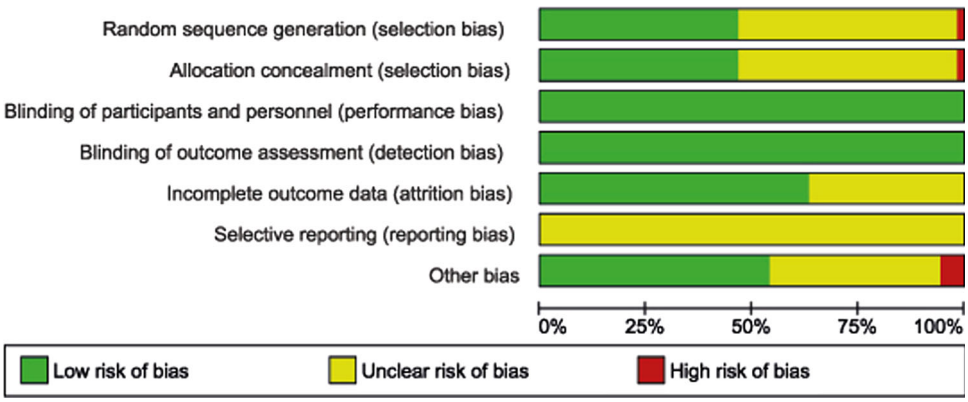
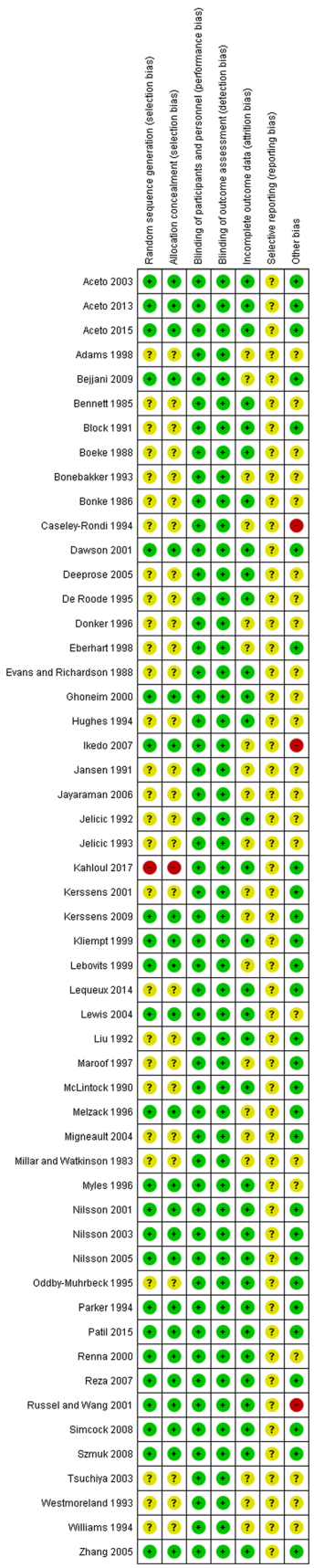


Fig. 4 Risk of bias graph.



◀**Fig. 5** Risk of bias summary.

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 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.[26,36,37] 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.[76,77] The underlying mechanism could involve an attenuating effect on the physiologic 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 be because different brain regions are active during music *vs* 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 with 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 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.[15,36,80] In contrast to previous meta-analyses,[9,10] 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 ($I^2 < 40\%$).[18] 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 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 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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References

1. *Sandin RH*, *Enlund G*, *Samuelsson P*, *Lennmarken C*. Awareness during anaesthesia: a prospective case study. Lancet 2000; 355: 707-11.
2. *Mashour GA*, *Shanks A*, *Tremper KK*, *et al*. Prevention of intraoperative awareness with explicit recall in an unselected surgical population: a randomized comparative effectiveness trial. Anesthesiology 2012; 117: 717-25.
3. *Errando CL*, *Aldecoa C*. Awareness with explicit recall during general anaesthesia: current status and issues. Br J Anaesth 2014; 112: 1-4.
4. *Gross WL*, *Lauer KK*, *Liu X*, *et al*. Propofol sedation alters perceptual and cognitive functions in healthy volunteers as revealed by functional magnetic resonance imaging. Anesthesiology 2019; 131: 254-65.
5. *Dueck MH*, *Petzke F*, *Gerbershagen HJ*, *et al*. Propofol attenuates responses of the auditory cortex to acoustic stimulation in a dose-dependent manner: a FMRI study. Acta Anaesthesiol Scand 2005; 49: 784-91.
6. *Weingarten E*, *Chen Q*, *McAdams M*, *Yi J*, *Hepler J*, *Albarracín D*. From primed concepts to action: a meta-analysis of the behavioral effects of incidentally presented words. Psychol Bull 2016; 142: 472-97.
7. *Andrade J*. Learning during anaesthesia: a review. Br J Psychol 1995; 86(Pt 4): 479-506.
8. *Ghoneim MM*, *Block RI*. Learning and memory during general anesthesia: an update. Anesthesiology 1997; 87: 387-410.
9. *Kühlmann AY*, *de Rooij A*, *Kroese LF*, *van Dijk M*, *Hunink MG*, *Jeekel J*. Meta-analysis evaluating music interventions for anxiety and pain in surgery. Br J Surg 2018; 105: 773-83.
10. *Fu VX*, *Oomens P*, *Klimek M*, *Verhofstad MH*, *Jeekel J*. The effect of perioperative music on medication requirement and hospital length of stay: a meta-analysis. Ann Surg 2020; 272: 961-72.
11. *Fu VX*, *Oomens P*, *Sneiders D*, *et al*. The effect of perioperative music on the stress response to surgery: a meta-analysis. J Surg Res 2019; 244: 444-55.
12. *Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; DOI: 10.1371/journal.pmed.1000097.
13. *Bramer WM*, *Rethlefsen ML*, *Mast F*, *Kleijnen J*. Evaluation of a new method for librarian-mediated literature searches for systematic reviews. Res Synth Methods 2018; 9: 510-20.
14. *Andrade J*. Does memory priming during anesthesia matter? Anesthesiology 2005; 103: 919-20.
15. *Deeprose C*, *Andrade J*, *Varma S*, *Edwards N*. Unconscious learning during surgery with propofol anaesthesia. Br J Anaesth 2004; 92: 171-7.
16. *Prytherch DR, Whiteley MS, Higgins B, Weaver PC, Prout WG, Powell SJ.* POSSUM and Portsmouth POSSUM for predicting mortality. Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. Br J Surg 1998; 85: 1217-20.
17. *Higgins JP*, *Altman DG*, *Gotzsche PC*, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011. DOI: https://doi.org/10.1136/bmj.d5928.
18. *Higgins JP, Green S.* Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011. Available from URL: https://handbook-5-1.cochrane.org/ (accessed March 2021).
19. *Wallace BC*, *Dahabreh IJ*, *Trikalinos TA*, *Lau J*, *Trow P*, *Schmid CH*. Closing the gap between methodologists and end-users: R as a computational back-end. J Stat Softw 2012. DOI: https://doi.org/10.18637/jss.v049.i05.
20. *Brice DD*, *Hetherington RR*, *Utting JE*. A simple study of awareness and dreaming during anaesthesia. Br J Anaesth 1970; 42: 535-42.
21. *Ghoneim MM*, *Block RI*, *Dhanaraj VJ*, *Todd MM*, *Choi WW*, *Brown CK*. Auditory evoked responses and learning and awareness during general anesthesia. Acta Anaesthesiol Scand 2000; 44: 133-43.
22. *Kerssens C*, *Gaither JR*, *Sebel PS*. Preserved memory function during bispectral index-guided anesthesia with sevoflurane for major orthopedic surgery. Anesthesiology 2009; 111: 518-24.
23. *Simcock XC*, *Yoon RS*, *Chalmers P*, *Geller JA*, *Kiernan HA*, *Macaulay W*. Intraoperative music reduces perceived pain after total knee arthroplasty: a blinded, prospective, randomized, placebo-controlled clinical trial. J Knee Surg 2008; 21: 275-8.
24. *Peretz I*, *Gaudreau D*, *Bonnel AM*. Exposure effects on music preference and recognition. Mem Cognit 1998; 26: 884-902.
25. *Caseley-Rondi G*, *Merikle PM*, *Bowers KS*. Unconscious cognition in the context of general anesthesia. Conscious Cogn 1994; 3: 166-95.
26. *Deeprose C*, *Andrade J*, *Harrison D*, *Edwards N*. Unconscious auditory priming during surgery with propofol and nitrous oxide anaesthesia: a replication. Br J Anaesth 2005; 94: 57-62.
27. *Renna M*, *Lang EM*, *Lockwood GG*. The effect of sevoflurane on implicit memory: a double-blind, randomised study. Anaesthesia 2000; 55: 634-40.
28. *Bejjani G*, *Lequeux PY*, *Schmartz D*, *Engelman E*, *Barvais L*. No evidence of memory processing during propofol-remifentanil target-controlled infusion anesthesia with bispectral index monitoring in cardiac surgery. J Cardiothorac Vasc Anesth 2009; 23: 175-81.
29. *Lequeux PY*, *Hecquet F*, *Bredas P*. Does anesthetic regimen influence implicit memory during general anesthesia? Anesth Analg 2014; 119: 1174-9.
30. *Millar K*, *Watkinson N*. Recognition of words presented during general anaesthesia. Ergonomics 1983; 26: 585-94.
31. *Parker CJ*, *Oates JD*, *Boyd AH*, *Thomas SD*. Memory for auditory material presented during anaesthesia. Br J Anaesth 1994; 72: 181-4.
32. *Melzack R*, *Germain M*, *Belanger E*, *Fuchs PN*, *Swick R*. Positive intrasurgical suggestion fails to affect postsurgical pain. J Pain Symptom Manage 1996; 11: 103-7.
33. *Russell IF*, *Wang M*. Absence of memory for intra-operative information during surgery with total intravenous anaesthesia. Br J Anaesth 2001; 86: 196-202.
34. *Westmoreland CL*, *Sebel PS*, *Winograd E*, *Goldman WP*. Indirect memory during anesthesia. The effect of midazolam. Anesthesiology 1993; 78: 237-41.

35. *Adams DC, Hilton HJ, Madigan JD, et al.* Evidence for unconscious memory processing during elective cardiac surgery. Circulation 1998; 98(19 Suppl): II289-92.
36. *Aceto P*, *Lai C*, *Perilli V*, *et al*. Stress-related biomarkers of dream recall and implicit memory under anaesthesia. Anaesthesia 2013; 68: 1141-7.
37. *Aceto P*, *Perilli V*, *Lai C*, *et al*. Minimum alveolar concentration threshold of sevoflurane for postoperative dream recall. Minerva Anestesiol 2015; 81: 1201-9.
38. *Aceto P*, *Valente A*, *Gorgoglione M*, *Adducci E*, *De Cosmo G*. Relationship between awareness and middle latency auditory evoked responses during surgical anaesthesia. Br J Anaesth 2003; 90: 630-5.
39. *De Roode A*, *Jelicic M*, *Bonke B*, *Bovill JG*. The effect of midazolam premedication on implicit memory activation during alfentanil-nitrous oxide anaesthesia. Anaesthesia 1995; 50: 191-4.
40. *Donker AG*, *Phaf RH*, *Porcelijn T*, *Bonke B*. Processing familiar and unfamiliar auditory stimuli during general anesthesia. Anesth Analg 1996; 82: 452-5.
41. *Jelicic M*, *De Roode A*, *Bovill JG*, *Bonke B*. Unconscious learning during anaesthesia. Anaesthesia 1992; 47: 835-7.
42. *Jelicic M*, *Asbury AJ*, *Millar K*, *Bonke B*. Implicit learning during enflurane anaesthesia in spontaneously breathing patients? Anaesthesia 1993; 48: 766-8.
43. *Jacoby LL*, *Woloshyn VE*, *Kelley C*. Becoming famous without being recognized: unconscious influences of memory produced by dividing attention. J Exp Psychol Gen 1989; 118: 115-25.
44. *Bonebakker AE*, *Bonke B*, *Klein J*, *Wolters G*, *Hop WC*. Implicit memory during balanced anaesthesia. Lack of evidence. Anaesthesia 1993; 48: 657-60.
45. *Kerssens C*, *Klein J*, *Van Der Woerd A*, *Bonke B*. Auditory information processing during adequate propofol anesthesia monitored by electroencephalogram bispectral index. Anesth Analg 2001; 92: 1210-4.
46. *Bennett HL*, *Davis HS*, *Giannini JA*. Non-verbal response to intraoperative conversation. Br J Anaesth 1985; 57: 174-9.
47. *Jansen CK*, *Bonke B*, *Klein J*, *Van Dasselaar N*, *Hop WC*. Failure to demonstrate unconscious perception during balanced anaesthesia by postoperative motor response. Acta Anaesthesiol Scand 1991; 35: 407-10.
48. *Hughes JA, Sanders LD, Dunne JA, Tarpey J, Vickers MD.* Reducing smoking. The effect of suggestion during general anaesthesia on postoperative smoking habits. Anaesthesia 1994; 49: 126-8.
49. *Myles PS*, *Hendrata M*, *Layher Y*, *et al*. Double-blind, randomized trial of cessation of smoking after audiotape suggestion during anaesthesia. Br J Anaesth 1996; 76: 694-8.
50. *Evans C*, *Richardson PH*. Improved recovery and reduced postoperative stay after therapeutic suggestions during general anaesthesia. Lancet 1988; 2: 491-3.
51. *Kahloul M*, *Mhamdi S*, *Nakhli MS*, *et al*. Effects of music therapy under general anesthesia in patients undergoing abdominal surgery. Libyan J Med 2017. DOI: https://doi.org/10.1080/19932820.2017.1260886.
52. *Liu WH*, *Standen PJ*, *Aitkenhead AR*. Therapeutic suggestions during general anaesthesia in patients undergoing hysterectomy. Br J Anaesth 1992; 68: 277-81.
53. *McLintock TT*, *Aitken H*, *Downie CF*, *Kenny GN*. Postoperative analgesic requirements in patients exposed to positive intraoperative suggestions. BMJ 1990; 301: 788-90.
54. *Nilsson U*, *Rawal N*, *Uneståhl LE*, *Zetterberg C*, *Unosson M*. Improved recovery after music and therapeutic suggestions during general anaesthesia: a double-blind randomised controlled trial. Acta Anaesthesiol Scand 2001; 45: 812-7.
55. *Nilsson U*, *Rawal N*, *Unosson M*. A comparison of intra-operative or postoperative exposure to music - a controlled trial of the effects on postoperative pain. Anaesthesia 2003; 58: 699-703.
56. *Nilsson U*, *Unosson M*, *Rawal N*. Stress reduction and analgesia in patients exposed to calming music postoperatively: a randomized controlled trial. Eur J Anaesthesiol 2005; 22: 96-102.
57. *Reza N*, *Ali SM*, *Saeed K*, *Abul-Qasim A*, *Reza TH*. The impact of music on postoperative pain and anxiety following cesarean section. Middle East J Anaesthesiol 2007; 19: 573-86.
58. *Szmuk P*, *Aroyo N*, *Ezri T*, *Muzikant G*, *Weisenberg M*, *Sessler DI*. Listening to music during anesthesia does not reduce the sevoflurane concentration needed to maintain a constant bispectral index. Anesth Analg 2008; 107: 77-80.
59. *Dawson P*, *Van Hamel C*, *Wilkinson D*, *Warwick P*, *O'Connor M*. Patient-controlled analgesia and intra-operative suggestion. Anaesthesia 2001; 56: 65-9.
60. *Eberhart LH*, *Döring HJ*, *Holzrichter P*, *Roscher R*, *Seeling W*. Therapeutic suggestions given during neurolept-anaesthesia decrease post-operative nausea and vomiting. Eur J Anaesthesiol 1998; 15: 446-52.
61. *Migneault B*, *Girard F*, *Albert C*, *et al*. The effect of music on the neurohormonal stress response to surgery under general anesthesia. Anesth Analg 2004; 98: 527-32.
62. *Jayaraman L*, *Sharma S*, *Sethi N*, *Sood J*, *Kumra V*. Does intraoperative music therapy or positive therapeutic suggestions during general anaesthesia affect the postoperative outcome ? - A double blind randomised controlled trial. Indian J Anaesth 2006; 50: 258-61.
63. *Lebovits AH*, *Twersky R*, *McEwan B*. Intraoperative therapeutic suggestions in day-case surgery: are there benefits for postoperative outcome? Br J Anaesth 1999; 82: 861-6.
64. *Maroof M*, *Ahmed SM*, *Khan RM*, *Bano SJ*, *Haque AW*. Intra-operative suggestions reduce incidence of post hysterectomy emesis. J Pak Med Assoc 1997; 47: 202-4.
65. *Williams AR*, *Hind M*, *Sweeney BP*, *Fisher R*. The incidence and severity of postoperative nausea and vomiting in patients exposed to positive intra-operative suggestions. Anaesthesia 1994; 49: 340-2.
66. *Bonke B, Schmitz PIM Verhage F, Zwaveling A.* Clinical study of so-called unconscious perception during general anaesthesia. Br J Anaesth 1986; 58: 957-64.
67. *Oddby-Muhrbeck E*, *Jakobsson J*, *Enquist B*. Implicit processing and therapeutic suggestion during balanced anaesthesia. Acta Anaesthesiol Scand 1995; 39: 333-7.
68. *Zhang XW*, *Fan Y*, *Manyande A*, *Tian YK*, *Yin P*. Effects of music on target-controlled infusion of propofol requirements during combined spinal-epidural anaesthesia. Anaesthesia 2005; 60: 990-4.
69. *Ikedo F*, *Gangahar DM*, *Quader MA*, *Smith LM*. The effects of prayer, relaxation technique during general anesthesia on recovery outcomes following cardiac surgery. Complement Ther Clin Pract 2007; 13: 85-94.
70. *Mashour GA*, *Avidan MS*. Intraoperative awareness: controversies and non-controversies. Br J Anaesth 2015; 115(Suppl 1): i20-6.
71. *de Quervain DJ*, *Aerni A*, *Schelling G*, *Roozendaal B*. Glucocorticoids and the regulation of memory in health and disease. Front Neuroendocrinol 2009; 30: 358-70.
72. *Lewis SR*, *Pritchard MW*, *Fawcett LJ*, *Punjasawadwong Y*. Bispectral index for improving intraoperative awareness and early postoperative recovery in adults. Cochrane Database Syst Rev 2019. DOI: https://doi.org/10.1002/14651858.CD003843.pub4.
73. *O'Boyle CA*. Benzodiazepine-induced amnesia and anaesthetic practice: a review. Psychopharmacol Ser 1988; 6: 146-65.
74. *Ghoneim MM*, *Mewaldt SP*. Benzodiazepines and human memory: a review. Anesthesiology 1990; 72: 926-38.

75. *Hirshman E*, *Passannante A*, *Henzler A*. The effect of midazolam on implicit memory tests. Brain Cogn 1999; 41: 351-64.
76. *Svensson I*, *Sjostrom B*, *Haljamae H*. Assessment of pain experiences after elective surgery. J Pain Symptom Manage 2000; 20: 193-201.
77. *Mwaka G*, *Thikra S*, *Mung'ayi V*. The prevalence of postoperative pain in the first 48 hours following day surgery at a tertiary hospital in Nairobi. Afr Health Sci 2013; 13: 768-76.
78. *Schirmer A*, *Fox PM*, *Grandjean D*. On the spatial organization of sound processing in the human temporal lobe: a meta-analysis. Neuroimage 2012; 63: 137-47.
79. *Whitehead JC*, *Armony JL*. Singing in the brain: neural representation of music and voice as revealed by fMRI. Hum Brain Mapp 2018; 39: 4913-24.
80. *Bethune DW*, *Ghosh S*, *Gray B*, *et al*. Learning during general anaesthesia: implicit recall after methohexitone or propofol infusion. Br J Anaesth 1992; 69: 197-9.
81. *Brown SM*, *Sneyd JR*. Nitrous oxide in modern anaesthetic practice. BJA Educ 2015; 16: 87-91.
82. *Block RI*, *Ghoneim MM*, *Ping ST*, *Ali MA*. Efficacy of therapeutic suggestions for improved postoperative recovery presented during general anesthesia. Anesthesiology 1991; 75: 746-55.
83. *Boeke S*, *Bonke B*, *Bouwhuis-Hoogerwerf ML*, *Bovill JG*, *Zwaveling A*. Effects of sounds presented during general anaesthesia on postoperative course. Br J Anaesth 1988; 60: 697-702.
84. *Kliempt P*, *Ruta D*, *Ogston S*, *Landeck A*, *Martay K*. Hemispheric-synchronisation during anaesthesia: a double blind randomised trial using audiotapes for intra-operative nociception control. Anaesthesia 1999; 54: 769-73.
85. *Lewis AK*, *Osborn IP*, *Roth R*. The effect of hemispheric synchronization on intraoperative analgesia. Anesth Analg 2004; 98: 533-6.
86. *Kalyani NP*, *Poonam GG*, *Shalini KT*. Impact of intraoperative music therapy on the anesthetic requirement and stress response in laparoscopic surgeries under general anesthesia. Ain Shams J Anaesthesiol 2015; 8: 580-4.
87. *Tsuchiya M*, *Asada A*, *Ryo K*, *et al*. Relaxing intraoperative natural sound blunts haemodynamic change at the emergence from propofol general anaesthesia and increases the acceptability of anaesthesia to the patient. Acta Anaesthesiol Scand 2003; 47: 939-43.