



MUSIC AND MUSICALITY IN BRAIN SURGERY

THE EFFECT ON DELIRIUM AND LANGUAGE

PABLO RAMON KAPPEN

2012 *Litmus*

Music and Musicality in Brain Surgery

The effect on delirium and language

Pablo R. Kappen

Colofon

The research in this thesis was financially supported by Erasmus MRace Efficiency Grant (call 2019).

ISBN:978-94-6483-350-8

Lay-out and printing: Ridderprint, www.ridderprint.nl of Ridderprint, the Netherlands

Cover design: Anita van Kempen | www.lapempi.nl

© Pablo Ramon Kappen, 2023

All rights reserved. No parts of this publication may be reproduced, stored in retrieval system or transmitted in any form by any means, electronical, mechanical, photocopying, recording or otherwise without permission of the author or, when appropriate the scientific journal in which parts of this thesis have been published.

Music and Musicality in Brain Surgery

The effect on delirium and language

Muziek en muzikaliteit in hersenchirurgie

Het effect op delier en taal

Proefschrift

Ter verkrijging van de graad van doctor aan de Erasmus Universiteit te Rotterdam

op gezag van de rector magnificus

Prof. dr. A.L. Bredenoord

en volgens besluit van het college voor promoties.

De openbare verdediging zal plaatsvinden op

vrijdag 27 oktober

om 13.00 uur

Pablo Ramon Kappen

geboren te Nijmegen

Promotiecommissie

Promotoren: Prof. dr. C.M.F. Dirven
Prof. dr. A.J.P.E. Vincent

Other members: Prof. dr. B.L. van Leeuwen
Prof. dr. A. van der Zwan
Prof. dr. W.J.G. Hoogendijk

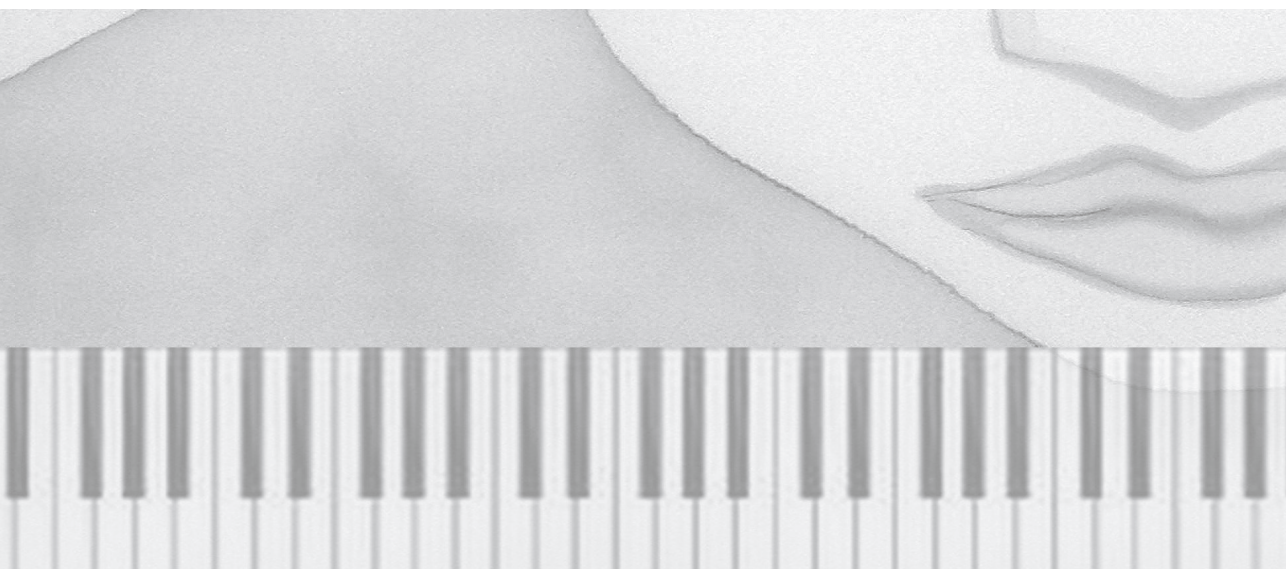
Copromotor: Prof. dr. J. Jeekel
Dr. M. Klimek

Paranimfen:

R. Brüning
C.S. Tabeling

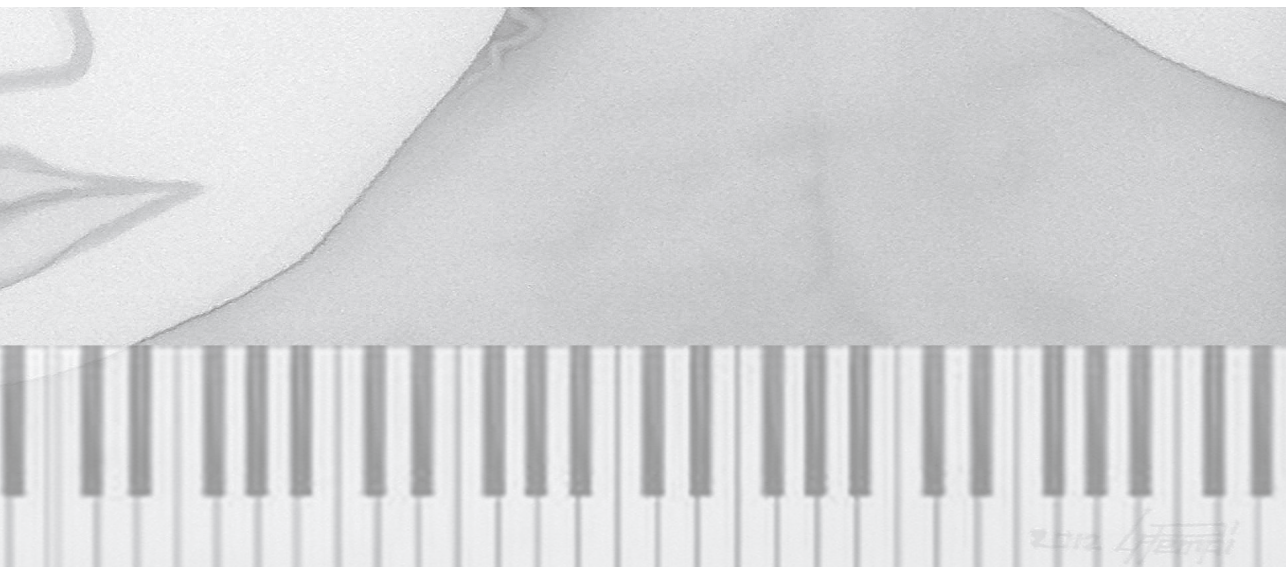
Table of Contents

Chapter 1	General Introduction	7
Part I	The effect of music on delirium after brain surgery	19
Chapter 2	Delirium in Neurosurgery: a systematic review and meta-analysis	21
Chapter 3	Post-operative delirium after Intracranial Surgery: a retrospective cohort study.	53
Chapter 4	The effect of Recorded music on pain ENDurance (CRESCENDO) trial: a randomized controlled trial	79
Chapter 5	Music to prevent deliriUm during neuroSurgerY (MUSYC) Clinical trial: a protocol paper for a randomized controlled trial	101
Chapter 6	Music to prevent deliriUm during neuroSurgerY (MUSYC) Clinical trial: a randomized controlled trial	123
Part II	Musicality and language in awake brain surgery	149
Chapter 7	The effect of musicality on language recovery after awake glioma surgery: a cohort study.	151
Chapter 8	The feasibility and added value of mapping music during awake craniotomy: a systematic review	179
Part III	General dicussion and summary	203
Chapter 9	General discussion	205
Chapter 10	Summary / Samenvatting	219
Appendices:		229
	Dankwoord	230
	PhD Portfolio	234
	List of Publications	235
	Curriculum Vitae	236



CHAPTER 1

General Introduction



Music in therapeutic healthcare: a historic perspective

Music is an universal form of communication and part of human nature. Important elements of music consist of melody, harmony and rhythm. Music may serve as a means of communication and is even used for therapeutic health care purposes. (1) The oldest musical instruments discovered so far are around 30,000–40,000 years old, but it is likely that the first *Homo sapiens* already made music. (2) Only humans learn to play musical instruments, and only humans play instruments cooperatively together in groups. It is assumed by some that human musical abilities played a role in the evolution of language, and that music-making behavior engaged and promoted evolutionarily important social functions. (3)

The history of music as medicine goes back cutting across time, languages, and cultures. Back in Biblical times, string instruments were applied to liberate kings from bad spirits. (4) Hippocrates (460-370 BC), the father of Greek medicine, was known to play music for his patients, while Aristotle described music as a force that purified the emotions. (1) Early documented cases of music in the context of surgery occurred in 1914 when Evan O’Neal Kane, a surgeon famous for conducting operations on himself such as the auto-appendectomy, published his report in *JAMA* on the use of the phonograph within the operating room as a means of calming and distracting his patients from the ‘horror of the surgery’. (5, 6)

The underlying beneficial mechanism of music is based on the decoding of acoustic information. Acoustic information is translated into neural activity in the cochlea, and transmitted towards the auditory brainstem through the 8th cranial nerve (i.e. the *nervus vestibulocochlearis*). Neural impulses are mainly sent towards the colliculus inferior, which is the principal midbrain nucleus of the auditory pathway, and involves the primary auditory cortex, which transforms acoustic features (such as frequency information) into percepts (such as pitch height). Parallel to this signaling, the mesolimbic dopaminergic system is activated which is active during reward. (7, 8) Besides giving rise to subjective reports of “thrills” and “chills”, the hypothalamic-pituitary-adrenal axis attenuates stress signals, mediated through the adrenal gland, and the inflammatory response. (8, 9)

Application of music in medicine has been increasingly described in scientific literature for a variety of indications either within or outside the field of surgery. Music in medicine is appealing, as it is pleasant for the patient and it is an easy

applicable intervention which can be applied effectively throughout the entire perioperative process. Several studies investigated the role of music, played through head phones, musical pillows, or background sound systems on patients' emotions and neurophysiology. (10, 11) Inspired by these studies, well-designed clinical randomized controlled trials in the surgical population have been published on the effects of music on patients in the surgical setting.

An emerging number of randomized controlled trials and meta-analyses show convincing evidence of music lowering pain, stress and anxiety in surgical patients. (12-20) These results have clinical implications. A recent published study found that the analgesic effect of perioperative music reduced opioid consumption up to 9.82mg ME and lowered the patients intraoperative propofol and midazolam requirement significantly. (15) As we are currently in an "opioid epidemic", with increased opioid-related deaths and a substantial financial burden, interest in these nonpharmacological interventions that can reduce both postoperative pain and opioid consumption is growing. (21) However, these clinical studies are characterized by a large variation in type of surgical procedures and patient characteristics which hinders a firm conclusion on the quantitative analgesic effect of peri-operative music. (16) Moreover, it is unclear whether this decrease in pain perception leads to a larger endurance of pain and through which underlying mechanisms this is achieved. We therefore evaluated the effect of music on pain endurance in an experimental randomized controlled trial.

Evolution of brain surgery

Trepanation, also referred to as craniotomy, is considered the oldest surgical procedure known to be practiced since the Stone Age. When it comes to the motivation behind the ancient practices of trepanation, there are more questions than answers: it seemed to vary from ritual / spiritual purposes or for medical indications. Inca doctors, dating back to A.D. 1000, appeared to be 'skilled' neurosurgeons applying trepanation to treat injuries suffered during combat. (22) But it was not until the late 19th century, that some general surgeons started to perform trepanations in order to try to alleviate high intracranial pressure caused by tumors, abscesses or bleeds. However, due to lack of physiological knowledge and means to control brain swelling, it lasted until the first half of the 20th century that brain surgery could be performed with acceptable mortality rates. Hereafter, a greater understanding of cerebral localization, antisepsis, anesthesia, hemostasis, and pre- and perioperative visualization led to an era of great

expansion in neurosurgical approaches. Large advancements have been made in the last five to six decades, referred to as modern neurosurgery with the development of tools such the operating microscope, pre-operative brain imaging, neuro-navigation and intra-operative monitoring of brain functions.

Nowadays neurosurgeons are able to treat a wide variety of diseases inferring on the brain by performing craniotomies and resecting, securing or correcting the pathological condition, such as tumors, hematomas, aneurysms and vascular anomalies. The goal of the surgeon is to limit or restore functional deterioration by removing space-occupying lesions, to reduce mass effect on the brain and to improve the patient's prognosis. Especially in neuro-oncological surgery, number and extent of surgical resections have increased due technical improvements of the last decades. (23) Limits of safe surgery, in other words maximal resection of the lesion without causing neurologic deficits, are being pushed further in recent years resulting in craniotomy being a safe, fast and routinely applied surgical procedure.

Music and delirium

Delirium is a relative frequently observed post-operative complication in neurosurgery. It is a psychiatric disorder affecting attention and cognition resulting in symptoms such as hallucinations, restlessness, somnolence or agitation. Delirium is often multifactorial in etiology and can be influenced by a number of predisposing (e.g. older age, cognitive impairment, multiple comorbidities) and precipitating factors (eg, anxiety, stress, pain, medications) factors. (24) Therefore, the treatment for delirium often relies on tackling these underlying eliciting factors.

Delirium most often occurs in the elderly when they are admitted to the hospital, undergo a surgical procedure or having an infection. However, after intracranial surgery the incidence of delirium seems to be higher than after general surgical procedures, its occurrence being reported in 4 to 44% of patients. This may be explained by the fact that in the pathophysiology of delirium neuro-inflammatory processes are thought to play a significant role, whereby intracranial surgery induces brain inflammation. Unfortunately, delirium in the neurosurgical population is under-investigated. One of the reasons being the lack of consensus on definition of delirium and therefore the challenge for an early and accurate diagnosis. Delirium is a severe disease since it not only causes a traumatic experience for the patient and his or her relatives and long-

term cognitive decline but also leads to prolonged length of stay in hospital, intensity of nursing hours, and increased number of re-operations. (25)

There is no good treatment for delirium. Results of pharmacologic treatments are inconsistent and often accompanied with unacceptable side effects. (26-28) Non-pharmacologic multi-component approaches for primary prevention, such as reorientation, early mobilization, hydration, nutrition and sleep strategies are effective but labor intensive. Therefore, streamlined implementation is not always feasible in the hospital setting. Although the use of volunteers or non-licensed professionals enhance feasibility of these approaches, in clinical practice they remain difficult to implement structurally. (29) Therefore the search of, easy to implement, preventive therapies of post-operative delirium in neurosurgical patients remains warranted.

Studies suggest a positive effect of music in preventing post-operative delirium. (30) However, whether this preventing effect can be achieved in patients undergoing brain surgery remains unclear. As peri-operative listening to recorded music has been proven to lower delirium-eliciting factors in the surgical population, especially anxiety, pain and stress, we evaluated the preventive effects of listening to music on delirium after brain surgery in a randomized controlled study.

Music and musicality and the relation with language function and recovery in neurosurgery.

One neurosurgical tool to preserve brain functions during neurosurgical procedures is the use of awake brain surgery during which brain functions are real time monitored. (31) Tumor may be extremely hard to discern from normal brain tissue during a neurosurgical procedure. During awake surgery, tumorous tissue can be identified from functional relevant brain tissue, by having the patient executing tasks and the surgeon electrically stimulating the presumed abnormal tissue. When functional tasks performed by the patient are not interrupted by the electrical stimulation this tissue maybe resected. This allows the surgeon to make an informed decision about which parts of the tumor should or should not be resected.

Despite these techniques, intraoperative mapping and language testing do not ensure complete maintenance of the patient's linguistic abilities. Patients' language processing brain maybe damaged, resulting in often temporary speech disorders also called aphasia. It is important to have an increased knowledge on factors contributing

to language recovery, as these can be used in clinical practice to inform the patients on their prognosis and could even aid in the final decision-making when considering to perform a surgical resection of a tumor in that specific area of the brain. Studies have shown that musical training positively affects the course of post-operative language recovery. (32) Both language and music require complex processing systems that share features, such as pitch, rhythm, timbre, and syntactic structure. (33) Recent fMRI data suggested that some brain regions that are associated with language functioning (e.g., Broca and Wernicke's areas) are also activated during music processing. (34-36) Furthermore, experimental evidence suggests that musical training can improve language function (in a so-called transfer of learning). (33) However, there is currently no evidence in the literature to support the hypothesis that training-related brain changes might also have a beneficial effect on language (-recovery) following neurosurgery. (37) In this thesis we therefore evaluate the effect of musicality on language recovery after awake glioma surgery.

Musicians occasionally have to undergo craniotomy, during which their musical ability is at stake. (38) Examples of famous musicians undergoing craniotomy are George Gershwin, famous for his work on *Rhapsody in Blue* who was operated on a glioblastoma multiforme, and Maurice Ravel a music composer of expressionism who underwent an exploratory craniotomy after a car accident. (38) But also less famous musical patients, in whom preservation of musical function was at stake, underwent craniotomies. (39, 40) Monitoring brain areas responsible for musicality by electrophysiological mapping during the awake surgical procedure, additional to speech/language and motor function, might be valuable when musicality determines quality of life. We therefore evaluated the feasibility and added value of mapping musicality during awake craniotomy.

Thesis outline

In **Chapter 1** we describe a short history of the therapeutic use of music, the appealing effect of this intervention, and hypothesize how music might aid in preventing delirium after brain surgery as it has been proven effective in lowering delirium-eliciting factors.

The first part of this thesis concerns the effect of music on delirium in brain surgery. Delirium is a complication which might affect recovery after brain surgery, hence we focus on delirium in **Chapter 2** by describing a systematic review which focuses on how

delirium is defined in the neurosurgical literature. Delirium is a neuropsychiatric clinical syndrome with overlapping symptoms with the neurologic primary disease, which is why delirium is such a difficult and under-exposed topic in neurosurgical literature. We therefore summarize and quantify the methods of diagnosis and discuss the factors contributing to delirium and the impact for the neurosurgical patients' recovery.

The review on delirium definition is followed by a large retrospective cohort study in **Chapter 3** in which we further evaluate the impact of delirium in our own center. It is not fully clear what the impact of delirium is on neurosurgical patients' recovery, as delirium is a temporary and often self-limiting complication. We therefore evaluate the influence of delirium on length of stay, discharge location and mortality. Moreover, it is important to be able to predict which patients develop delirium, as currently no effective treatment exists. We addressed this issue by identifying risk factors and building prediction models.

As listening to recorded music has been proven to lower delirium-eliciting factors in the surgical population, such as anxiety, pain and stress, we were interested in the size of analgesic effect and its underlying mechanism before applying this into our clinical setting. In **Chapter 4** we describe the results of an experimental randomized controlled trial in healthy volunteers, which was based on a unique pain model and discuss the clinical implications.

As our prior chapters increased our knowledge on the significance of delirium on the post-operative recovery after brain surgery and the possible beneficial effects of music, we decided to design a randomized controlled trial. In **Chapter 5** we describe the protocol for this randomized controlled trial. Besides the preventive effects on delirium, we also describe other secondary outcomes which substantiate the effect of music or which correlate with post-operative recovery, such as hospitalization length or discharge location.

The results of this randomized controlled trial are described in **Chapter 6**, in which we describe the results during hospitalization. We discuss the clinical implications for patient recovery and the further steps that should be taken.

In the second part of this thesis the focus shifts towards maintaining musicality and language functions around awake craniotomy. Intra-operative mapping of language does not ensure complete maintenance with often temporary deteriorating language

functions after tumor resection. Most patients recover to their baseline whereas others remain to suffer from aphasia affecting their quality of life. In **Chapter 7** we evaluate the effect of musicality on language recovery after awake glioma surgery in a cohort study. Moreover, occasionally musicians undergo awake craniotomy and musicality may determine their quality of life. Therefore, we evaluate in **Chapter 8** in a systematic review whether it is feasible and what the additional value is of mapping musicality during awake craniotomy.

The third part of this thesis concludes with **Chapter 9** which presents a general discussion and a vision for future research options. **Chapter 10** summarizes the main findings presented in this thesis in English and Dutch.

References

1. Babikian TR, ZL. Music as Medicine: A Review and Historical Perspective. *Alternative and Complementary Therapies*. 2013;19(5):251 - 4.
2. Conard NJ, Malina M, Munzel SC. New flutes document the earliest musical tradition in southwestern Germany. *Nature*. 2009;460(7256):737-40.
3. Cross I. MI. The evolution of music: Theories, definitions and nature of the evidence. *Communicative Musicality: Exploring the Basis of Human Companionship*. 2010;1(5).
4. Davison K. Historical aspects of mood disorders. *Psychiatry*. 2006;5(4):115-18.
5. Pankratz L. Do it yourself section: Surgery. *JAMA*. 1986;255-324.
6. Kane EO. Phonograph in Operating-Room. *JAMA*. 1914;62(23):1829.
7. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci*. 2001;21(16):RC159.
8. Goldstein A. Thrills in response to music and other stimuli. *Physiol Psychol* 1980;8 (1), 126–129.
9. Blood AJ, Zatorre RJ. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc Natl Acad Sci U S A*. 2001;98(20):11818-23.
10. Croom AM. Music, neuroscience, and the psychology of well-being: a precis. *Front Psychol*. 2012;2:393.
11. Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ. Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat Neurosci*. 2011;14(2):257-62.
12. Cerejeira J, Batista P, Nogueira V, Vaz-Serra A, Mukaetova-Ladinska EB. The stress response to surgery and postoperative delirium: evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased suppression of the GH/IGF-1 Axis. *J Geriatr Psychiatry Neurol*. 2013;26(3):185-94.
13. Clegg A YJ. Which medications to avoid in people at risk of delirium: a systematic review. 2011(40:23–29).
14. Fu VX, Oomens P, Sneiders D, van den Berg SAA, Feelders RA, Wijnhoven BPL, et al. The Effect of Perioperative Music on the Stress Response to Surgery: A Meta-analysis. *J Surg Res*. 2019;244:444-55.
15. Fu VX OP, Klimek M, Verhofstad MHJ, Jeekel J. The effect of perioperative music on medication requirement and hospital length of stay: a meta-analysis. *Annals of Surgery*. July 2019;272(6):961 - 72.
16. Kuhlmann AYR, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. Meta-analysis evaluating music interventions for anxiety and pain in surgery. *Br J Surg*. 2018;105(7):773-83.
17. Lee JH. The Effects of Music on Pain: A Meta-Analysis. *J Music Ther*. 2016;53(4):430-77.
18. Leung JM SL, Paul S. Does postoperative delirium limit the use of patient-controlled analgesia in older surgical patients? 111:625–631. 2009.
19. Schor JD, Levkoff SE, Lipsitz LA, Reilly CH, Cleary PD, Rowe JW, et al. Risk factors for delirium in hospitalized elderly. *JAMA*. 1992;267(6):827-31.

20. Hole J, Hirsch M, Ball E, Meads C. Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. *Lancet*. 2015;386(10004):1659-71.
21. Shah A, Hayes CJ, Martin BC. Factors Influencing Long-Term Opioid Use Among Opioid Naive Patients: An Examination of Initial Prescription Characteristics and Pain Etiologies. *J Pain*. 2017;18(11):1374-83.
22. Wickens AP. A History of the Brain: from Stone Age surgery to modern neuroscience. Psychology Press. 2014;1(1):404.
23. Chaichana KL, Quinones-Hinojosa A. The need to continually redefine the goals of surgery for glioblastoma. *Neuro Oncol*. 2014;16(4):611-2.
24. Oh ES, Fong TG, Hsieh TT, Inouye SK. Delirium in Older Persons: Advances in Diagnosis and Treatment. *JAMA*. 2017;318(12):1161-74.
25. Budėnas A, Tamašauskas Š, Šliaužys A, Navickaitė I, Sidaraitė M, Pranckevičienė A, et al. Incidence and clinical significance of postoperative delirium after brain tumor surgery. *Acta Neurochir*. 2018;160(12):2327-37.
26. Janssen TL, Alberts AR, Hooft L, Mattace-Raso F, Mosk CA, van der Laan L. Prevention of postoperative delirium in elderly patients planned for elective surgery: systematic review and meta-analysis. *Clin Interv Aging*. 2019;14:1095-117.
27. Liu Y, Li XJ, Liang Y, Kang Y. Pharmacological Prevention of Postoperative Delirium: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Evid Based Complement Alternat Med*. 2019;2019:960-71.
28. Vlisides P, Avidan M. Recent Advances in Preventing and Managing Postoperative Delirium. *F1000Res*. 2019;8:1 - 8.
29. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911-22.
30. Golubovic J, Neerland BE, Aune D, Baker FA. Music Interventions and Delirium in Adults: A Systematic Literature Review and Meta-Analysis. *Brain Sci*. 2022;12(5).
31. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N Engl J Med*. 2008;358(1):18-27.
32. Merrett DL, Peretz I, Wilson SJ. Moderating variables of music training-induced neuroplasticity: a review and discussion. *Front Psychol*. 2013;4:606.
33. Besson M, Schon, D.,. Comparison Between Language and Music. *Annals of the New York Academy of Sciences*. 2001;930(1):232-58.
34. Maess B, Koelsch S, Gunter TC, Friederici AD. Musical syntax is processed in Broca's area: an MEG study. *Nat Neurosci*. 2001;4(5):540-5.
35. Abrams DA, Bhatara A, Ryali S, Balaban E, Levitin DJ, Menon V. Decoding temporal structure in music and speech relies on shared brain resources but elicits different fine-scale spatial patterns. *Cereb Cortex*. 2011;21(7):1507-18.
36. Levitin DJ, Menon V. Musical structure is processed in "language" areas of the brain: a possible role for Brodmann Area 47 in temporal coherence. *Neuroimage*. 2003;20(4):2142-52.
37. Omigie D, Samson S. A protective effect of musical expertise on cognitive outcome following brain damage? *Neuropsychol Rev*. 2014;24(4):445-60.
38. Gasenzer ER, Kanat A, Neugebauer E. The Unforgettable Neurosurgical Operations of Musicians in the Last Century. *World Neurosurg*. 2017;101:444-50.

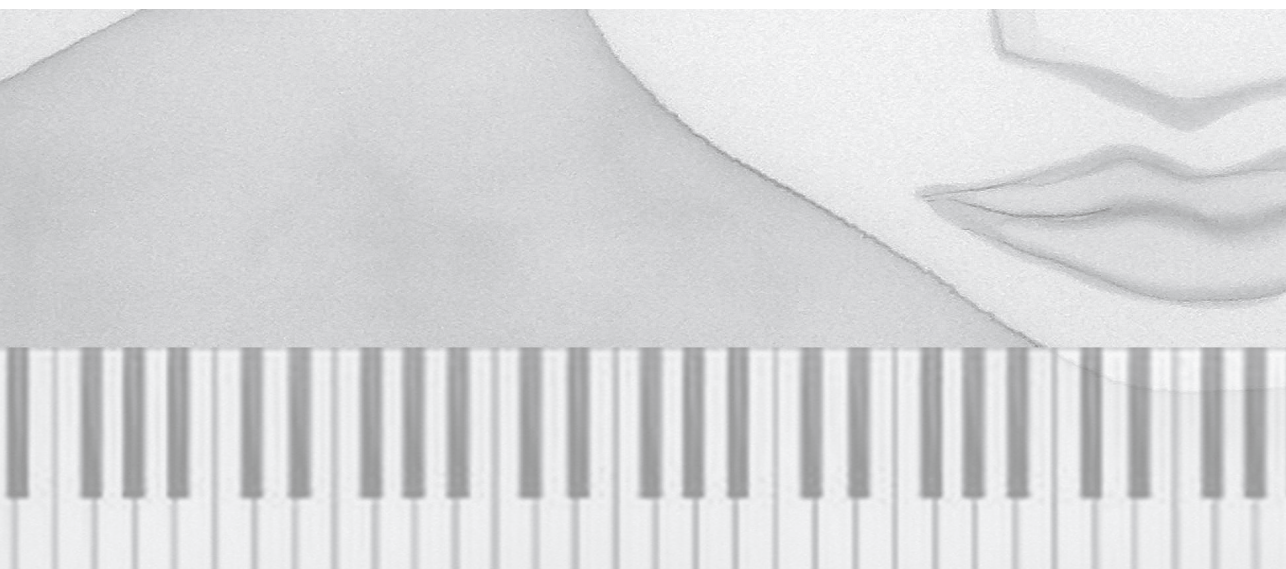
39. Bittman B, Berk L, Shannon M, Sharaf M, Westengard J, Guegler KJ, et al. Recreational music-making modulates the human stress response: a preliminary individualized gene expression strategy. *Med Sci Monit.* 2005;11(2):BR31-40.
40. de Witte M, Spruit A, van Hooren S, Moonen X, Stams GJ. Effects of music interventions on stress-related outcomes: a systematic review and two meta-analyses. *Health Psychol Rev.* 2020;14(2):294-324.



PART I

The effect of music on delirium after
brain surgery



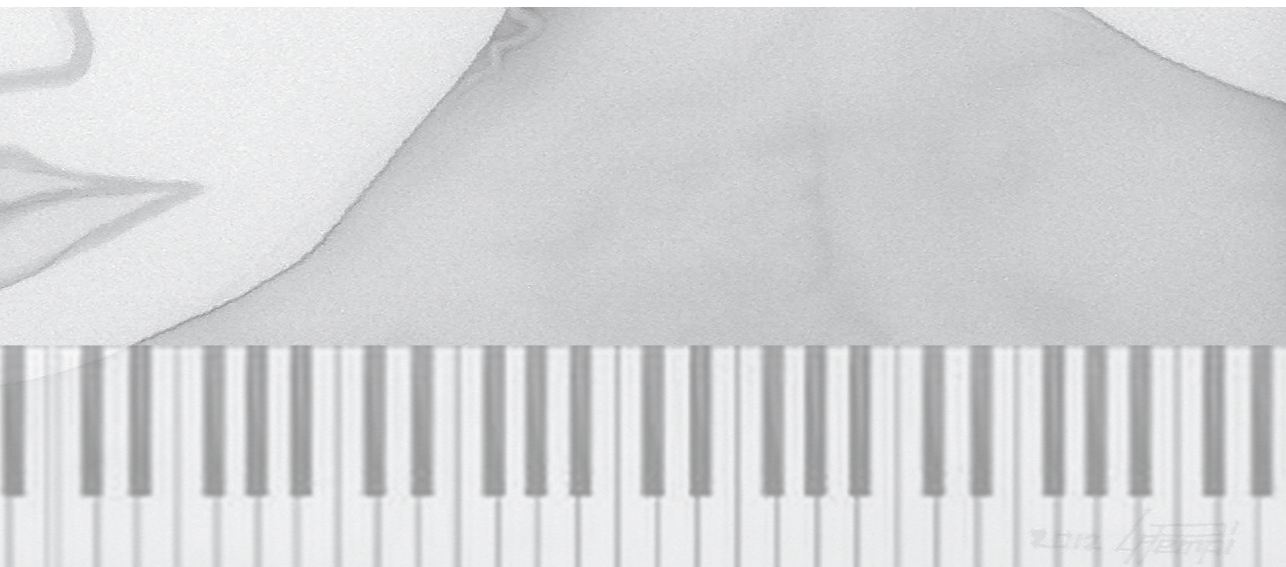


CHAPTER 2

Delirium in Neurosurgery: a systematic review and meta-analysis

P.R. Kappen, M.D., E. Kakar, M.D., C.M.F. Dirven, M.D., PhD, M. van der Jagt, M.D., PhD, M. Klimek, M.D., PhD, R.J. Osse, M.D., PhD, A.P.J.E. Vincent, M.D., PhD

Neurosurgical Review, 2022



Abstract

Delirium is a frequent occurring complication in surgical patients. Nevertheless, a scientific work-up of the clinical relevance of delirium after intracranial surgery is lacking.

We conducted a systematic review (CRD42020166656) to evaluate the current diagnostic work-up, incidence, risk factors and health outcomes of delirium in this population. Five databases (Embase, Medline, Web of Science, PsycINFO, Cochrane Central) were searched from inception through March 31st 2021. Twenty-four studies (5589 patients) were included for qualitative analysis and twenty-one studies for quantitative analysis (5083 patients). Validated delirium screening tools were used in 70% of the studies, consisting of the Confusion Assessment Method (- Intensive Care Unit) (45%), Delirium Observation Screening Scale (5%), Intensive Care Delirium Screening Checklist (10%), Neelon and Champagne Confusion Scale (5%), and Nursing Delirium Screening Scale (5%). Incidence of post-operative delirium after intracranial surgery was 19%, ranging from 12 – 26% caused by variation in clinical features and delirium assessment methods. Meta-regression for age and gender did not show a correlation with delirium. We present an overview of risk factors and health outcomes associated with the onset of delirium. Our review highlights the need of future research on delirium in neurosurgery, which should focus on optimizing diagnosis, and assessing prognostic significance and management.

Introduction

Delirium is characterized by a temporary decline in the patient's mental status affecting attention, awareness, cognition, language, and/or visuospatial ability,¹ caused by dysregulation of neuronal activity.² Intracranial surgery evokes a parenchymal inflammatory reaction resulting in oxidative stress, which is subsequently aggravated by impaired oxygenation of the surrounding tissue due to the formation of edema. Hypotheses describing the pathophysiology of delirium include neuro-inflammatory and oxidative reactions within the brain. Considering this, neurosurgical patients are vulnerable to delirium.²

Unfortunately, delirium in the neurosurgical population has been under-investigated. This may be explained by the lack of consensus on definition and challenge with respect to its diagnosis.³⁻⁵ Therefore, reported incidences vary, especially in case of hypoactive delirium.⁶ Delirium is considered a severe complication in other populations, being a traumatic experience for patients and contributing to prolonged hospital stay, higher risk for re-operation, mortality, and cognitive decline.⁷⁻¹⁰ These consequences of delirium led to increased research on delirium, including in the neurosurgical population.^{5, 7, 9, 11}

In order to assess the current knowledge regarding the diagnostic work-up, incidence, risk factors, and health outcomes associated with post-operative delirium in hospitalized neurosurgical patients with primary brain pathologies, we conducted a systematic review and meta-analysis.

Methods

Protocol and registration

This study follows the guideline from Meta-Analysis of Observational Studies in Epidemiology (MOOSE)¹² and is registered in the PROSPERO database (CRD42020166656).

Search strategy

The literature search was conducted with a dedicated biomedical information specialist. The electronic databases Embase, Medline, Web of Science, PsycINFO, and Cochrane Central were searched from date of inception through March 31st 2021.

Study selection and eligibility criteria

Two reviewers (PK/EK) independently screened title/abstract according to a standardized protocol.¹³ Of note, we have decided to only include patients that underwent intracranial surgery (with and/or without requirement of bone-flap removal) to assess delirium as a post-operative complication to improve the uniformity of the study population, which is a minor adaptation from the original protocol as registered in PROSPERO. Prospective, retrospective cohort studies and randomized controlled trials (RCTs) were included. Exclusion criteria were; extra-cranial neurosurgical procedures, case-series with a sample size of <10 patients and English full text not available. Full-text screening required a clear number of patients that underwent intracranial surgery and reproducible diagnosis of delirium, with or without the use of a validated tool (e.g. just mentioning delirium without detail on diagnostic assessment would lead to exclusion).

Data extraction and data items

Data, including author name, year of publication, study design, baseline characteristics, method of delirium assessment, cohort size (including incidence of delirium), risk factors and health outcomes, were extracted independently by the same two reviewers (PK/EK). The primary outcome was method of delirium assessment (validated vs non-validated tools, daily frequency, and follow-up). Secondary outcomes included the incidence, risk factors and delirium-related health outcomes associated with post-operative delirium. In case of a RCT only data of the control group were used. Risk factors and health-related outcomes were evaluated in studies using validated delirium assessment tools (i.e. delirium assessment tools validated within any hospital based population).¹⁴

Risk of bias assessment

The same two reviewers (PK/EK) independently evaluated the risk of bias. For RCTs the Cochrane Collaboration's Risk of Bias tool was used.¹⁵ Non-randomized trials were evaluated using the Newcastle-Ottawa Scale (NOS). The NOS's was adapted, after individually appraising the first five articles, due to its poor inter-observer reliability (Cohen's Kappa =0.29, appendix B).^{16, 17} The grade of certainty across studies was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Statistical analysis

Descriptive statistics were presented as counts (n, %) and means (standard deviation (SD)). Medians, in case of skewed variables, were used as approximation of the mean. Inter quartile ranges (IQR) were divided by 1.35 as approximation of the SD. Reported confidence intervals (95%CI) were used to approximate the SD ($=((CI \text{ upper limit} - CI \text{ lower limit})/3.92) * (\text{root square of the cohort size})$). The widths of reported ranges were divided by four as approximation of the SD.

Meta-analysis of proportions was performed using the random effects model with the restricted maximum likelihood method, since within and between-study variance was expected. Proportions were defined as the fraction of patients with delirium. Before pooling, all data were transformed, using the Freeman-Tukey double arcsine transformation, to correct for extreme proportions (e.g. <0.2 and >0.8) and small sample sizes.¹⁸ Heterogeneity was assessed using the I^2 statistics. Outliers were identified by screening for externally studentized residuals of >3 and excluded if the outlier caused significant changes in the meta-analysis.¹⁹ Subgroup analysis was performed based on clinical features and delirium diagnosis method. Delirium-associated significant multi-variate risk factors and health outcomes were presented as odds ratio's (ORs) with CIs. Meta-regression was performed for risk factors if ≥ 8 studies were available. We did qualitative analysis for delirium –related risk factors and health outcomes, when studies reported multivariable associations. Data were analyzed using R version 4.0.0 and a p-value of <0.05 was considered statistically significant.

Results

Systematic search

Our search, last update conducted the 31st of March 2021, yielded 6974 studies (Appendix B). A total of 4290 studies were screened on title/abstract. Eventually, 47 studies were assessed full text, of which 27 excluded: delirium diagnosis not reproducible (n_s (number of studies)=9),²⁰⁻²⁸ full text not found (n_s =3),²⁹⁻³¹ duplicate (n_s =3),^{18, 32} pediatric patients (n_s =1)³³, overlapping populations (n_s =3),^{4, 34, 35} no delirium assessment (n_s =1),³⁶ no original data (n_s =2)^{37, 38} and an unclear number of patients undergoing intracranial surgery (n_s =5)³⁹⁻⁴³ Finally, 20 paper were included in the qualitative analysis and 18 papers in the quantitative analysis (n_p (number of patients) = 5083).

Study and patient characteristics

Table 1 describes the study and patient characteristics. Two RCTs, seven prospective, and eleven retrospective cohort studies were included. Disease type for patients undergoing intracranial surgery were categorized in: mixed (33.9%, $n_p=1478$),^{4, 10, 21, 32, 39, 41-48} functional neurosurgery (26.8%, $n_p=552$),^{11, 46, 49-51} neurovascular (10.5%, $n_p=145$),⁵²⁻⁵⁴ neuro-oncology (18.4%, $n_p=1969$)^{5, 7, 55}, traumatic brain injury (TBI: 4.3%, $n_p=27$),^{56, 57} and microvascular decompression (MVD: 6.2%, $n_p=912$).⁹ The mixed group included neurovascular, neuro-oncologic, TBI or hydrocephalus operations, and functional neurosurgery (solely deep brain stimulation (DBS) in patients with Parkinson's disease). Twelve studies assessed delirium in neurosurgical patients in the nursing ward,^{7, 9-11, 23, 39, 41-43, 45, 46, 49-52, 56, 57} six studies in the ICU,^{4, 32, 46-48, 53, 54} and two studies in both.^{44, 55} Six studies did not specify the number of patients undergoing craniotomy (i.e. requiring bone-flap removal).^{10, 21, 39, 44, 46-48, 52, 54, 56, 57} Six studies did not report age and seven studies did not report gender within the intracranial operated cohort.^{45, 47-49, 52-54} Pooled age in years (mean/SD, $n_s=14$)^{4, 5, 7, 9-11, 32, 44, 46, 49-51, 55, 56} and percentage of males ($n_s=13$)^{5, 7, 9-11, 32, 44, 46, 50, 51, 55, 56} of the remaining studies was 60.32 (4.47), respectively 49.6%.

Delirium diagnosis

Fourteen (70.0%) studies used validated delirium assessment tools (Table 2). One (5.0%) study confirmed delirium, in patients using Delirium Observation Screening Scale (DOS) scores >2 , in combination with the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria.^{9, 39} Most studies ($n_s=9$ (45.0%)) used the Confusion Assessment Method (CAM) or the modified version for the Intensive Care Unit (CAM-ICU) as a diagnostic or screening tool. The CAM (-ICU) in all studies was defined as positive for delirium when three out of four items were scored positive.^{4, 7, 32, 42, 45-48, 51, 53, 55} Two (10.0%) studies assessed delirium using the Intensive Care Delirium Screening Checklist (ICDSC).^{10, 39, 41, 54} One (5.0%) study, assessed delirium using the Neelon and Champagne (NEECHAM) Confusion Scale, defined delirium as positive in case of once a score of <24 or a score of <27 for two consecutive days.⁵² One (5.0%) study used the Nursing Delirium Screening Scale (Nu-DESC), as an alternative for the CAM-ICU, and considered delirium positive in case of a score ≥ 2 .⁴⁴

Six (30.0%) studies used non-validated, but reproducible, screening tools for delirium. One study, assessing delirium with either the Mini-Mental State Examination (MMSE)

or CAM-ICU did not separately report values for the CAM-ICU, and was therefore considered non-validated.⁴⁵ The remaining studies predefined their tools based on own defined criteria.^{11, 21, 49, 50, 56}

A follow-up period for delirium assessment was reported in all but one study⁵⁶, which varied from 24 hours to 30 days. Frequency of daily delirium screening was specified in eight (40.0%) studies: three times per day ($n_s=2$),^{32, 39, 43, 55} twice per day ($n_s=4$)^{10, 46, 48, 53}, and once per day ($n_s=2$).^{4, 46, 51, 57}

Incidence of delirium

One study did not report the incidence of delirium within the operated population.⁴⁸ Meta-analysis was conducted for 18 studies, after excluding one outlying study (Appendix C),⁵⁴ resulting in a pooled incidence of post-operative delirium after intracranial surgery of 19.0% ($n_p=5083$; 0.19; CI 0.12–0.26, Figure 1/2).^{5, 7, 9-11, 32, 44-47, 49-53, 55, 56} The mean/SD of onset in days, reported in three studies, was 2.8/0.6.^{9, 45, 53} Four studies, distinguishing the delirium subtypes, reported the hypoactive form in 38.9–68.1%, hyperactive form in 17.2–50.8%, and the mixed form in 7.57-29.6% of the patients.^{4, 5, 53, 55}

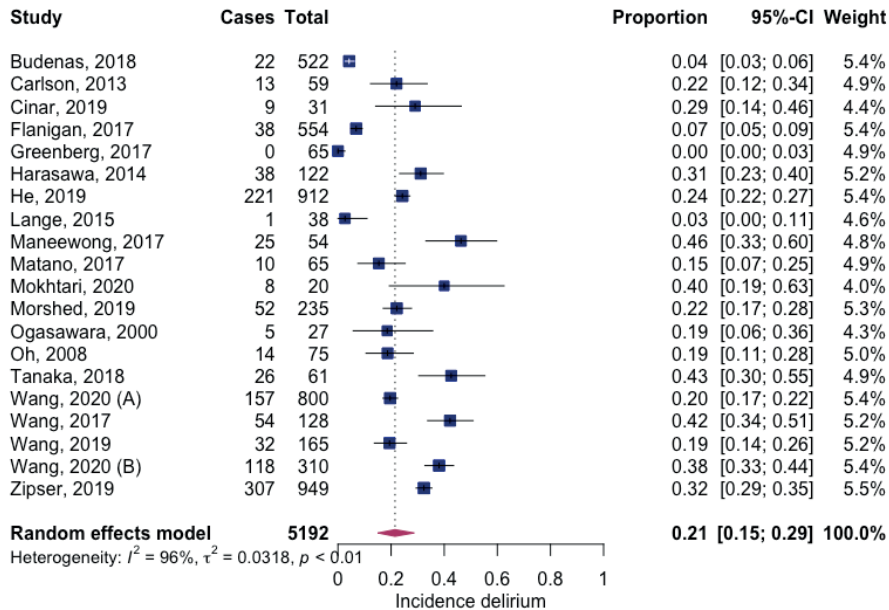


Figure 1. Pooled incidence delirium in neurosurgery

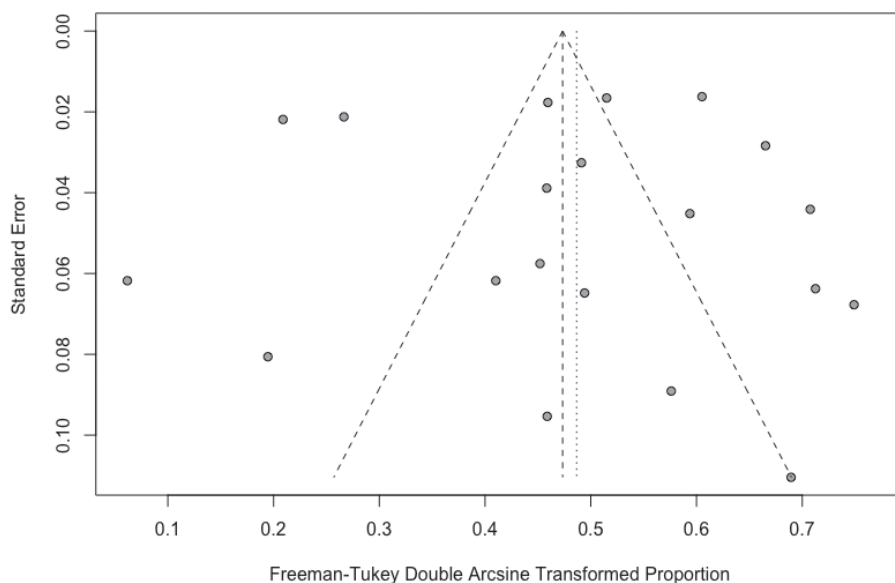


Figure 2. Funnel plot pooled incidence delirium in neurosurgery

Subgroup analysis

Delirium assessment tools

The incidence of delirium in studies using validated tools and non-validated tools was 20.0% ($n_p=4269$; 0.20; CI 0.14–0.27)^{7, 9, 10, 32, 44, 46, 47, 51, 52, 55} and 17.0% respectively ($n_p=814$; 0.17; CI 0.07–0.30, figure 3).^{5, 11, 45, 49, 50, 56, 57} The delirium incidence rates were 19.0%, 15.0%, 24.0%, and 30.0% when using the CAM(-ICU),^{4, 7, 32, 44, 46-48, 51, 53, 55} ICDSC,^{10, 39} DOS,^{9, 43} and NEECHAM⁵² respectively.

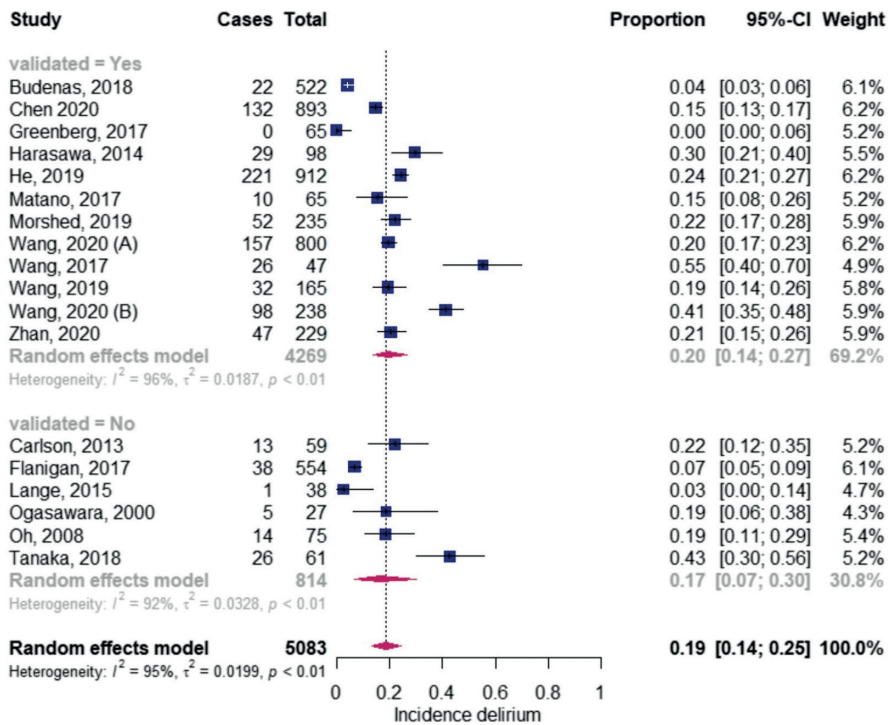


Figure 3. Subgroup analysis validated vs. non-validated screening tools.

Frequency and follow up of daily delirium assessment

Pooled analysis of studies which did not report frequency of delirium assessment resulted in an incidence of 18.0% ($N=2746$; 0.18; CI 0.11–0.25),^{5, 7, 9, 11, 23, 44–46, 49, 50, 52, 56} 20.0% ($n_p=1029$; 0.20; CI 0.17–0.22)^{46, 47, 51, 57} in case of screening once per day, 36.0% ($N=350$; 0.36; CI 0.17–0.57)^{10, 46–48, 53} in case of screening twice per day and 5.0% ($n_p=958$; 0.05; CI 0.00–0.28)^{8, 32} in case of screening three times per day. Pooled analysis of studies assessing delirium during <3 days resulted in an incidence of 18.0% ($n_p=3775$; 0.18; CI 0.12–0.24)^{5, 7, 9, 11, 32, 44–46, 49–52, 56, 57} and in 21.0% ($n_p=1308$; 0.21; CI 0.07–0.40) in case of ≥ 3 days.^{4, 5, 7, 9–11, 32, 39, 43–45, 47–50, 52, 53, 55}

Clinical features

The pooled analysis of patients undergoing craniotomy (i.e. requiring boneflap removal) led to an delirium incidence of 15.0% ($n_p=2954$; 0.15; CI 0.04–0.32).^{7, 9, 23,}

^{32, 52, 53, 55} The incidence of delirium varied per type of neurosurgical disease; incidence of 8.0% in neuro-oncologic patients ($n_p = 1969$; 0.08; CI 0.03-0.15)^{7, 23, 55}, 20% in functional neurosurgical patients ($n_p = 552$; 0.20; 0.12–0.30), 24.0% in microvascular decompression patients ($n_p = 912$; 0.24; CI 0.22–0.27),⁹ 19.0% in TBI patients ($n_p = 27$; 0.19; CI 0.06–0.36),^{56, 57} 42.0% in neurovascular patients ($n_p = 145$; 0.42; CI 0.18–0.67),^{52, 53} and 17.0% in the mixed neurosurgical population ($n_p = 1478$; 0.17; CI 0.09–0.28).^{4, 10, 32, 39, 43–45, 47, 48} Delirium incidence in patients admitted to the ICU, ward or both were respectively 24.0% ($n_p = 1150$; 0.24; CI 0.08–0.46),^{4, 5, 7, 9–11, 32, 39, 43, 45, 47, 49, 50, 52, 53, 56, 57} 17.0% ($n_p = 2805$; 0.17; 0.11–0.25).^{7, 9–11, 23, 45, 46, 49–52, 56} and 18.0% ($n_p = 1128$; 0.19; 0.11–0.26).^{4, 32, 44, 47, 48, 53, 55}

Risk factors and health outcome

Risk factors

Independent risk factors from eight studies presented in Table 3A. Age was reported as significant risk factor in four,^{7, 44, 46, 55} male gender in three,^{9, 51, 55} sleep disturbances^{9, 46} and longer surgery duration in two studies.^{4, 55} All other risk factors were each described in only one study.

Meta-regression

Meta-regression was performed for age and gender (from baseline characteristics), for which no significant correlation was found with delirium occurrence ($p = 0.91$, respectively $p = 0.37$, Figure 4/5).^{4, 7, 9, 10, 32, 43, 44, 46–48, 51–53, 55}

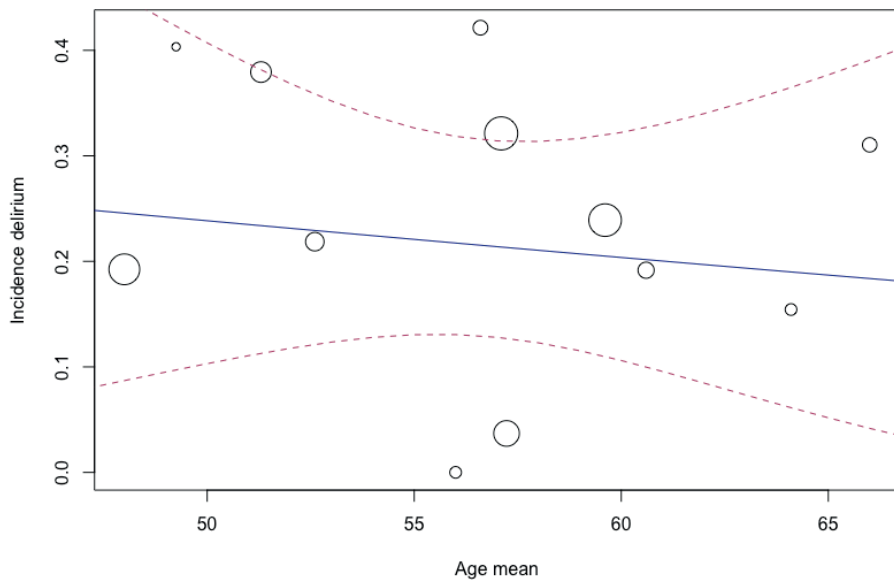


Figure 4. Meta-regression: age and incidence delirium

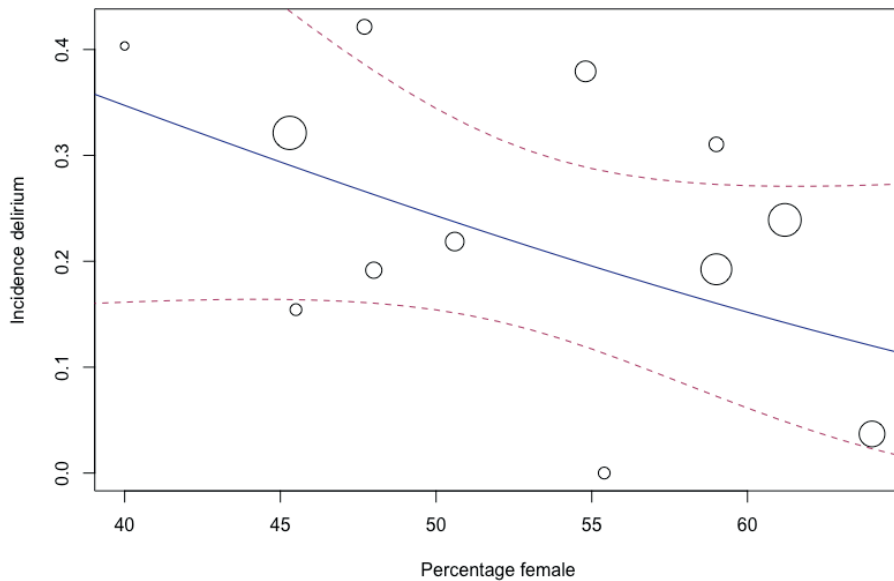


Figure 5 . Meta-regression: gender and incidence delirium

Health outcomes

Health outcomes were assessed in four studies. Table 3B illustrates health outcomes related to delirium. Delirium was significantly associated with restraint/fixation of patients in three studies^{10, 53, 55, 58} and with an unfavorable Glasgow Outcome Scale at discharge⁷, increased length of ICU, catheterization, and disease in one study.⁵⁵

Risk of Bias

An overview of the risk of bias assessment is presented in Appendix D. The quality of evidence was considered poor to moderate. The risk of bias in the study of Greenberg et al.³² was considered with “some concerns” due to unclear allocation concealment and missing data. The risk of bias in the study of Mokhtari et al.⁴⁸ was considered high due to incomplete data and exclusion of patients admitted to the ICU after randomization.

The quality of evidence in the cohort studies was poor in 11 (55.0%) studies, fair in three (15.0%) studies, and good in six (30.0%) studies. Only three studies assessed delirium at baseline.^{21, 52, 55, 56} Inter-observer reliability between the two researchers (PK/EK) for the NOS was “moderate” (Cohen’s Kappa (range); 0.62(0.50–0.73)).¹⁶

GRADE certainty rating

The quality of evidence was moderate for the studies included in the meta-analysis. *Imprecision* was considered moderate since the 95%CI was wide. *Inconsistency* was considered high since the 95%CI of the individual studies in the meta-analysis did not all overlap, which is confirmed by the heterogeneity test ($I^2=95.0\%$, $p<0.01$). The risk for *indirectness* was considered moderate, although the type of neurosurgical patients included (neuro-oncology, neurovascular etc.) did differ, delirium was investigated in the population of interest. The risk for publication bias is considered high illustrated by the asymmetrical scattering in the funnel plot (Figure 2). Based on the previous, the GRADE certainty rating is low to moderate.

Discussion

To our knowledge this is the first systematic review and meta-analysis studying delirium in patients undergoing intracranial surgery. We found an overall incidence of 19%, but the diagnostic method to assess the presence of delirium and the type of

neurosurgical patients were highly variable. Although the incidence rate is significant, the current evidence is too limited to draw firm conclusions on risk factors and health outcomes associated with delirium in this specific group of patients.

In this review it was not possible to investigate which delirium assessment tool was most suitable for the neurosurgical population, since diagnostic accuracy was not determined in any of the included studies and no specific reference standard exists for this population, apart from the DSM-criteria. The CAM was mostly used as a screening tool, which is considered a reliable assessment instrument for delirium in postsurgical patients.⁵⁹ The second most used assessment tool in this review was the ICDSC, a tool primarily developed for the ICU.⁶⁰ The CAM-ICU has a higher sensitivity and specificity compared to the ICDSC (80% and 96%, respectively 74% and 82%) in critically ill patients⁶¹, which might explain the slightly higher incidence (CAM-ICU; 19%, ICDSC; 15%). Future studies should further validate these screening tools as certain symptoms specific to the neurosurgical patient overlap with diagnostic criteria of delirium.

A considerable proportion of the studies in our review used non-validated tools.^{5, 11, 21, 45, 49, 50, 56, 57} Most of these studies were retrospective with delirium assessment based on 'positive' symptoms.¹¹ These assessments might fail to recognizing delirium, especially the hypoactive type which comprises 26–58% of delirium in this population.^{4, 5, 23, 53} Structured screening done once vs twice per day increased the incidence (20.0 vs 36.0%) but in studies screening three times per day incidence surprisingly decreased (5.0%). This might have been caused by one study, which screened three times per day, reporting 0% incidence with short follow-up time (within 24 hours).³² Still, future studies should assess delirium at several moments per day, as delirium fluctuates and infrequent assessments might falsely decrease delirium detection.¹

In our study, post-operative delirium after intracranial surgery occurred in 19% (range 5%–37%), comparable to the pooled incidence (12–43%) reported by Patel et al., evaluating delirium in neurocritical care patients.⁶² The difference in incidence between the ICU compared to the ward was not as large as we expected (24.0 vs 17.0%). Explanations for this might include: all ICU patients were diagnosed with a valid delirium assessment tool, as opposed to only half of the patients on the ward. The clear criteria of validated delirium screening tools compared to the more loose non-validated criteria in many other studies might have affected these incidence rates.

Moreover, use of sedatives might artificially decrease the incidence of delirium since delirium is by definition undetectable in a drug-induced coma.

The highest incidence of delirium was found in patients undergoing neurovascular surgery (42%).^{52, 53} A possible explanation for this may be cerebral ischemia, hypoxia and oxidative stress, induced by e.g. temporary clipping and bypass techniques, which are described as mechanisms in the pathophysiology of delirium.² Moreover, neurovascular procedures are often characterized by a relative long duration of anesthesia and require frequent postoperative sedation and mechanical ventilation.^{4, 43} A relatively lower incidence was observed in the TBI study, possibly caused by the low surgical invasiveness in this cohort, as only patients undergoing burr hole drainage without craniotomy (i.e. requiring boneflap removal) were included.⁵⁶

We did not find a correlation between age and delirium, in contrary to literature in other populations.⁶³ An explanation might be the relatively low range in age (47.8–64.1 years) of the patients in the studies, which is representative of the neurosurgical population. Moreover, the metaregression analysis might have been underpowered due to high heterogeneity.⁶⁴ On the other hand, age might be a less relevant factor after intracranial surgery as it was only described as a risk factor for delirium in four studies^{7, 44, 46, 55} and not confirmed in the other five studies.^{9, 10, 38, 46}

Limitations

The most important limitation in our study is the high heterogeneity of our included studies caused by the differences in delirium assessment methods and clinical differences. Moreover scattering in the funnel plot indicates a high probability of publication bias. Hence the findings, especially the quantitative analysis, of this review should be interpreted carefully and be regarded as hypothesis-generating.

Future research

Future research should assess delirium at several moments per day, focus on the validation of structural delirium assessment tools and the prognostic relevance of delirium for clinical outcomes and surgical complications in neurosurgical patients. This is desirable before interventional trials are undertaken to assess optimal management. Furthermore, our analyses indicate that the definition of delirium after intracranial surgery requires consensus to enhance further research. Further, details on depth

and length of anesthesia for surgical procedures and timing of delirium assessments relative to the surgery should be taken into account, to distinguish anesthesia effects from the impact of structural cerebral pathologies on the phenomenology of delirium.

2

Conclusion

This is the first systematic review and meta-analysis on delirium after intracranial surgery in neurosurgical patients. Delirium is frequently occurring adverse event in the neurosurgical clinical practice but limited consensus exists on the diagnostic criteria. Future research should focus on validating delirium assessment methods in the neurosurgical population and define the prognostic impact of delirium

References

1. American Psychiatric A. American Psychiatric Association DSM-5 Task Force (2013): Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, DC: American Psychiatric Association;
2. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry*. 2013;21(12):1190-222.10.1016/j.jagp.2013.09.005
3. Stienen MN. Delirium in neurosurgery. *Acta Neurochir (Wien)*. 2019.10.1007/s00701-019-03928
4. Wang CM, Huang HW, Wang YM, He X, Sun XM, Zhou YM, et al. Incidence and risk factors of postoperative delirium in patients admitted to the ICU after elective intracranial surgery: A prospective cohort study. *Eur J Anaesthesiol*. 2020.10.1097/EJA.0000000000001074
5. Flanagan PM, Jahangiri A, Weinstein D, Dayani F, Chandra A, Kanungo I, et al. Postoperative Delirium in Glioblastoma Patients: Risk Factors and Prognostic Implications. *Neurosurgery*. 2018;83(6):1161-72.10.1093/neuros/nyx606
6. Hosker C, Ward D. Hypoactive delirium. *BMJ*. 2017;357:j2047.10.1136/bmj.j2047
7. Budėnas A, Tamašauskas Š, Šliaužys A, Navickaitė I, Sidaraitė M, Pranckevičienė A, et al. Incidence and clinical significance of postoperative delirium after brain tumor surgery. *Acta Neurochir*. 2018;160(12):2327-37.10.1007/s00701-018-3718-2
8. Chen L, Xu M, Li GY, Cai WX, Zhou JX. Incidence, Risk Factors and Consequences of Emergence Agitation in Adult Patients after Elective Craniotomy for Brain Tumor: A Prospective Cohort Study. *PLoS One*. 2014;9(12):e114239.10.1371/journal.pone.0114239
9. He Z, Cheng H, Wu H, Sun G, Yuan J. Risk factors for postoperative delirium in patients undergoing microvascular decompression. *PLoS One*. 2019;14(4):e0215374.10.1371/journal.pone.0215374
10. Matano F, Mizunari T, Yamada K, Kobayashi S, Murai Y, Morita A. Environmental and Clinical Risk Factors for Delirium in a Neurosurgical Center: A Prospective Study. *World Neurosurg*. 2017;103:424-30.10.1016/j.wneu.2017.03.139
11. Tanaka M, Tani N, Maruo T, Oshino S, Hosomi K, Saitoh Y, et al. Risk Factors for Postoperative Delirium After Deep Brain Stimulation Surgery for Parkinson Disease. *World neurosurgery*. 2018;114:e518-e23.10.1016/j.wneu.2018.03.021
12. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-12.10.1001/jama.283.15.2008
13. Bramer WM RM, Mast F, . Evaluation of a new method for librarian-mediated literature searches for systematic reviews. *Res Synth Methods* 2018;9(4):510-20.10.1002/jrsm.1279
14. Jayita De A, Wand. Delirium Screening: A Systematic Review of Delirium Screening Tools in Hospitalized Patients. *The Gerontologist*. 2015;55(6):1079 - 99.10.1093/geront/gnv100
15. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.10.1136/bmj.d5928

16. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159-74
17. Hartling L, Hamm M, Milne A, Vandermeer B, Santaguida PL, Ansari M, et al. Validity and Inter-Rater Reliability Testing of Quality Assessment Instruments. 2012/04/27 ed2012 Mar.
18. Wan N. How to Conduct a Meta-Analysis of Porportions in R: A Comprehensive Tutorial. 2018.10.13140/RG.2.2.27199.00161
19. B.G. Tabachnick LSF. *Using Multivariate Statistics*: Pearson; 2013.
20. Bouajram RH, Bhatt K, Croci R, Baumgartner L, Puntillo K, Ramsay J, et al. Incidence of Dexmedetomidine Withdrawal in Adult Critically Ill Patients: A Pilot Study. *Crit Care Explor*. 2019;1(8):e0035.10.1097/CCE.0000000000000035
21. Brown EG, Josephson SA, Anderson N, Reid M, Lee M, Douglas VC. Evaluation of a multicomponent pathway to address inpatient delirium on a neurosciences ward. *BMC Health Serv Res*. 2018;18(1):106.10.1186/s12913-018-2906-3
22. Cao J, Jiao J, Du Z, Xu W, Sun B, Li F, et al. Combined Hyperactive Dysfunction Syndrome of the Cranial Nerves: A Retrospective Systematic Study of Clinical Characteristics in 44 Patients. *World Neurosurg*. 2017;104:390-7.S1878-8750(17)30708-8
23. Flanigan PM, Jahangiri A, Kuang R, Truong A, Choi S, Chou A, et al. Developing an Algorithm for Optimizing Care of Elderly Patients With Glioblastoma. *Neurosurgery*. 2018;82(1):64-75.10.1093/neuros/nyx148
24. Moeini M, Mahmoudian SN, Khalifezadeh A, Pour AH. Reviewing time intervals from onset of the symptoms to thrombolytic therapy in patients with ST segment elevation myocardial infarction (STEMI). *Iran J Nurs Midwifery Res*. 2010;15(Suppl 1):379-85
25. Lukasiewicz AM, Grant RA, Basques BA, Webb ML, Samuel AM, Grauer JN. Patient factors associated with 30-day morbidity, mortality, and length of stay after surgery for subdural hematoma: a study of the American College of Surgeons National Surgical Quality Improvement Program. *J Neurosurg*. 2016;124(3):760-6.10.3171/2015.2.JNS142721
26. Pledl HW, Hoyer C, Rausch J, Ebert AD, Seiz M, Arp M, et al. Decompressive Hemicraniectomy in Malignant Middle Cerebral Artery Infarction: The 'Real World' Beyond Studies. *Eur Neurol*. 2016;76(1-2):48-56.10.1159/000446564
27. Shinozaki G, Braun PR, Hing BWQ, Ratanatharathorn A, Klisares MJ, Duncan GN, et al. Epigenetics of Delirium and Aging: Potential Role of DNA Methylation Change on Cytokine Genes in Glia and Blood Along With Aging. *Front Aging Neurosci*. 2018;10:311.10.3389/fnagi.2018.00311
28. Starmark JE, Stalhammar D, Holmgren E, Rosander B. A comparison of the Glasgow Coma Scale and the Reaction Level Scale (RLS85). *J Neurosurg*. 1988;69(5):699-706.10.3171/jns.1988.69.5.0699
29. Kim HW KH. The effectiveness of combination therapy with quetapine and valproic acid in delirium with aggressive tendency: a prospective, controlled trial study. . *European neuropsychopharmacology* 2015.25:S591-S2.
30. MahantNEE, Owler B. . Outcomes of shunting for idiopathic normal pressure hydrocephalus (iNPH) *Movement Disorders* 2013;;28:S279-.10.1227/01.neu.0000168187.01077.2f
31. Mahta A MA, Reznik MM, Park SS, Agarwal SS, Roh DD. Post-operative hemorrhage: a possible predictor of delirium in brain tumor patients. *Neurocritical Care*. 2016

32. Greenberg S, Murphy GS, Avram MJ, Shear T, Benson J, Parikh KN, et al. Postoperative Intravenous Acetaminophen for Craniotomy Patients: a Randomized Controlled Trial. *World neurosurgery*. 2017.10.1016/j.wneu.2017.10.021
33. Brendan P. George JPV, Karisa K. Harland, Brett Faine, Stacey Rewitzer, Anne Zepeski, Brian M. Fuller, Nicholas M. Mohr, Azeemuddin Ahmed. Sedation Depth is Associated with Increased Hospital Length of Stay in Mechanically Ventilated Air Medical Transport Patients: A Cohort Study. *Journal Prehospital Emergency Care* 2019;24(6):783 - 92.10.1080/10903127.2019.1705948
34. Boettger S, Zipser CM, Bode L, Spiller T, Deuel J, Osterhoff G, et al. The prevalence rates and adversities of delirium: Too common and disadvantageous. *Palliat Support Care*. 2020:1-9.10.1017/s1478951520000632
35. Maria Schubert RS, Soenke Boettger, David Garcia Nuñez, Urs Schwarz, Dominique Bettex, Josef Jenewein, Jasmina Bogdanovic, Marina Lynne Staehli, Rebecca Spirig and Alain Rudiger. A hospital-wide evaluation of delirium prevalence and outcomes in acute care patients - a cohort study. *BMC Health Services Research*. 2018.10.1186/s12913-018-3345-x
36. Herrero S, Carrero E, Valero R, Rios J, Fabregas N. Postoperative surveillance in neurosurgical patients - usefulness of neurological assessment scores and bispectral index. *Rev Bras Anesthesiol*. 2017;67(2):153-65.10.1016/j.bjan.2016.12.001
37. Gelinas C, Puntillo KA, Levin P, Azoulay E. The Behavior Pain Assessment Tool for critically ill adults: a validation study in 28 countries. *Pain*. 2017;158(5):811-21
38. He X, Cheng KM, Zhang L, Gu H, Qu X, Xu Y, et al. Dexmedetomidine for the prevention of postoperative delirium in patients after intracranial operation for brain tumours (DEPOD study): a study protocol and statistical plan for a multicentre randomised controlled trial. *BMJ Open*. 2020;10(11):e040939.10.1136/bmjopen-2020-040939
39. Çınar F, Eti Aslan F. Evaluation of Postoperative Delirium: Validity and Reliability of the Nursing Delirium Screening Scale in the Turkish Language. *Dement Geriatr Cogn Dis Extra*. 2019;9(3):362-73.10.1159/000501903
40. Patel S, Carey C, Cotter D, Murphy KC. A psychoeducational intervention increases use of a delirium protocol by Neurologists and Neurosurgeons in patients with brain disorders. *Ir J Psychol Med*. 2020.10.1017/ipm.2020.98
41. Yu A, Teitelbaum J, Scott J, Gesin G, Russell B, Huynh T, et al. Evaluating pain, sedation, and delirium in the neurologically critically ill-feasibility and reliability of standardized tools: a multi-institutional study. *Crit Care Med*. 2013;41(8):2002-7.10.1097/CCM.0b013e31828e96c0
42. Zipprich HM, Arends MC, Schumacher U, Bahr V, Scherag A, Kwetkat A, et al. Outcome of Older Patients with Acute Neuropsychological Symptoms Not Fulfilling Criteria of Delirium. *J Am Geriatr Soc*. 2020.10.1111/jgs.16422
43. Zipser Z, Deuel J, Ernst J, Schubert M, von Kanel R, Bottger S. The predisposing and precipitating risk factors for delirium in neurosurgery: a prospective cohort study of 949 patients. *Acta Neurochir (Wien)*. 2019;161(7):1307-15.10.1007/s00701-019-03927-z
44. Morshed RA, Young JS, Safae M, Sankaran S, Berger MS, McDermott MW, et al. Delirium Risk Factors and Associated Outcomes in a Neurosurgical Cohort: A Case-Control Study. *World Neurosurg*. 2019;126:930-6.10.1016/j.wneu.2019.03.012

45. Oh YS, Kim DW, Chun HJ, Yi HJ. Incidence and risk factors of acute postoperative delirium in geriatric neurosurgical patients. *J Korean Neurosurg Soc.* 2008;43(3):143-8.10.3340/jkns.2008.43.3.143
46. Wang XQ, Zhuang HX, Zhang LX, Chen X, Niu CS, Zhao M. Nomogram for Predicting Postoperative Delirium After Deep Brain Stimulation Surgery for Parkinson's Disease. *World Neurosurg.* 2019;130:e551-e7.10.1016/j.wneu.2019.06.151
47. Wang J, Ji Y, Wang N, Chen W, Bao Y, Qin Q, et al. Establishment and validation of a delirium prediction model for neurosurgery patients in intensive care. *Int J Nurs Pract.* 2020:e12818.10.1111/ijn.12818
48. Mokhtari M, Farasatinasab M, Jafarpour Machian M, Yaseri M, Ghorbani M, Ramak Hashemi SM, et al. Aripiprazole for prevention of delirium in the neurosurgical intensive care unit: a double-blind, randomized, placebo-controlled study. *Eur J Clin Pharmacol.* 2020.10.1007/s00228-019-02802-1
49. Carlson JD, Neumiller JJ, Swain LDW, Mark J, McLeod P, Hirschauer J. Postoperative delirium in Parkinson's disease patients following deep brain stimulation surgery. *J Clin Neurosci.* 2014;21(7):1192-5.10.1016/j.jocn.2013.12.007
50. Lange M, Zech N, Seemann M, Janzen A, Halbing D, Zeman F, et al. Anesthesiologic regimen and intraoperative delirium in deep brain stimulation surgery for Parkinson's disease. *J Neurol Sci.* 2015;355(1-2):168-73.10.1016/j.jns.2015.06.012
51. Zhan L, Wang XQ, Zhang LX. Nomogram Model for Predicting Risk of Postoperative Delirium After Deep Brain Stimulation Surgery in Patients Older Than 50 Years with Parkinson Disease. *World Neurosurg.* 2020;139:e127-e35.10.1016/j.wneu.2020.03.160
52. Harasawa N, Mizuno T. A novel scale predicting postoperative delirium (POD) in patients undergoing cerebrovascular surgery. *Arch Gerontol Geriatr.* 2014;59(2):264-71.10.1016/j.archger.2014.05.007
53. Wang J, Ji Y, Wang N, Chen W, Bao Y, Qin Q, et al. Risk factors for the incidence of delirium in cerebrovascular patients in a Neurosurgery Intensive Care Unit: A prospective study. *J Clin Nurs.* 2017;27(1-2):407-15.10.1111/jocn.13943
54. Hosoya R, Sato Y, Ishida E, Shibamoto H, Hino S, Yokote H, et al. Association between Delirium and Prehospitalization Medication in Poststroke Patients. *J Stroke Cerebrovasc Dis.* 2018;27(7):1914-20.10.1016/j.jstrokecerebrovasdis.2018.02.038
55. Chen H, Jiang H, Chen B, Fan L, Shi W, Jin Y, et al. The Incidence and Predictors of Postoperative Delirium After Brain Tumor Resection in Adults: A Cross-Sectional Survey. *World Neurosurg.* 2020;140:e129-e39.10.1016/j.wneu.2020.04.195
56. Ogasawara K, Ogawa A, Okuguchi T, Kobayashi M, Suzuki M, Yoshimoto T, et al. Postoperative hyperperfusion syndrome in elderly patients with chronic subdural hematoma. *Surg Neurol.* 2000;54(2):155-9.10.1016/s0090-3019(00)00281-0
57. Maneewong J, Maneeton B, Maneeton N, Vaniyapong T, Traisathit P, Sricharoen N, et al. Delirium after a traumatic brain injury: predictors and symptom patterns. *Neuropsychiatr Dis Treat.* 2017;13:459-65.10.2147/NDT.S128138
58. Wang CG, Qin YF, Wan X, Song LC, Li ZJ, Li H. Incidence and risk factors of postoperative delirium in the elderly patients with hip fracture. *J Orthop Surg Res.* 2018;13(1):186.10.1186/s13018-018-0897-8

59. Maybrier HR, Mickle AM, Escallier KE, Lin N, Schmitt EM, Upadhyayula RT, et al. Reliability and accuracy of delirium assessments among investigators at multiple international centres. *BMJ Open*. 2018;8(11):e023137.10.1136/bmjopen-2018-023137
60. Boettger S, Garcia Nunez D, Meyer R, Richter A, Rudiger A, Schubert M, et al. Screening for delirium with the Intensive Care Delirium Screening Checklist (ICDSC): a re-evaluation of the threshold for delirium. *Swiss Med Wkly*. 2018;148:w14597.10.4414/smww.2018.14597
61. Gusmao-Flores D, Salluh JI, Chalhoub RA, Quarantini LC. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Crit Care*. 2012;16(4):R115.10.1186/cc11407
62. Patel MB, Bednarik J, Lee P, Shehabi Y, Salluh JI, Slooter AJ, et al. Delirium Monitoring in Neurocritically Ill Patients: A Systematic Review. *Crit Care Med*. 2018;46(11):1832-41.10.1097/CCM.0000000000003349
63. Vasilevskis EE, Han JH, Hughes CG, Ely EW. Epidemiology and risk factors for delirium across hospital settings. *Best Pract Res Clin Anaesthesiol*. 2012;26(3):277-87.10.1016/j.bpa.2012.07.003
64. Reeves B DJ, Higgins JP. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, U.K: John Wiley & Sons; 2008.

Table 1. Baseline characteristics

Author	Study design	Context	Type of disease ¹	Cohort size intracranial ²	Cohort size craniotomy ³	Age ⁴	Gender ⁵
Budenas, 2018	Prospective cohort	Ward	Neuro-oncology	522	446	57.2/15.0	63.3
Carlson, 2013	Retrospective cohort	Ward	Functional	59	0	65.0/8.7	NR
Flanigan, 2017	Retrospective cohort	Ward	Neuro-oncology	554	500	60.8/12.8	41.0
Greenberg, 2017	RCT	ICU	Mixed	65	65	56.0/15.0	55.4
Harasawa, 2014	Prospective cohort	Ward	Neurovascular	97	98	NR	NR
He, 2019	Retrospective cohort	Ward	MVD	912	912	59.6/10.6	61.2
Hosoya, 2018	Retrospective	ICU	Neurovascular	32	13	NR	NR
Lange, 2015	Retrospective cohort	Ward	Functional	38	0	64.1/17.8	34.2
Matano, 2017	Prospective	Ward	Mixed	65	NR	64.1/18.75	45.5
Mokhtari, 2020	RCT	ICU	Mixed	16	NR	NR	NR
Morshed, 2019	Retrospective cohort	Ward and ICU	Mixed	235	NR	52.6/15.3	50.6
Ogasawara, 2000	Prospective cohort	Ward	TBI	27	NR	80.4/3.8	25.9
Oh, 2008	Retrospective cohort	Ward	Mixed	75	0	NR	NR
Tanaka, 2018	Retrospective cohort	Ward	Functional	61	0	65.6/9.2	55.7
Wang, 2020A	Prospective cohort	ICU	Mixed	800	0	48.0/12.5	59.0
Wang, 2017	Prospective cohort	ICU	Neurovascular	40	40	NR	NR
Wang, 2019	Retrospective cohort	Ward	Functional	165	NR	60.6/9.21	48.0
Wang, 2020B	Prospective cohort	ICU	Mixed	238	NR	NR	NR
Overall				4009	2074	60.5/7.8	50.2

1. Patients operated for either neurovascular, neuro-oncologic, traumatic brain or hydrocephalus. 2. Sample size of patients having undergone intracranial surgery (i.e. biopsy, ventricular drainage) 3. Sample size patients undergoing intracranial surgery requiring bone flap removal. 4. Age: mean and standard deviation 5. Gender: percentage female, MVD; microvascular decompression, RCT; Randomized Controlled Trial, TBI; traumatic brain injury, NR; not reported

Table 2. Delirium diagnosis

Author	Definition delirium diagnosis	Instrument	Validated¹	Period delirium screening²	Frequency screening³
Budenas, 2018	One positive CAM-ICU; 3 out of 4 positive features	CAM-ICU	Y	Day 2 – 7	NR
Carlson, 2013	Occurrences of any event of hallucinations, delusions or disorientation to circumstance, even if apparently benign.	Own definition	N	Until discharge	NR
Flanigan, 2017	Acute state of confusion and disorientation with changes in arousal/attention. Confusion without changes in arousal was considered mutually exclusive with delirium.	Own definition	N	Within 72h	NR
Greenberg, 2017	Positive CAM-ICU	CAM - ICU	Y	Within 24h	Three times
Harasawa, 2014	Neecham (0-30) with cut-off 24 or less OR 27 two consecutive days	NEECHAM	Y	Day 1 – 3	NR
He, 2019	DOS (three or greater) confirmed with DSM-5 by psychiatrist	DOS	Y	Day 2 – 5	NR
Hosoya, 2018	ICDSC 4 or higher	ICDSC	Y	Until discharge	NR
Lange, 2015	Altered mental state of reduced cooperation due to fear, psycho-motor agitation and impaired or lost orientation.	Own definition	N	Day 1 – 30	NR
Matano, 2017	ICDSC 4 or higher	ICDSC	Y	Day 1 – 7	Two times
Mokhtari, 2020	Positive CAM-ICU	CAM-ICU	Y	Day 1 – 7	Two times
Morshed, 2019	Either CAM-ICU (1 and 2 and 3 and/of 4) or Nu-DESC (2 or higher) once positive	CAM-ICU / Nu-DESC	Y	Until discharge	NR
Ogasawara, 2000	Vivid hallucination, delusion, extreme agitation, irritability and signs of over activity in the autonomic nervous system.	Own definition	N	NR	NR

Author	Definition delirium diagnosis	Instrument	Validated ¹	Period delirium screening ²	Frequency screening ³
Oh, 2008	Positive for delirium when MMSE less than 23 OR positive CAM-ICU (1 and 2 and 3 and/of 4)	MMSE / CAM-ICU	N	Day 1 – 3	NR
Tanaka, 2018	Any event involving hallucinations, delusions, or disorientation to circumstance including any attempt to remove the urinary catheter or peripheral venous catheter.	Own definition	N	Day 1 – 14	NR
Wang, 2020A	Positive CAM-ICU (either 1 and 2 with 3 and/or 4)	CAM-ICU	Y	Day 1 – 3	One time
Wang, 2017	Positive CAM-ICU (either 1 and 2 with 3 and/or 4)	CAM-ICU	Y	Until discharge	Two times
Wang, 2019	Positive CAM-ICU (either 1 and 2 with 3 and/or 4)	CAM-ICU	Y	Day 1	NR
Wang, 2020B	According to guidelines: ICU guidelines	CAM-ICU	Y	Until discharge	Two times

1. Validated tools for delirium screening. 2. Follow-up duration for delirium screening. 3. Daily frequency of delirium screening. NR; not reported

Table 3A. Risk factors

Risk factors	Author	Odd's ratio (OR)	95% CI	P value
Age	Budenas, 2018	4.6	1.7 - 12.1	0.002
	Morshed, 2019	1.05	1.01 - 1.08	0.006
	Wang (A) 2020	1.0	1.02 - 1.06	<0.001
Sleep disturbance	He, 2019	4.95	2.95 - 8.29	<0.001
	Wang 2019	0.058	0.051 - 0.067	0.021
Cerebrovascular disease	Wang 2020A	3.2	1.57 - 6.53	0.001
Lesser than secondary education	Budenas, 2018	3.5	1.3 - 9.1	0.011
Poor functional status		4.7	1.9 - 11.8	0.001
Low haemoglobin		5	1.1 - 22.5	0.036
Male sex	He, 2019	2.66	1.91 - 3.71	<0.001
Hypertension		2.25	1.53 - 3.30	<0.001
Mount Fuji sign		3.24	2.10 - 4.99	<0.001
Severe white matter lesions (Fazekas classification 2 and 3)	Matano, 2017	15	2 - 134	0.001
Surrounding monitor		6	1 tot 32	0.001
Surrounding delirium patients		14	2 - 75	0.026
Presence neurologic deficit	Morshed, 2019	5.31	1.87 - 15.11	0.002
Length of ICU stay		1.23	1.07 - 1.43	0.004
Benign tumour¹	Wang, 2020A			
Malignant tumour¹		2.82	1.52 - 4.88	<0.001
Frontal approach craniotomy		3.01	1.79 - 5.05	<0.001
Duration surgery		1.00	1.00 - 1.01	0.016
Episode of SpO₂<90% at ICU admission		8.22	1.38 - 48.92	0.021
Emergence delirium: inadequate²		11.15	4.8 - 25.88	<0.001
Emergence delirium: hyperactive²		14.60	5.4 - 39.45	<0.001
Emergence delirium: hypoactive²		11.64	7.75 - 20.10	<0.001
NRS for pain		1.19	1.02 - 1.38	0.028
Immobilising factor		1.64	1.3 - 2.08	<0.001
Non-motor symptoms scale of PD (NMSS)	Wang, 2019	8.191	5.629 - 11.917	0.002
Unified Parkinson's disease rating scale (UPDRS III)		2.284	1.614 - 3.232	0.047
Preoperative length of stay		1.230	1.053 - 1.437	0.009
Preoperative brain atrophy		3.912	3.597 - 4.255	0.038

1. Compared to benign tumour. 2. Compared to none emergence delirium.

Table 3B. Health outcomes

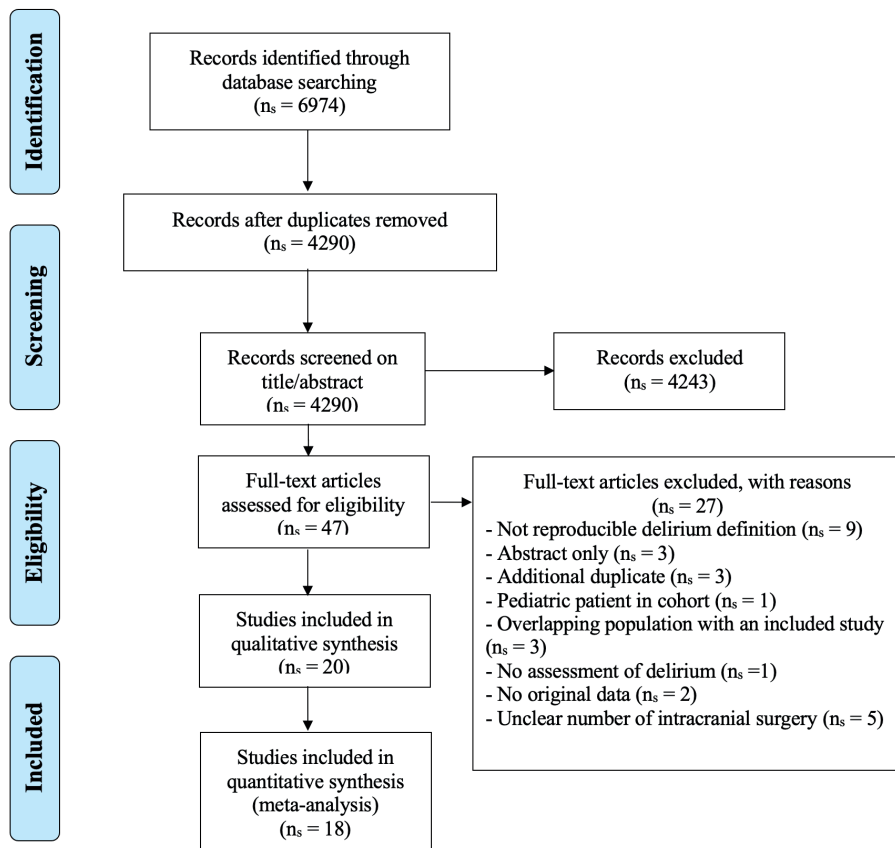
Health outcome	Author	Odd's ratio (OR)	95% CI	P value
Unfavourable functional outcome	Budenas, 2018	5.3	2.1 - 13.4	0.0005
Patient restraint/fixation	Matano, 2017	8	1 - 75	0.001
	Wang 2017	22.51	5.25 - 96.49	0.000

Appendix A: the Newcastle-Ottawa Scale criteria.

Criteria ¹	Acceptable ² (star awarded):	Unacceptable ² (star not awarded):
<i>Selection: representativeness of exposed cohort</i>	Entire study must represent neurosurgical cohort or adequately specify in case of mixed group.	Neurosurgical cohort mixed with other types of patients, not further specified.
<i>Selection: representativeness of non-exposed cohort</i>	Same setting as exposed (delirium) cohort.	Different setting from exposed (delirium) cohort.
<i>Selection: ascertainment of exposure</i>	Ascertainment of delirium must be through a completely clear scoring system (i.e. three out of four CAM features).	Delirium assessment definition without clear scoring system.
<i>Selection: demonstration outcome interest not present at start study</i>	Must be stated that delirium was excluded at baseline/before operation.	No exclusion of delirium at baseline (or before operation) or no statement on this.
<i>Comparability</i>	Type of neurosurgical intervention must be described and comparable between delirium and non-delirium group.	Type of neurosurgical intervention undefined or incomparable between delirium and non-delirium group.
	Timing of delirium assessment must be similar between delirium and non-delirium group.	Different timing of delirium assessment between groups or no clear definition/statement on this.
<i>Exposure: follow up duration</i>	Delirium assessment procedure: validated delirium screening + DSM criteria by two independent and blinded researchers.	Delirium definition procedure otherwise.
<i>Exposure: adequacy follow-up</i>	Follow-up of delirium from date of craniotomy up to least 3 days.	Shorter follow-up delirium.
<i>Exposure: non-response rate</i>	In case of missing data: amount of missed data must be similar between the delirium and non-delirium group.	Significant difference in missing data between the delirium and non-delirium group or more than 10% of the entire sample size.

1. Criteria of the Newcastle Ottawa Scale. 2. Adaption of the criteria for quality appraisal of the included studies in this review.

Appendix B. PRISMA Flowchart



Appendix C. identifying outlying and influential studies.

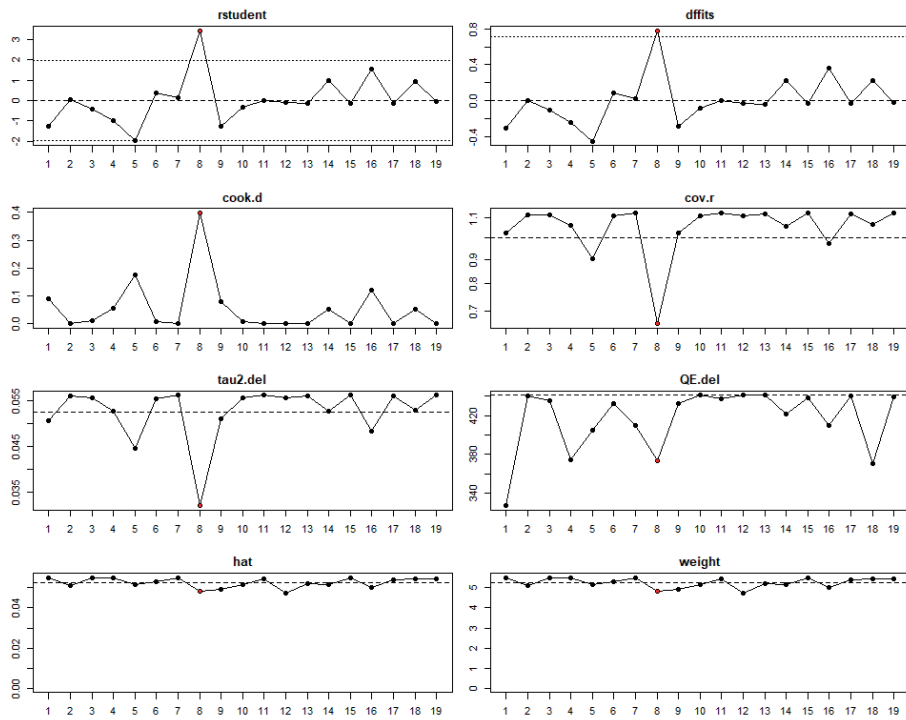
1. Budenas, 2018
2. Carlson, 2013
3. Chen, 2020
4. Flanigan, 2017
5. Greenberg, 2017
6. Harasawa, 2014
7. He, 2019
8. Hosoya, 2018
9. Lange, 2015
10. Matano, 2017
11. Morshed, 2019
12. Ogasawara, 2000
13. Oh, 2008
14. Tanaka, 2018
15. Wang, 2020 (A)
16. Wang, 2017
17. Wang, 2019
18. Wang, 2020 (B)
19. Zhan, 2020

Z value above 3 indicates a statistical outlier (in red):

resid		se	z
8	0.6979	0.2039	3.4229
5	-0.4477	0.2257	-1.9831
16	0.3696	0.2373	1.5574
1	-0.2940	0.2326	-1.2639
9	-0.3072	0.2459	-1.2495
4	-0.2331	0.2373	-0.9826
14	0.2380	0.2445	0.9734
18	0.2223	0.2389	0.9308
3	-0.0971	0.2433	-0.3993
6	0.0955	0.2475	0.3858
10	-0.0810	0.2504	-0.3235
13	-0.0370	0.2501	-0.1478
17	-0.0303	0.2468	-0.1228
7	0.0296	0.2444	0.1213
15	-0.0292	0.2445	-0.1194
12	-0.0296	0.2608	-0.1136
19	-0.0161	0.2460	-0.0656
2	0.0075	0.2519	0.0299
11	0.0044	0.2460	0.0178

Leaving study 8 (Hosoya, 2018) out reveals the largest change in incidence (illustrated in red and with a red dot in the graph):

	estimate	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.2291	9.2120	0.0000	0.1445	0.3260	326.9867	0.0000	0.0506	97.9407	48.5597
2	0.2153	8.5153	0.0000	0.1295	0.3153	440.3039	0.0000	0.0560	98.3251	59.7059
3	0.2201	8.6236	0.0000	0.1336	0.3206	435.8726	0.0000	0.0556	97.9727	49.3278
4	0.2263	8.9777	0.0000	0.1407	0.3249	374.3800	0.0000	0.0527	98.0072	50.1799
5	0.2346	9.9355	0.0000	0.1540	0.3260	405.1772	0.0000	0.0445	97.8997	47.6123
6	0.2114	8.4617	0.0000	0.1266	0.3106	432.6104	0.0000	0.0555	98.2947	58.6418
7	0.2143	8.4649	0.0000	0.1284	0.3145	409.5760	0.0000	0.0562	97.9837	49.5953
8	0.1877	10.3372	0.0000	0.1243	0.2603	373.4364	0.0000	0.0320	97.1216	34.7421
9	0.2282	9.1912	0.0000	0.1438	0.3251	432.6441	0.0000	0.0510	98.1736	54.7519
10	0.2191	8.6173	0.0000	0.1329	0.3194	441.1688	0.0000	0.0557	98.3132	59.2828
11	0.2154	8.4915	0.0000	0.1294	0.3158	437.6484	0.0000	0.0562	98.2588	57.4324
12	0.2168	8.5849	0.0000	0.1311	0.3166	441.1904	0.0000	0.0557	98.3297	59.8679
13	0.2173	8.5530	0.0000	0.1311	0.3176	441.1376	0.0000	0.0560	98.3184	59.4664
14	0.2053	8.5509	0.0000	0.1235	0.3010	421.4747	0.0000	0.0526	98.2198	56.1743
15	0.2170	8.5200	0.0000	0.1306	0.3176	438.1105	0.0000	0.0562	98.0273	50.6917
16	0.1999	8.7943	0.0000	0.1221	0.2908	409.5013	0.0000	0.0482	98.0671	51.7357
17	0.2170	8.5311	0.0000	0.1307	0.3175	440.7493	0.0000	0.0561	98.2855	58.3258
18	0.2055	8.5201	0.0000	0.1233	0.3016	370.1912	0.0000	0.0529	98.1522	54.1179
19	0.2164	8.5117	0.0000	0.1302	0.3169	439.6458	0.0000	0.0562	98.2610	57.5052



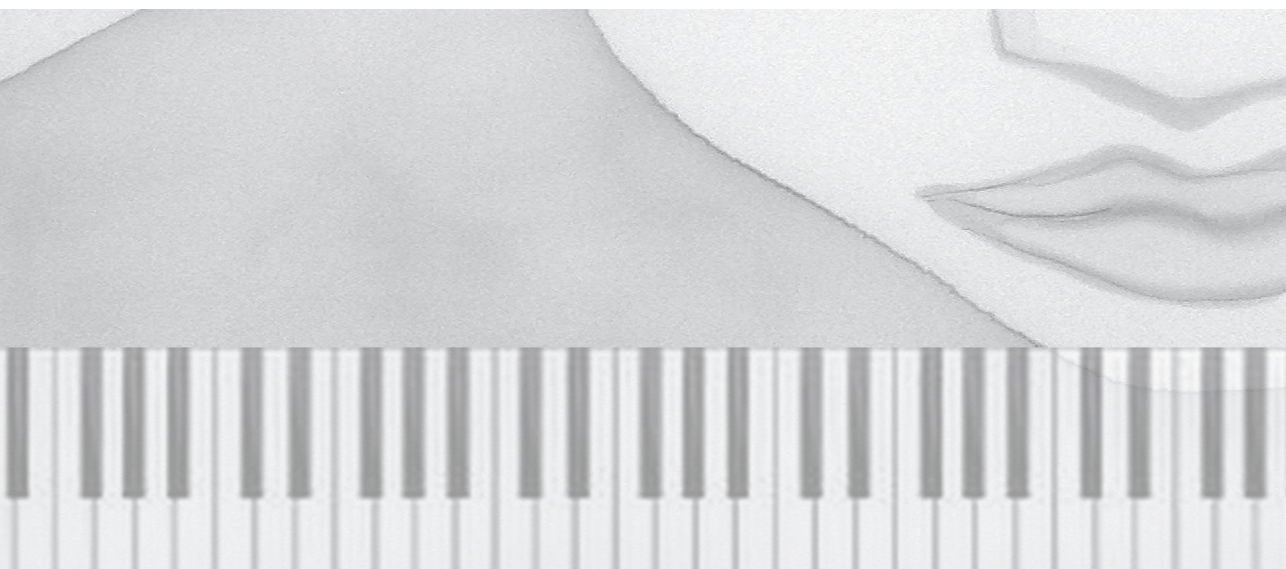
Appendix D: overview of risk of bias assessment

Risk of Bias: Cochrane Risk of Bias tool for Randomized Controlled Trials

Study ID	Method of randomization	Allocation concealment	Blinding participants	Blinding Assessors	Incomplete Outcome	Selection of reporting	Adequately Assessed	Other Bias	Overall
Greenberg, 2017	Low	Unclear	Low	Low	Unclear	Low	Low	Low	Some concerns
Mohktari, 2020	Low	Unclear	Low	Low	High	Low	High	High	High

Risk of Bias: Newcastle-Ottawa Scale (NOS) for cohort-studies

	Selection			Comparability			Exposure		Overall
	Representativeness cohort	Selection non-exposed	Ascertainment exposure	Outcome baseline	Specificity groups	Frequent assessment	Ascertainment exposure	Adequacy follow-up	
Budenas, 2018	*	*	*	-	N/A	-	-	-	Poor
Carlson, 2014	*	*	-	-	N/A	-	-	*	Poor
Chen, 2020	*	*	-	*	*	*	-	*	Good
Flanigan, 2017	*	*	-	-	N/A	-	-	*	Poor
Harasawa, 2014	*	*	*	*	N/A	*	-	*	Good
He, 2019	*	*	*	-	N/A	*	-	*	Poor
Hosoya, 2018	-	*	*	-	*	-	-	-	Poor
Lange, 2015	*	*	-	-	N/A	-	-	*	Poor
Matano, 2017	-	*	*	-	-	*	-	*	Fair
Morshed, 2019	*	*	*	-	*	-	-	*	Poor
Ogasawara, 2020	*	*	-	*	N/A	-	-	-	Poor
Oh, 2008	*	*	*	-	-	-	-	*	Poor
Tanaka, 2018	*	*	-	-	N/A	-	-	*	Poor
Wang, 2020 (A)	*	*	*	-	*	*	-	*	Good
Wang, 2017	*	*	*	-	N/A	*	-	*	Good
Wang, 2019	*	*	*	-	N/A	-	-	-	Poor
Wang, 2020 (B)	*	*	-	-	-	*	-	*	Fair
Zhan, 2020	*	*	*	-	*	*	-	-	Good

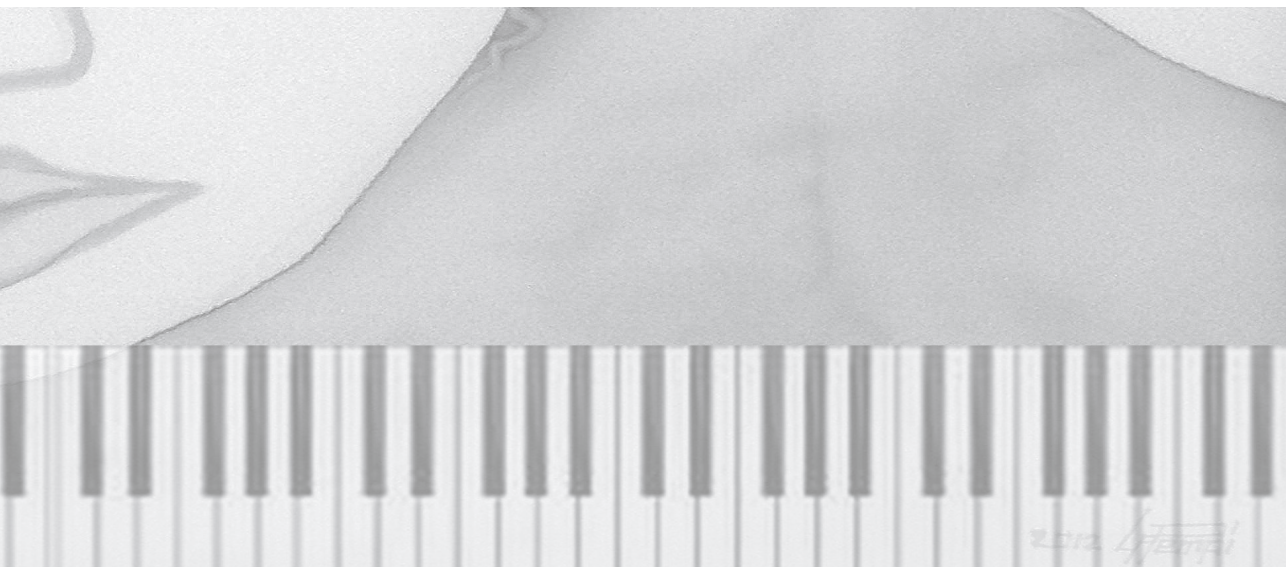


CHAPTER 3

Post-operative Delirium after Intracranial Surgery: a retrospective cohort study

Pablo R. Kappen M.D, Hilbert J. Kappen PhD, Clemens M.F. Dirven M.D. PhD,
Markus Klimek M.D. PhD, Johannes Jeekel M.D PhD, E.R. Andrinopoulou PhD,
Robert J. Osse M.D. PhD, Arnaud J.P.E. Vincent, M.D. PhD

World Neurosurgery, 2023



Abstract

Introduction

The clinical relevance of post-operative delirium (POD) in neurosurgery remains unclear and should be investigated as these patients are vulnerable. Hence we investigated the impact of POD, by means of incidence and health outcomes, and identified independent risk factors.

Methods

Adult patients undergoing an intracranial surgical procedure in the Erasmus MC Rotterdam between June 2017 and September 2020 were retrospectively included. POD incidence, defined in case of a Delirium Observation Screening Scale (DOSS) ≥ 3 or antipsychotic treatment for delirium within 5 days after surgery, was calculated. Logistic regression analysis on the full data set was conducted for the multivariable risk factor and health outcome analyses.

Results

After including 2901 intracranial surgical procedures, POD was present in 19.4% with a mean (SD) onset in days of 2.62 (1.22) and associated with more Intensive Care Unit (ICU) admissions and more discharge towards residential care. Onset of POD was not associated with increased length of hospitalization or mortality. We identified several independent non-modifiable risk factors such as age, pre-existing memory problems, emergency operations, craniotomy compared to burr-hole surgery and severe blood loss. Moreover, we identified modifiable risk factors such as low pre-operative potassium and opioid and dexamethasone administration.

Conclusions

Our POD incidence rates and correlation with more ICU admission and discharge towards residential care suggest a significant impact of POD on neurosurgical patients. We identified several modifiable and non-modifiable risk factors, which shed light on the pathophysiologic mechanisms of POD in this cohort and could be targeted for future intervention studies.

Introduction

Delirium is a neurocognitive disorder characterized by an acute disruption of attention and/or awareness, accompanied with other cognitive deficits, with fluctuating severity during the course of a day.(1) Its occurrence is common after surgery, especially in elderly patients, with an incidence between 5.1% and 52.2%.(2-4) Moreover, postoperative delirium (POD) is a serious complication, as it is associated with increased risk for re-surgery and mortality.(5)

Hypotheses for the pathophysiology of POD propose neuroinflammatory and oxidative reactions, resulting in acute encephalopathy.(6) Similar reactions, including inflammation, formation of edema and oxidative stress, are evoked after brain operations. Patients undergoing intracranial surgery could therefore be particularly vulnerable to the development of POD. This is confirmed in studies reporting incidence rates between 7 - 31%.(7-9) Moreover, POD after intracranial surgery is associated with an unfavorable functional outcome at discharge and increased length of admission.(5) These data suggest a clinically relevant impact of POD in neurosurgical patients.

Current management of POD is focused on pre-operative counseling and preventive therapies, as currently no effective treatment exists for POD in any surgical population. (10)

Hence, identifying modifiable risk factors, and being able to predict POD, play a crucial role in lowering the incidence after intracranial surgery. However, literature on this topic is limited with small sample sizes, unclear definition of investigated cohort and limited statistical analysis. (5)

We therefore conducted this retrospective study in a large cohort to assess the impact of POD, by means of incidence and delirium-related health outcomes. Second, we identified independent risk factors and developed a prediction model for risk assessment in future patients.

Methods

Availability of data and material

Data cannot be shared publicly because of the privacy legislation our research project adheres to. However, data are available for researchers who meet the criteria for access to confidential data.

Study design

This retrospective cohort study was conducted in a single academic medical center in the Erasmus Medical Center Rotterdam (Erasmus MC). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement and the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) was followed for the reporting of this study. (11, 12)

Eligibility criteria and delirium definition

All data from electronic patient files in the Erasmus MC are stored and managed by the Competence Center Business Intelligence (CCBI) since June 2017. Hence all adult neurosurgical patients (i.e. age ≥ 18 years) undergoing intracranial surgery between June 2017 and September 2020 in the Erasmus MC were included.

Post-operative delirium (POD) was defined in case of a Delirium Observation Screening Scale (DOSS) score ≥ 3 or newly prescribed antipsychotic medication (i.e. Haloperidol) within 5 days after the intracranial procedure. The DOSS, a standardized delirium-screening tool validated in the hospital-wide population, was chosen as it is currently standard of clinical care at the neurosurgical ward of the Erasmus MC. (13) A score of ≥ 3 suggests delirium and is reported with high sensitivity (90%) and specificity (92%) in non-neurosurgical cohorts. (14-16) DOSS was not systematically assessed in alle admitted patients but applied in case of a clinical suspicion by the nurse or treating physician, so we added newly prescribed antipsychotic medication to our definition; although we acknowledge that this is no formal DSM criteria for POD, it does reflect the likelihood of POD in clinical practice. The 5 days window was chosen as the onset of post-operative delirium after intra-cranial surgery has been reported on 2.8/0.6 days.(5)

Data extraction

The CCBI manages and disseminates all data hospital broad for qualitative and scientific purposes. We requested the data, relevant for our research question, from the CCBI to assure a large cohort size. We first validated this CCBI data by separately extracting a random sample within this cohort by an independent researcher (T.L.). Second, inter-observer reliability from both datasets was calculated with respect to the diagnosis of POD using Cohen's kappa (κ) coefficient and deemed valid in case of a $\kappa > 0.81$ (i.e. almost perfect agreement). (17) (18)

Subsequently, preoperative data including baseline characteristics (demographic data, nutritional status, patient functionality, prior delirium, cognitive function), pre-operative hospital data (lab results, medication use, prior neurosurgical interventions), surgical details (type of disease operated, craniotomy / requirement of bone flap removal, emergency category, duration and blood loss) and post-operative hospital data (admission length, intensive care unit/ICU admission, discharge location and mortality) were extracted based on relevant delirium-related factors identified from other published studies. (5, 9, 19)

Statistical analysis

All statistical analysis was conducted using R (version 4.1.1).

Missing data were imputed by means of a random forest algorithm using the missForest package (see appendix A for a more detailed description on imputation steps). (20-22) We evaluated whether our missing data were at random by observing the missing rates per group (POD vs. non-POD) and ran all analyses again, after excluding covariates with large missing rates, to investigate whether the missing values would influence the outcomes.

The incidence of POD for all included patients was calculated and expressed with a 95% confidence interval (95%CI). A sub-analysis of incidence was conducted for only those patients with a DOSS. For risk factor and health outcome identification a multivariable analysis was conducted by including all covariates within a logistic regression analysis on the full dataset. Odds ratios (ORs) and their 95% CIs were used to assess the independent contribution of significant factors. A Cox proportional hazard regression was conducted to analyze the influence of delirium on survival. We included covariates which we expected to influence survival, and the proportional hazard assumption was tested with the Schoenfeld Individual test (appendix B).

A recent systematic review reported that machine learning algorithms outperformed regression analyses in neurosurgical literature.(41) Motivated by this research, we also investigated machine learning approaches (Support Vector Machine, Gradient Boosting Machine and Artificial Neural Network) and compared these with two regression techniques (Logistic Regression and Lasso and Elastic-Regularized Generalized Linear Models). All predictive models were optimized using the exact same steps with the Caret package from R, to assure fair comparison. The total cohort was randomly split into a training and hold-out test set based on an 75/25 ratio. All

covariates, whether significant or not on the basis of the univariate analysis, were included in the predictive analysis. Five-fold cross-validation was ten times repeated over the training set for parameter optimization and hyperparameter tuning. Each algorithm, either regression and machine learning, was then trained based on a range of model specific hyperparameters. To investigate the predictive performance of the models we assumed the Area Under the Curve (AUC) measure. To correct for optimism, we performed a cross validation procedure (see appendix C for a more detailed description on pre-processing of our prediction models).

Results

Data inclusion and preparation

A total of 4344 neurosurgical procedures were consecutively conducted between June 2017 and September 2019 at the Erasmus MC. Neurosurgical interventions not performed in the operation room ($n = 52$) or solely spinal surgeries ($n = 1391$) were excluded resulting in 2901 intracranial surgeries included in the dataset. Comparison with an independently extracted dataset, of 270 intracranial surgeries between June 2018 and September 2018, resulted in an agreement of 96% ($\kappa = 0.81$). We therefore deemed the dataset of 2901 surgeries valid and continued for analysis (appendix D).

Missing data (%) were imputed ten times for prior delirium (38.5%), need of daily assistance (38.4%), memory problems (38.3%), sodium (15.8%), potassium (18.3%) levels, duration of surgery (10.3%), obesity (4.4%), admitted from residential care (0.5%) and gender (0.3%).

Impact of POD: incidence and health-related outcomes

POD was found in 19.3% ($n = 561$, 95% CI; 0.18 – 0.21) as determined by an increased DOSS ($n = 481$, 16.7%) and/or Haldol treatment ($n = 203$, 6.9%). Incidence was 44.1% (95%CI: 0.41-0.47) in those patients with DOSS assessment ($n = 1105$). We found patients with DOSS assessment and Haldol in 4.3% (95%CI; 0.04-0.05). The mean (SD) onset of POD was 2.62 (1.22) days. Incidence and distribution of the included covariates between the POD and non-POD groups are illustrated in table 1.

Multivariable analyses showed that onset of POD was correlated (OR/95%CI) with intensive care unit admission (ICU, 1.795, 1.447-2.226, $p < 0.001$) and discharge to

residential care (2.553, 2.059-3.163, $p < 0.001$) after correcting for age, obesity and gender (table 2). POD was not correlated with length of hospitalization (15.0 vs 18.0 days, $p = 0.165$) or thirty-day mortality (10.5 vs 8.7%, $p = 0.640$). No correlation was found between POD ($p = 0.464$) on the length of survival after correcting for age ($p < 0.001$), gender ($p < 0.001$) and obesity ($p = 0.112$, figure 1).

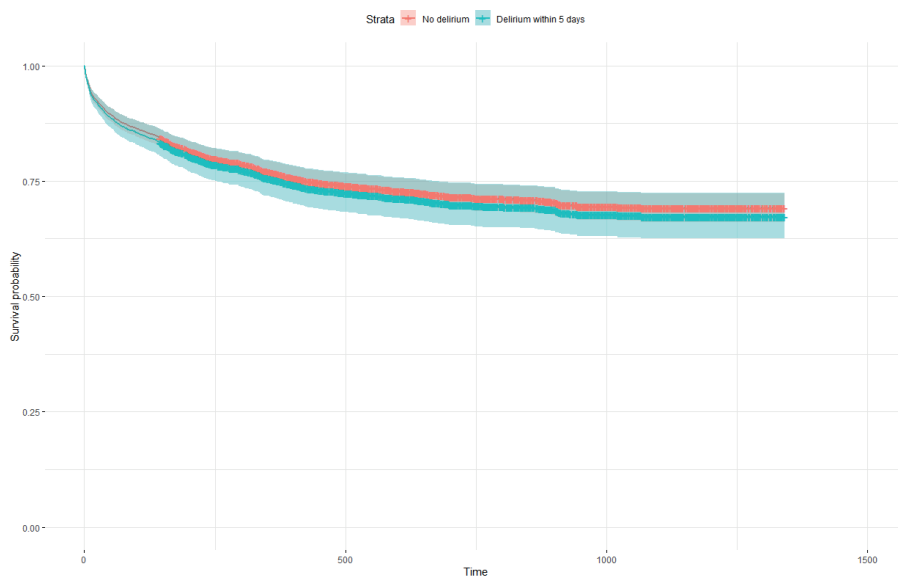


Figure 1. Cox Proportional Hazard Survival Curve: Kaplan Meier Survival Curve

Legend: survival non-delirium (in red, non-POD) vs. delirium (in blue, POD) group after intracranial surgery. Onset of POD did not significantly change length of survival ($p = 0.464$) after correcting for female gender ($p < 0.001$), age ($p < 0.001$) and obesity ($p = 0.112$).

Risk factor identification

All extracted covariates, illustrated in table 1, were used for multivariable risk factor identification which can be found in table 3. Independent risk factors (OR / 95% CI) associated with increased risk for POD included the following: age (1.028 / 1.021 – 1.035, $p < 0.001$), admitted from residential care (1.519/1.197-1.927, $p < 0.001$), need for daily assistance (1.833/ 1.368-2.457, $p < 0.001$), memory problems (1.772/ 1.335-2.351, $p = 0.001$), post-operative opioid administration (1.499/1.147-1.961, $p = 0.003$), dexamethasone administration (1.308/1.024-1.671, $p = 0.031$), emergency

operations (2.102/1.606-2.75, $p < 0.001$), craniotomy (1.928/1.370- 2.713, $p < 0.001$) and blood loss (1.000/1.000-1.001, $p < 0.001$)

Independent risk factors associated with decreased risk for POD included the following: female gender (0.798/0.649-0.982, $p=0.033$), increased body mass index (BMI, 0.973/ 0.952-0.995, $p=0.018$) and potassium levels (0.682/0.537-0.864, $p=0.002$), oncologic (0.252/0.092-1.690, $p = 0.007$) and trauma (0.223/0.079-0.625, $p=0.004$) surgeries.

The performance (AUC) of the prediction models was between 0.64 – 0.78. We found no difference in our prediction models between the machine learning and regression algorithms with respect to the discrimination and calibration properties (appendix E).

Discussion

Our incidence rates of 19.3%, with more ICU admission and admission towards residential care suggests an impact of POD after intracranial surgery. We were able to identify several modifiable and non-modifiable risk factors. Clinical implications and limitations are discussed below.

Incidence and definition

Until present several studies have been published on risk factors for POD in intracranial surgery but these studies vary between each other in delirium definition as different types of screening instruments were used. (5) Neurosurgical studies on delirium defined by the DOSS, a widely validated instrument developed in the Netherlands, has only been published once and determining the clinical relevance and risk factors of delirium diagnosed with this definition might aid in neurosurgical practices handling DOSS. Our incidence rates are in line with a recent systematic review showing a pooled estimate of 19%. (5) This high incidence is plausible, as intracranial surgery encompasses high risk interventions in patients with vulnerable brains. (23) This percentage incidence also confirms a recent published prospective intracranial surgery cohort describing emergence delirium (ED) in 22% of the cases. (24) Although ED and POD overlap in symptomatology and are correlated with each other, the entity of these diseases is considered differently. POD is associated with worse outcomes such as longer hospital stays, higher costs and lowered quality of life and, in contrast, ED is likely related to the effects of residual general anesthetics

and is “self-limiting” without sequelae.(25) Antipsychotic treatment was only administered in 36.2% of our POD population, which could have several reasons: it could be a delirium without psychotic features, as in the current guideline in the Netherlands the use of antipsychotics in delirium is debated and not stimulated. Moreover, it could be delirium without any problematic behavior on the ward. Last, perhaps a contradiction (i.e. challenge of external drain at that time, which mandates observation of the awareness / prolonged cardiac QT interval) could have intervened with antipsychotic treatment. Whilst we selected only patients undergoing intracranial surgery for our study, it should not be forgotten, that also cervical spinal procedures can cause intracranial complications presenting themselves with delirium as one of the symptoms.(26) Although we did not analyze this, we expect a different incidence in spinal surgeries as the pathophysiology of POD relies on neuroinflammatory and oxidative reactions, resulting in acute encephalopathy. Similar reactions, including inflammation, formation of edema and oxidative stress, are evoked after brain operations which intuitively leads to higher incidence rates in cranial rather than spinal surgery cohort populations. (6) Moreover, the definition in spinal surgery is less complex as the criteria of delirium do not overlap with the primary neurologic symptoms as opposed to intracranial surgery patients.

Clinical relevance

Onset of delirium did not independently correlate with hospitalization length or mortality. Although many studies suggest an increased mortality in patients with delirium, this is not found when controlling for pre-specified confounders in either the neurosurgical or non-neurosurgical literature. (5, 27) We did find that POD patients were more often discharged towards residential care and more often admitted to the ICU. Causation remains unclear, since it could be argued that ICU admission led to POD, instead of the other way around. We do not suspect this as DOSS is not used as a screening instrument on our ICU.

Underlying mechanisms and risk factors

It could be argued that all the different pathways, varying from demographic variation to type of surgery, hinders an overall conclusion on this population. However, we state that POD is defined by its phenomenologic presentation in which the etiology is nearly always multifactorial. Shedding light on which factors contribute to this

clinical presentation could aid in the pre-operative decision-making and create targets for future intervention studies (28) Older age and memory problems seemed to be risk factors for the development of POD. This was not surprising as older age, associated with neuro-inflammatory induced degeneration, is associated with less cognitive resilience. Signaling of inflammation by the operation in these older patients induces acute encephalopathy, rather than just fever and sickness behavior. (28) Moreover, admission from residential care and pre-operatively needing daily assistance were independent risk factors for delirium. This was suspected, as early mobilization has proven to decrease the onset of delirium on the ICU and is currently an element in advised multi-component strategies. (29) Strikingly, neurovascular was no independent factor for delirium development, which we did not expect as clipping procedure compromises brain oxygenation inducing the onset of POD. (28)

Although dexamethasone does reduce the inflammatory response, which subsequently could have led to a decrease of delirium, it resulted in more delirium in our cohort. It is common lore that steroids can induce neuropsychiatric manifestations but no cohort studies up to date supported this assertion, which was based on case reports. (30, 31) Lowering dexamethasone dosages around intracranial surgeries could be considered when high risk of POD development is suspected. Pre-operative low potassium was a risk factor for the development of POD. Poor nutritional status, associated with low potassium, might have increased the frailty and therefore POD incidence in these patients. (32) Indeed higher BMI seemed protective for the development of delirium in our cohort. Hence, correcting pre-operative potassium and improving nutritional status could be a target for the prevention of POD. (33) Strikingly, the protective function of BMI was even present when comparing the healthy (BMI: 20-25) range with the severe obesity (BMI>30) range (incidence 22.9 vs. 13.2%). A recent published study showed BMI to be protective to POD through several cerebrospinal fluid biomarkers, confirming the ‘obesity paradox’. (34) As the negative effects of obesity are obvious such as increasing risk on cardiovascular events, for which we did not correct, it remains to be determined whether the impact of higher BMI on neurosurgical patients will be more beneficial or harmful. (35)

Post-operative opioids were independently associated with onset of POD. Morphine which is widely used in our unit, has anticholinergic properties, that may favor the development of delirium. (36) However, it could be debated whether opioid could be an epiphenomenon of more postoperative pain and more complications resulting in

more delirium. Moreover, opioids are used for pain treatment as increase in pain level after surgery also is a significant risk factor for postoperative delirium.(37) Therefore, other analgesic treatment, such as scalp blocks or non-pharmacologic alternatives, may be considered as both treatment with opioids and under-treatment of pain may initiate delirium. (38, 39)

Prediction models

Being able to predict POD, for pre-operative counseling and preventive measures, is of crucial importance as currently no treatment exists for POD. Our prediction models were able to correctly identify which patient develop POD in 65 – 78% of the cases. (40) Moreover, we did not find machine learning to perform better than regression algorithms, in contrast to a recent systematic review, which found an overall better performance of machine learning compared to traditional regression statistics in neurosurgical studies. (41) This difference might have been caused as we took identical steps for all algorithms, in contrast to other papers adjusting pre-processing and parameter tuning to enhance the machine learning algorithms performances.(41) Our prediction model should be validated on an external cohort to assess its true predictive performance.

Limitations

It could be debated that our definition of delirium overestimates the POD incidence as DOSS is a screening tool which should be confirmed by the DSM-5 criteria to diagnose POD. Besides the argument that we were limited by our study design, we argue that the DOS-scale was only applied in case of a clinical suspicion of POD and potentially treated with antipsychotic drugs in case of psychotic symptoms. Our definition therefore does reflect the clinical suspicion of POD at that time and might therefore also have contributed to under estimation of POD incidence rates: this is substantiated by our sub-analysis which showed a significant increase of POD incidence in only those patients who underwent a DOSS screening. (7, 42, 43) (44) Moreover, the fact that some items in the DOSS could also reflect the primary symptoms of the neurosurgical patient, stresses the clinical relevance of delirium in this population. However, this is refuted by the patients not showing delirium-like symptoms and makes the analyses between POD and non-POD on the health-outcomes clinically relevant. Last, we did not analyze post-operative imaging features and therefore do

not know whether a bleeding, ischemia or hydrocephalus could have been a cause of POD in our cohort. We chose not to analyze this, as most of the included studies in our previous published review did not describe radiologic features to be predictive for the onset of delirium. (5, 9)

Conclusion

Our incidence rates and correlation with more ICU admission and discharge towards residential care suggests an impact of POD after intracranial surgery. However, no correlation was found of POD on length of hospitalization and mortality. Moreover, we identified several modifiable risk factors, such as dexamethasone, opioid administration and low pre-operative potassium, which can be used for future intervention studies. We built a prediction model, after comparing regression with machine learning algorithms, which should be validated on an external cohort to assess its true predictive value.

Key points

- We report an incidence rate of 19.3% after intracranial surgery.
- An impact of POD after intracranial surgery is suggested as it is associated with more ICU admission and more discharge towards residential care but not with length of hospitalization or mortality.
- Opioid and dexamethasone administration and low pre-operative potassium are modifiable risk factors associated with the onset of POD.
- We build a prediction model, with similar performance of regression vs. machine learning algorithms.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th edition. 2013.
2. Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. *J Am Geriatr Soc*. 2006;54(10):1578-89.
3. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911-22.
4. Marcantonio ER. Postoperative delirium: a 76-year-old woman with delirium following surgery. *JAMA*. 2012;308(1):73-81.
5. Kappen PR, Kakar E, Dirven CMF, van der Jagt M, Klimek M, Osse RJ, et al. Delirium in neurosurgery: a systematic review and meta-analysis. *Neurosurg Rev*. 2021.
6. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry*. 2013;21(12):1190-222.
7. Flanigan PM, Jahangiri A, Weinstein D, Dayani F, Chandra A, Kanungo I, et al. Postoperative Delirium in Glioblastoma Patients: Risk Factors and Prognostic Implications. *Neurosurgery*. 2018;83(6):1161-72.
8. Harasawa N, Mizuno T. A novel scale predicting postoperative delirium (POD) in patients undergoing cerebrovascular surgery. *Arch Gerontol Geriatr*. 2014;59(2):264-71.
9. He Z, Cheng H, Wu H, Sun G, Yuan J. Risk factors for postoperative delirium in patients undergoing microvascular decompression. *PLoS One*. 2019;14(4):e0215374.
10. Siddiqi N, Stockdale R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. *Cochrane Database Syst Rev*. 2007(2):CD005563.
11. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. *BMC Med*. 2015;13:1.
12. von Elm E AD, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Lancet*. 2007;Oct 20;370(9596):1453-7.
13. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. *Res Theory Nurs Pract*. 2003;17(1):31-50.
14. Gavinski K, Carnahan R, Weckmann M. Validation of the delirium observation screening scale in a hospitalized older population. *J Hosp Med*. 2016;11(7):494-7.
15. Neefjes ECW, van der Vorst M, Boddaert MSA, Verdegaal B, Beeker A, Teunissen SCC, et al. Accuracy of the Delirium Observational Screening Scale (DOS) as a screening tool for delirium in patients with advanced cancer. *BMC Cancer*. 2019;19(1):160.
16. Park J, Jeong E, Lee J. The Delirium Observation Screening Scale: A Systematic Review and Meta-Analysis of Diagnostic Test Accuracy. *Clin Nurs Res*. 2021;30(4):464-73.
17. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)*. 2012;22(3):276-82.
18. Hartling L, Hamm M, Milne A, Vandermeer B, Santaguida PL, Ansari M, et al. Validity and Inter-Rater Reliability Testing of Quality Assessment Instruments. 2012/04/27 ed2012 Mar.

19. Wang CM, Huang HW, Wang YM, He X, Sun XM, Zhou YM, et al. Incidence and risk factors of postoperative delirium in patients admitted to the ICU after elective intracranial surgery: A prospective cohort study. *Eur J Anaesthesiol*. 2020.
20. Waljee AK, Mukherjee A, Singal AG, Zhang Y, Warren J, Balis U, et al. Comparison of imputation methods for missing laboratory data in medicine. *BMJ Open*. 2013;3(8).
21. Stekhoven DJ, Bühlmann P. MissForest--non-parametric missing value imputation for mixed-type data. *Bioinformatics*. 2012;28(1):112-8.
22. Gravesteijn BY, Sewalt CA, Venema E, Nieboer D, Steyerberg EW, Collaborators C-T. Missing Data in Prediction Research: A Five-Step Approach for Multiple Imputation, Illustrated in the CENTER-TBI Study. *J Neurotrauma*. 2021;38(13):1842-57.
23. Maldonado JR. Acute Brain Failure: Pathophysiology, Diagnosis, Management, and Sequelae of Delirium. *Crit Care Clin*. 2017;33(3):461-519.
24. Bharadwaj S, Konar S, Akash VS, Gopalakrishna KN, Chakrabarti D, Kamath S. Emergence delirium after intracranial neurosurgery- a prospective cohort study. *J Clin Neurosci*. 2022;104:12-7.
25. Zhang Y, He ST, Nie B, Li XY, Wang DX. Emergence delirium is associated with increased postoperative delirium in elderly: a prospective observational study. *J Anesth*. 2020;34(5):675-87.
26. Habunaga H, Nakamura H. Intracranial subdural hematoma as a cause of postoperative delirium and headache in cervical laminoplasty: A case report and review of the literature. *SAS J*. 2011;5(1):1-3.
27. Hamilton GM, Wheeler K, Di Michele J, Lalu MM, McIsaac DI. A Systematic Review and Meta-analysis Examining the Impact of Incident Postoperative Delirium on Mortality. *Anesthesiology*. 2017;127(1):78-88.
28. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *Int J Geriatr Psychiatry*. 2018;33(11):1428-57.
29. Tammy T. Hsieh MD, 1,4 Jirong Yue, M.D., 2 Esther Oh, M.D., 3 Margaret Puelle, 4 Sarah Dowal, M.S., 4 Thomas Trivison, PhD, 4, 5, * and Sharon K. Inouye, M.D., MPH, 4, 5, *. Effectiveness of multi-component non-pharmacologic delirium interventions: A Meta-analysis. *JAMA Intern Med*. 2016;175(4): 512–520.
30. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. *J Affect Disord*. 1983;5(4):319-32.
31. Marcantonio ER, Juarez G, Goldman L, Mangione CM, Ludwig LE, Lind L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA*. 1994;272(19):1518-22.
32. Rosted E, Prokofieva T, Sanders S, Schultz M. Serious Consequences of Malnutrition and Delirium in Frail Older Patients. *J Nutr Gerontol Geriatr*. 2018;37(2):105-16.
33. Setti SE, Littlefield AM, Johnson SW, Kohman RA. Diet-induced obesity attenuates endotoxin-induced cognitive deficits. *Physiol Behav*. 2015;141:1-8.
34. Xiyuan Deng PQ, Bin Wang, Yanlin Bi. The relationship between body mass index and postoperative delirium. *Brain and Behavior*. 2022;12, e2534.
35. Ades PA, Savage PD. The obesity paradox: perception vs knowledge. *Mayo Clin Proc*. 2010;85(2):112-4.

36. Marcantonio ER, Goldman L, Mangione CM, Ludwig LE, Muraca B, Haslauer CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA*. 1994;271(2):134-9.
37. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: the importance of pain and pain management. *Anesth Analg*. 2006;102(4):1267-73.
38. Swart LM, van der Zanden V, Spies PE, de Rooij SE, van Munster BC. The Comparative Risk of Delirium with Different Opioids: A Systematic Review. *Drugs Aging*. 2017;34(6):437-43.
39. Darmawikarta D, Sourour M, Couban R, Kamath S, Reddy KK, Shanthanna H. Opioid-Free Analgesia for Supratentorial Craniotomies: A Systematic Review. *Can J Neurol Sci*. 2019;46(4):415-22.
40. DW Hosmer SL. *Applied Logistic Regression*. 2nd Ed Chapter 5, John Wiley and Sons, New York, NY. 2000.
41. Senders JT, Staples PC, Karhade AV, Zaki MM, Gormley WB, Broekman MLD, et al. Machine Learning and Neurosurgical Outcome Prediction: A Systematic Review. *World Neurosurg*. 2018;109:476-86 e1.
42. Chen L, Xu M, Li GY, Cai WX, Zhou JX. Incidence, Risk Factors and Consequences of Emergence Agitation in Adult Patients after Elective Craniotomy for Brain Tumor: A Prospective Cohort Study. *PLoS One*. 2014;9(12):e114239.
43. Wang J, Ji Y, Wang N, Chen W, Bao Y, Qin Q, et al. Risk factors for the incidence of delirium in cerebrovascular patients in a Neurosurgery Intensive Care Unit: A prospective study. *J Clin Nurs*. 2017;27(1-2):407-15.
44. Peterson JF, Pun BT, Dittus RS, Thomason JWW, Jackson JC, Shintani AK, et al. Delirium and Its Motoric Subtypes: A Study of 614 Critically Ill Patients. *Journal of the American Geriatrics Society*. 2006;54(3):479-84.

Table 1. Baseline characteristics

Variables ¹	POD – (n = 2340)	POD + (n = 561)	Overall (n = 2901)
Pre-hospital demographics			
Age in years	53.7 (16.8)	62.7 (14.8)	55.5 (16.8)
Female gender	1212 (51.8%)	267 (47.6%)	1479 (51.0%)
BMI ²	26.4 (5.10)	25.7 (4.56)	26.3 (5.01)
Admitted from residential care ³	597 (25.5%)	259 (46.2%)	856 (29.5%)
Daily assistance ⁴	290 (12.4%)	167 (29.8%)	457 (15.8%)
Prior delirium	130 (5.6%)	71 (12.7%)	201 (6.9%)
Memory problems ⁵	353 (15.1%)	168 (29.9%)	521 (18.0%)
In-hospital data			
Medication ⁶			
Antithrombotic	56 (2.4%)	19 (3.4%)	75 (2.6%)
Dexamethasone	1366 (58.4%)	354 (63.1%)	1720 (59.3%)
Benzodiazepine	66 (2.8%)	17 (3.0%)	83 (2.9%)
Opioid	402 (17.2%)	103 (18.4%)	505 (17.4%)
Prior neurosurgery	645 (27.6%)	128 (22.8%)	773 (26.6%)
Lab results ⁷			
Sodium level	140 (3.86)	139 (4.23)	140 (3.94)
Potassium level	4.11 (0.423)	4.02 (0.519)	4.10 (0.444)
Surgical details			
Type of surgery			
Functional	17 (0.7%)	6 (1.1%)	23.0 (0.8%)
Hydrocephalus	661 (28.2%)	153 (27.3%)	814 (28.1%)
Infection	21 (0.9%)	6 (1.1%)	27.0 (0.9%)
Oncologic	1000 (42.7%)	166 (29.6%)	1166 (40.2%)
Trauma	465 (19.9%)	130 (23.2%)	595 (20.5%)
Vascular	176 (7.5%)	100 (17.8%)	276 (9.5%)
Emergency operation ⁸	976 (41.7%)	345 (61.5%)	1321 (45.5%)
Craniotomy ⁹	1197 (51.2%)	304 (54.2%)	1501 (51.7%)
Duration surgery ¹⁰	287 (294)	280 (292)	286 (294)
Blood loss ¹¹	166 (479)	232 (640)	179 (515)

POD; post-operative delirium 1. All continuous variables are in mean/SD. 2. Body mass index 3. Admitted from other than own or family home such as residential care, other hospital or nursing place 4. Need of daily assistance in the last 24 hours before surgery. 5. Anamnestic reports of memory problems 6. Perioperative dexamethasone and antithrombotic agents (i.e. vitamin K antagonist, DOAC or thrombocyte aggregation inhibitors): 5 days before until 5 days after surgery and post-operative opioid and benzodiazepine: day 1 until day 5 after surgery. 7. Pre-operative sodium and potassium in milli-equivalents per liter (mEq/L) 8. Emergency operation in case of indication to operate within 72 hours. 9. Intracranial surgery requiring bone-flap removal. 10. Duration surgery in minutes 11. Amount of blood loss in milliliters.

Table 2. Delirium-related health outcomes

Variables	POD -	POD +	Adjusted Odds Ratio (OR)	95%CI	P-value
Admission days hospital ¹	15.0 (30.0)	18.0 (26.1)	0.675	0.456 - 0.969	0.165
ICU admission ²	593 (25.3%)	232 (41.4%)	1.795	1.447 - 2.226	<0.001
Discharge to residential care ³	788 (33.7%)	363 (64.7%)	2.553	2.059 - 3.163	<0.001
Thirty day mortality	203 (8.7%)	59 (10.5%)	1.085	0.770 - 1.528	0.640

POD; post-operative delirium. All outcomes were corrected for covariates which were expected to influence health outcomes: age, gender, obesity. 1. Mean / SD hospitalization days. 2. Admitted to the ICU during hospitalization. 3. Discharged towards residential care, other hospital or nursing place.

Table 3. Multivariable risk factor analysis

Variables ¹	Adjusted odds ratio (OR)	95% confidence interval (CI)	P value
<i>Pre-hospital demographics</i>			
Age in years	1.033	1.025-1.041	<0.001
Female gender	0.798	0.649-0.982	0.033
BMI	0.973	0.952-0.995	0.018
Admission from residential care	1.519	1.197-1.927	<0.001
Daily assistance	1.833	1.368-2.457	<0.001
Prior delirium	1.076	0.729-1.589	0.711
Memory problems	1.772	1.335-2.351	<0.001
<i>In-hospital data</i>			
<i>Medication</i>			
Antithrombotic	0.871	0.487-1.555	0.639
Benzodiazepine	1.336	0.743-2.403	0.333
Opioid	1.499	1.147-1.961	0.003
Dexamethasone	1.308	1.024-1.671	0.031
Prior neurosurgery	0.862	0.667-1.114	0.257
<i>Lab results</i>			
Sodium levels	0.986	0.963-1.011	0.294
Potassium levels	0.682	0.537-0.864	0.002
<i>Surgical details</i>			
Emergency operation	2.102	1.606-2.75	<0.001
<i>Type of surgery²</i>			
Hydrocephalus	0.497	0.176-1.405	0.188
Infection	0.442	0.107-1.826	0.259
Oncologic	0.252	0.092-0.690	0.007
Trauma	0.223	0.079-0.625	0.004
Vascular	0.735	0.262-2.063	0.559
Craniotomy	1.928	1.370- 2.713	<0.001
Duration surgery	0.999	0.999-1.001	0.786
Blood loss	1.000	1.000-1.001	<0.001

1. All the covariates from the baseline table were included in the multivariable analysis, see table 1 for description of each covariable. 2. All the types of operations were compared to functional surgery, hence not illustrated in this table..

Appendix A. MissForest imputation steps

Missing data were imputed by means of a random forest algorithm, using the missForest package.

The missForest method divides the dataset into two parts according to whether the variable is observed or missing in the original dataset. The observed observations are used as the training set, and the missing observations are used as the prediction set. The missing part of the variable is replaced under imputation by prediction from the random forest algorithms. This imputation process is iteratively repeated until the Normalized Root Mean Square Error (NRMSE), or proportion of falsely classified entries for categorical variables (FPC), between the current and the previous imputation result increases and missForest outputs the previous imputation as the final result.

Table. Error-rate imputation

Imputation round	Number iterations ¹	NRMSE	FPC
1	9	0.00006576	0.06136555
2*	4	0.00006560	0.06061277
3	4	0.00006580	0.06182948
4	5	0.00006585	0.06057829
5	10	0.00006614	0.06197665
6	10	0.00006579	0.06131717
7	4	0.00006607	0.06158825
8	9	0.00006597	0.06174034
9	5	0.00006626	0.06137780
10	8	0.00006646	0.06038606

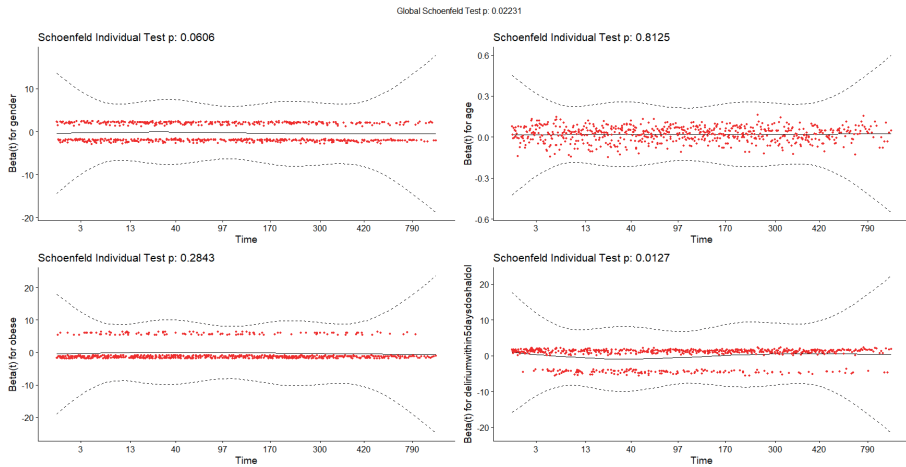
*NRMSE; normalized root mean squared error; FPC; proportion of falsely classified *imputation round with least error-rate as determined by NRMSE and FPC was chosen for further analysis.*

This procedure was ten times repeated, and a single imputed dataset with the least imputed error was chosen, as machine learning algorithms do not incorporate uncertainty into their parameter estimates (see table).

Appendix B. Cox Proportional Hazard Ratio assumption

We included the following covariates – additional to onset of delirium - in the proportional hazard ratio, as we expected these variables to influence health outcome: age, gender, obesity.

Before inspecting our model, we tested the proportional hazard assumption, with the Schoenfeld Individual test (see below).



Although we do see that the test is significant for delirium ($p=0.0127$), we do not observe any deviation from the midline. Hence, we attribute the significance to the skewed distribution between delirium (0.19) and no delirium (0.81) and suspect no violation of the proportional hazard assumption.

Appendix C. Method prediction model

Types of algorithms

For our prediction model we used five algorithms; two regression and three machine learning algorithms.

Regression algorithms

The regression techniques included standard logistic regression (LR), which uses a logistic function to model a binary dependent variable, and also penalized regression: Lasso and Elastic-Regularized Generalized Linear Models (GLMNET) which has two parameters to interpolate between Ridge and Lasso, both logistic regression analyses with additional regularization by punishing less relevant predictors, based on optimal values.

Machine learning algorithms

The machine learning algorithms included were Support Vector Machine (SVM), Gradient Boosting Machine (GBM) and Artificial Neural Network (aNN). SVM classify data points by selecting the “separating hyperplane” that maximize the distance from the 2 closes points on either side. GBM are decision trees, which make predictions or classifications based on several input features using bifurcation, but with a large number of trees and start the combining process at the beginning, instead of at the end (such as random forests). ANN are multilayer perceptrons starting with an input layer (containing predictors), and output layer to generate predictions, and then one or more hidden layers in between (referred to as hidden neurons). The networks can be built with different gradients of complexity.

Pre-processing and training

All predictive models were optimized using the exact same steps with the Caret package from R, to assure fair comparison. The total cohort was randomly split into a training and hold-out test set based on an 75/25 ratio. All covariates, whether significant or not on the basis of the univariate analysis, were included in the predictive analysis. Five-fold cross-validation was ten times repeated over the training set for parameter optimization and hyperparameter tuning. Each algorithm, either regression and machine learning, was then trained based on a range of model

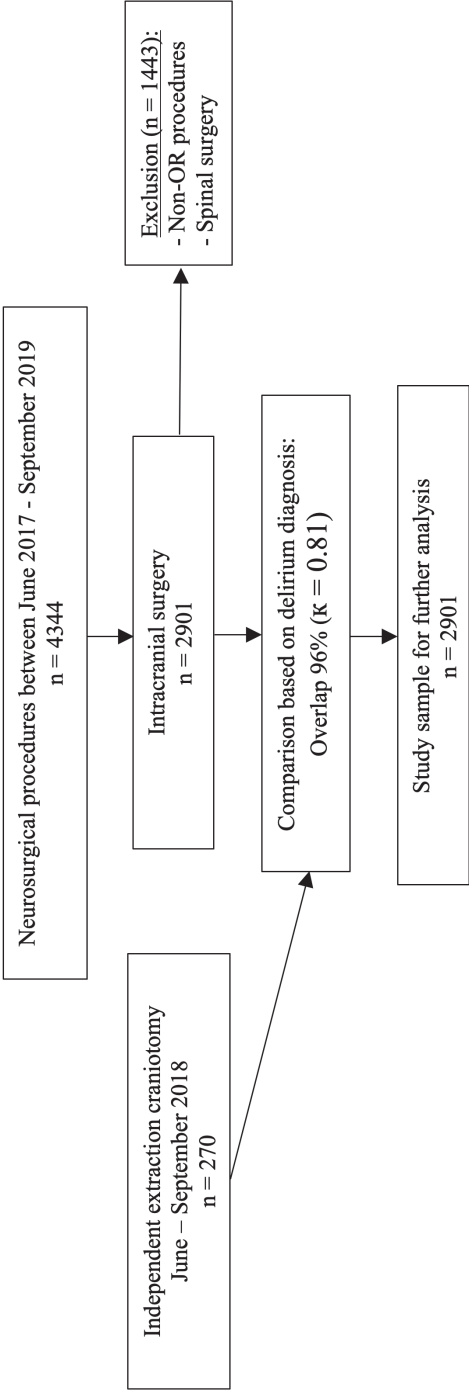
specific hyperparameters (such as the number of trees in the GBM and the number of middle neurons in aNN, see table below).

Algorithm	Parameters [range]	Optimal hyper parameter settings*
LR	-	-
GLMNET	Alpha [0.10 – 1.00]	Alpha = 0.1
	Lambda [0.00-0.017]	Lambda = 0.017
SVM	Sigma constant [0.00 – 0.900]	Sigma = 0.1
	Cost [0.00 – 5.00]	Cost = 0.01
GBM	N trees [50 – 1500]	N. trees = 50
	Interaction depth [1 – 9]	Interaction depth = 5
	Shrinkage [0.1]	Shrinkage = 0.1
		n.minobsinnode = 20
NN	Hidden neurons [2-25]	Hidden neurons = 2
	Decay [10^{-9} – 1.0]	Decay = 1.0

LR; logistic regression, GLMNET; lasso and ridge elastic-net, SVM; support vector machines, GBM; gradient boosting machine, aNN; artificial neural network. *hyper parameter specific to each algorithm

The trained model with optimized hyperparameter setting were then evaluated on the hold-out test set, which had not been used for preprocessing and hyper parameter tuning in any form. This process was ten-times repeated and the results with its confidence intervals were illustrated in a boxplot.

Appendix D. Inclusion flowchart



K = inter-rater reliability; *OR* = operation room

Appendix E. Results of prediction models

See figure below for the discrimination performance of each algorithm presented in a boxplot.

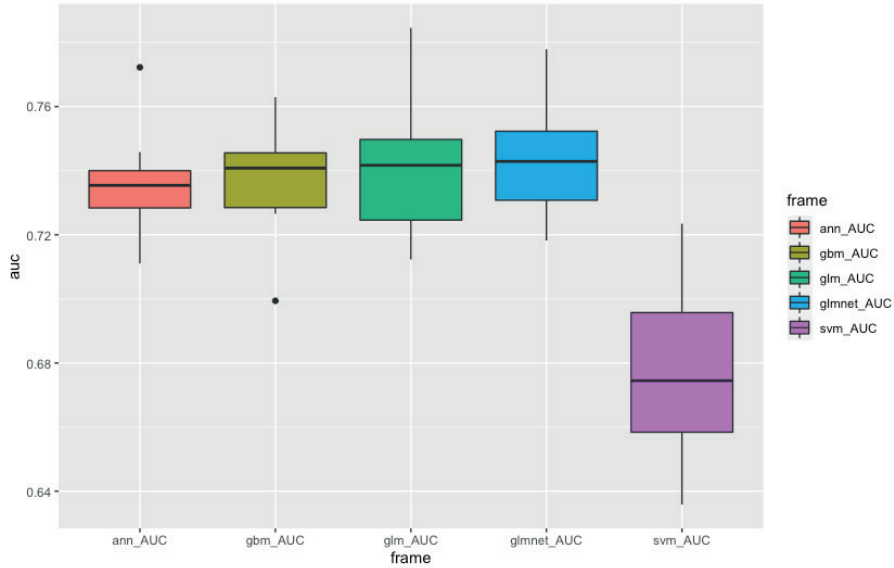


Figure. Performance prediction model - discrimination Legend: AUC = Area Under the Curve. Regression techniques; GLMNET = Lasso and Elastic-Regularized Generalized Linear Models, glm = logistic regression analysis. Machine learning techniques; ANN = artificial neural networks, GBM = Gradient Boosting Machine, SVM = Support Vector Machines. Overall a performance of 0.65 – 0.78.

See figure below the calibration performance of each prediction model.

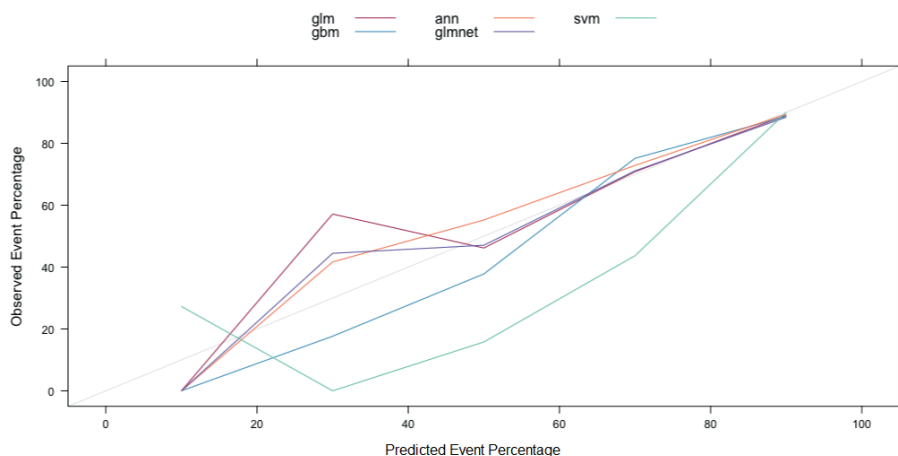
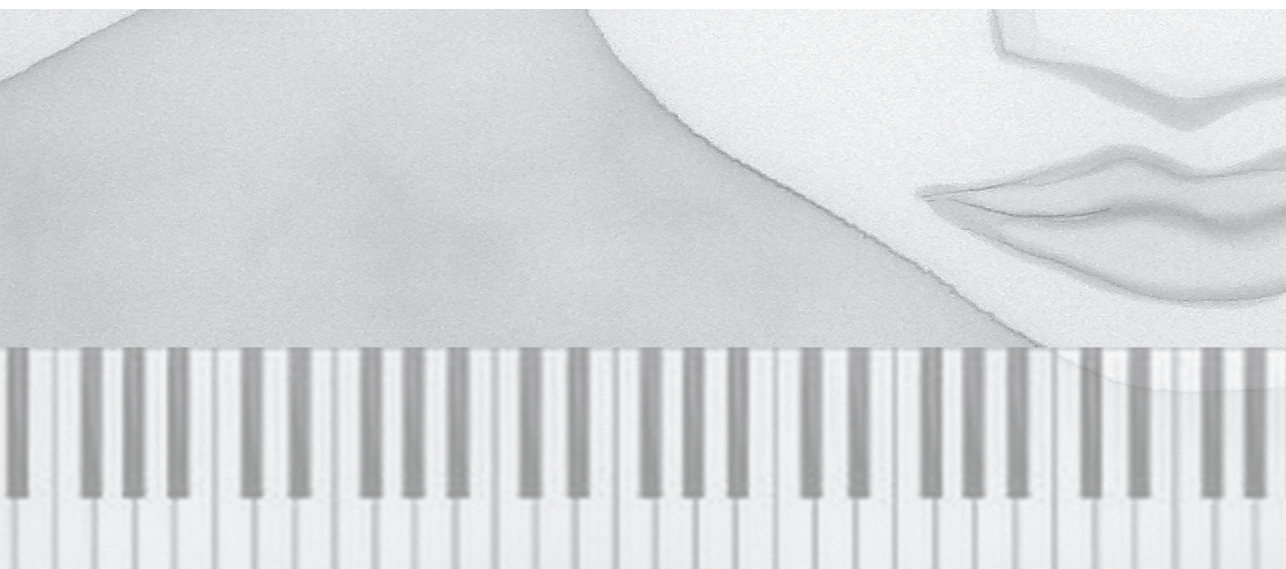


Figure. Performance prediction model – calibration slope Legend: the Y axis corresponds to the observed events and the X-axis to the predicted event of each algorithm. The ideal line is the 45-degree straight line. Each colored lines corresponds to an algorithm. | Glm; logistic regression, ann; artificial neural networks, svm; support vector machines, gb; gradient boosting machine, glmnet; Lasso and Elastic-Regularized Generalized Linear Models Calibration. | Calibration plot demonstrates an over-estimation of POD in low-risk patients by glm, gb, ann and an under-estimation of svm and glmnet for either low and high-risk patients.

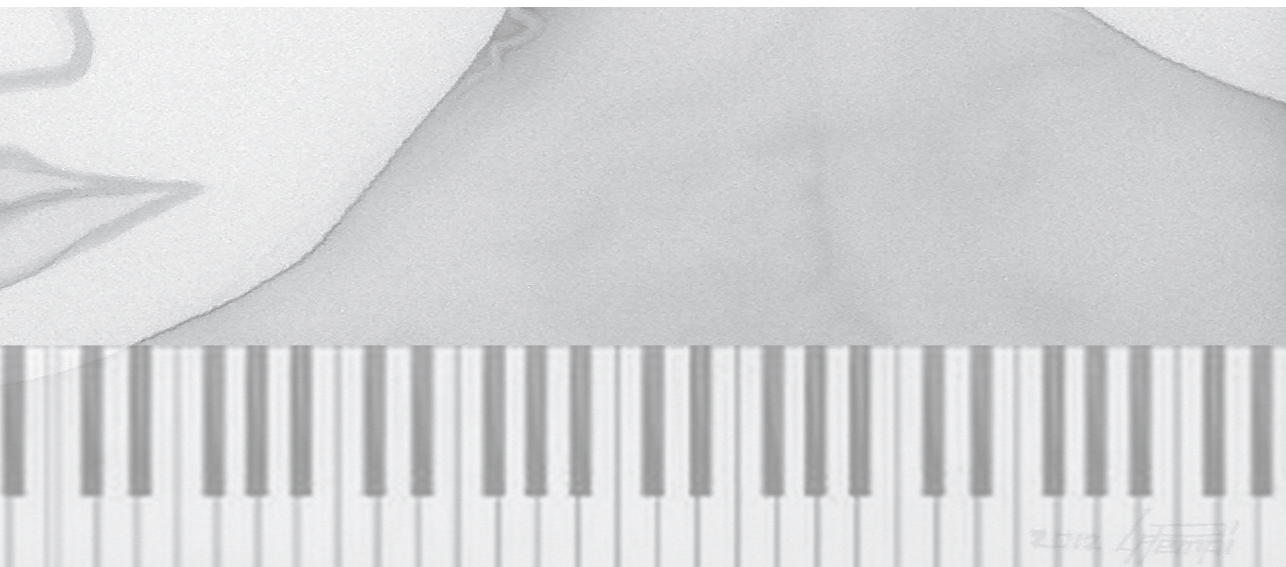


CHAPTER 4

The effect of recorded music on pain endurance (CRESCENDo) – a randomized controlled trial

R.J. Billar, P.R. Kappen, S. Mohammadian, C. van den Berg, Y.B. de Rijke,
E.L.T. van den Akker, J. van Rosmalen, J.M. Schnater, A.J.P.E. Vincent, C.M.F. Dirven,
M. Klimek, R.M.H. Wijnen, J. Jeekel, F.J.P.M. Huygen, J. Tiemensma³

Complementary Therapies in Medicine (2023)



Abstract

Introduction

Clarifying the effect of music on pain endurance in an experimental design could aid in how music should be applied during both surgical and non-surgical interventions. This study aims to investigate the effect of music on pain endurance and the involvement of the sympathetic adrenomedullary axis (SAM) and the hypothalamic-pituitary-adrenocortical axis (HPA).

Materials and methods

In this randomized controlled trial all participants received increasing electric stimuli through their non-dominant index finger. Participants were randomly assigned to the music group (M) receiving a 20-minute music intervention or control group (C) receiving a 20-minute resting period. The primary outcome was pain endurance, defined as amount milliampere tolerated. Secondary outcomes included anxiety level, SAM-axis based on heart rate variability (HRV) and salivary alpha-amylase, and HPA-axis activity based on salivary cortisol.

Results

In the intention-to-treat analysis, the effect of music on pain tolerance did not statistically differ between the M ($n = 35$) and C ($n = 35$) group. A significant positive effect of music on pain endurance was noted after excluding participants with a high skin impedance ($p = 0.013$, CI 0.35; 2.85). Increased HRV was observed in the M-group compared to the C-group for SDNN (B/95%CI: 13.80/2.22; 25.39, $p = 0.022$), RMSSD (B/95%CI: 15.97/1.64; 30.31, $p = 0.032$), VLF (B/95%CI: 212.08/60.49; 363.67, $p = 0.008$) and HF (B/95%CI: 821.15/150.78; 1491.52, $p = 0.0190$). No statistical significance was observed in other secondary outcomes.

Conclusions

The effect of the music intervention on pain endurance was not statistically significant in the intention-to-treat analysis. The subgroup analyses revealed an increase in pain endurance in the music group after correcting for skin impedance, which could be attributed to increased parasympathetic activation.

Introduction

Accumulating literature is available regarding the positive effects of music on pain reduction predominantly performed in surgical patients.(1-5) The strongest decrease in pain perception is suggested in self-selected or preferred music. (6-9) The non-invasive nature of this intervention invites to offer music throughout all sorts of painful procedures and painful medical conditions. The clinical studies on this topic however, are characterized by a large variation of patients and thus medical conditions, which hinders a firm conclusion on the quantitative analgesic effect of music.(6, 10, 11) Moreover, it is unclear whether this decrease in pain perception leads to a better endurance of pain. Clarifying these matters may expand the analgesic indications for music in clinical care. This could be tackled in experimental studies, as these allow for controlling the amount of pain.

Current experimental studies on the effect of music on pain tolerance are scarce and only involve the cold pressure test (thermal stimulation). These studies showed a significant increase in pain tolerance when listening to preferred music.(12, 13) These studies may show promising results, but the evidence remains limited due to small sample sizes and a large heterogeneity in study arms, making it hard to draw definite conclusions. Additionally, using electrical stimulation instead of thermal stimulation allows studying objective outcome measurements (amperage), rather than depending solely on subjective outcome measurements for pain, such as the Visual Analogue Scale.

Furthermore, multiple studies showed that listening to preferred music act as an inducer of emotion by activating the anterior cingulate region, part of the limbic system responsible for emotional modulation, rather than in the operculum/insular region, which is responsible for pain processing (14, 15) This emotional aspect of pain is a sensory response accompanied by a fast autonomic response via the sympathetic-adrenomedullary (SAM) axis and a delayed neuroendocrine response via the hypothalamic-pituitary-adrenocortical (HPA) axis, implying that music could influence the SAM and HPA-axis.(16-19)

We therefore performed a randomized controlled trial in an experimental setting using electrical stimuli investigating the effect of recorded music on pain endurance and the involvement of the SAM and HPA-axis.

Materials and methods

Study and design

This trial was an experimental, single-center randomized controlled trial comparing the effect of a music intervention (M-group) with that of a control (C-group) on healthy adult participants' pain endurance. This study was performed at the outpatient clinic of the Center for Pain Medicine. Reporting followed the CONSORT (Consolidated Standards of Reporting Trials) guidelines for non-pharmacological treatments.(23, 24) The study was approved by the Erasmus MC Medical Ethics Committee (MEC-2020-0559) and registered in the Dutch Trial Register (Identifier: NL8859).

Participants

Healthy adults were encouraged to sign up to participate through communication strategies of the Communication Department of Erasmus MC. Inclusion criteria were age ≥ 18 years and < 70 years (considering that people aged 70 years and older show a significant reduced responsiveness in autonomic activity)(25), and sufficient knowledge of the Dutch language. The following criteria were reason for exclusion: significant hearing impairments, impeding listening to music; tinnitus; current use of analgesic, anti-depressant, anti-anxiety medication, antihypertensive medication or corticosteroids; current treatment by a medical specialist or general practitioner; self-reported (suspected) pregnancy; self-reported severe mental or psychiatric disorder; presence of acute pain or chronic pain syndromes (defined as ongoing pain lasting longer than 3 months), or an history of cardiac rhythm disorders.

Procedure

All study procedures were conducted between 12:00 PM and 5:15 PM in order to control for cortisol fluctuations during the day (Appendix A). To ensure quality of saliva and avoid temporary elevation of cortisol levels, participants were instructed to refrain from eating, smoking, consuming caffeine, drinking beverages other than water, brushing their teeth, or vigorously exercising in the 30 minutes before arriving for the study. (26, 27) At the start of the study, the participant was randomized to either the music group or the control group, see statistical paragraph 2.6), received a heart-rate variability (HRV) chest strap and salivary swab samples were taken. Furthermore, all participants were connected to a STIMUSOL (version MA 5.3.0) device in which

two electrodes were placed on the index finger of the non-dominant hand: at the moment the participant presses the button, an increasing electric stimulus is delivered (0.5mA/second) with a maximum of 30 milliampere (mA).(28) The participant feels the electric stimulation, but is blinded for the amperage.

This study was then divided into three phases: detection, tolerance, and experimental phase. Standardized instructions were given to all participants during each phase. Instructions differed per phase and each phase was repeated three consecutive times:

During the *detection phase*, the participants were instructed to press and hold the button until the moment any stimulus was detected. This phase was meant to assure that the STIMUSOL device was working properly.

During the *tolerance phase*, the participants were instructed to hold the button down as long as possible (aiming at numeric rating scale/NRS pain of ≥ 8).

The researcher then left the room. Participants in the C-group rested for 20 minutes. Participants in the M-group chose from the available playlists and listened to preferred music for 20 minutes, which continued throughout the experimental phase.(6) During the *experimental phase*, participants in both groups were again encouraged to hold the button down as long as possible (aiming at NRS pain ≥ 8).

At the end of the study, salivary swab samples were again taken (at 10 and 30 minutes after the experimental phase) and participants in both group filled out a questionnaire on their baseline characteristics.

Outcome measurements

The primary outcome was average pain endurance (expressed in mA) assessed during the experimental study phase. The average pain endurance was also calculated during the detection and tolerance phases.

Secondary outcomes – assessed to substantiate the effects of music on pain endurance – included anxiety level before each phase (self-reported using the 11-point VAS-A scale in which 0 implies no anxiety and 10 the worst anxiety possible), the sympathetic-adrenomedullary axis activity (SAM) (measured using HRV(29-31) and salivary alpha-amylase (sAA)(18). Continuous HRV measurements were conducted by using a validated BMI Acentas Chest Strap provided by BioCheck® and the following HRV

parameters were extracted: standard deviation of normal sinus beats (SDNN), root mean square of successive differences between normal heartbeats (RMSSD), high frequency (HF), low frequency (LF), and very low frequency (VLF). (32) SAA samples (U/ml) from oral mucosa using Salivettes were collected at baseline, 10 and 30 minutes after the experimental electric stimulus, as the peak increase of sAA is 5 -10 minutes after stress induction.(33) Salivary cortisol (sCortisol, mcg/dL) samples were collected at baseline and 30 minutes after the experimental electric stimulus, as the peak increase of sCortisol occurs 20-40 minutes after stress induction. (34)

Additional baseline characteristics were assessed: sex, age, highest level of education, hand dominance, medication use, use of oral contraceptives, smoking, use of drugs, use of alcohol, and importance of music using a questionnaire based on prior clinical music studies. (35)

Statistical analysis

Sample size and randomization

A recent meta-analysis, which investigated effects of music interventions on pain in surgical patients, found an overall effect size of Cohen's $d=0.54$ (CI 0.15; 0.93).(36) We assumed a slightly larger effect (Cohen's d of 0.60) on amperage tolerance, due to the controlled setting. Our sample size calculation was based on a power analysis using an analysis of covariance (ANCOVA) model with adjustment for baseline value (measured in the tolerance phase) and treatment arm. A moderate correlation (0.5) was assumed. The sample size was calculated at 33 participants per study arm (power: 80%, two-sided significance level: 5%). To account for possible dropouts, the sample size was chosen to be 35 participants per study arm, resulting in a total sample size of 70 participants. Randomization was performed using blocked randomization with in a 1:1 ratio, by a secured online software program (ALEA; FormVision, Abcoude, the Netherlands) and stratified by sex, as studies suggest females to be more sensitive to electric stimuli.(37) Variable block sizes were used for both groups and were equally represented in each block.

Analysis of outcome parameters

The main analysis was based on the intention-to-treat principle. Pain endurance (mA) during the experimental phase was compared between the M-group and C-group

by using an analysis of covariance (ANCOVA) model, with adjustment for sex and endurance (mA) during the tolerance phase. Subsequently, statistical outliers were detected using boxplots and Q-Q plots. Subgroup analyses on the primary outcome were performed on the following instances: after identification and exclusion of statistical outliers using the Q-Q plots, non-adherence to protocol (determined in case of mean NRS of <8 over the phases), increased skin impedance (identified and defined as $>2\text{mA}$ during the detection phase), and in those who reported music to be important in their life (reported score of ≥ 7 on the music importance questionnaire).

An ANCOVA model was utilized to analyze the following secondary outcomes: anxiety level before the experimental phase adjusted for sex and baseline anxiety, and sAA-10 and 30 minutes and sCortisol-30 minutes adjusted for baseline measurements. Five-minute samples of the continuous HRV values were assigned to different time points (see Figure 4). Subsequently, a linear mixed model was run, as within-subject variability in this continuous outcome was suspected (38), with group (M or C), time point, sex, and the interaction between group and time point as independent variables. A two-sided p-value of 0.05 or less was considered statistically significant. Post-hoc pairwise comparisons were performed after significant effects were found in case of three or more levels of a factor. All statistical analyses were conducted using R (version 4.1.1).

Results

Participants

Ninety-nine adults signed up to participate. Twenty-nine of them did not meet the inclusion criteria, due to no informed consent ($n = 23$), use of analgesic medication ($n = 1$), use of corticosteroid inhibitors ($n = 1$), current ($n = 2$) or chronic treatment by a physician ($n = 1$), and chronic pain syndrome ($n = 1$). This resulted in our target sample size of seventy participants within 11 months (March 2020 to August 2021), randomized to the M-group ($n = 35$) or C-group ($n = 35$, appendix B)

The mean (SD) age in years of the included participants was 38.0(15), and $n = 38$ (54%) were female (table 1). Right-handed dominance was observed in 60 (86%), while consumption of alcohol was reported by $n = 46$ (66%) and higher education by $n = 37$ (53%) participants. Thirty-six (51%) participants reported to play an instrument or sing and 61 (87%) participants reported music to be important in their life. In the

M-group, pop music ($n = 12$, 37%) was most often chosen followed by classical music ($n = 6$, 17%) and jazz & blues ($n = 5$, 14%). The mean (SD) detection threshold was 1.75 (0.496) mA and the mean (SD) baseline anxiety was 1.31(1.14

Primary outcome and subgroup analysis

See table 2 for the results on the primary outcome. The ITT analyses revealed no significant differences in pain endurance (mA) between the groups (B/95%CI: 0.47/-0.85;1.79, $p = 0.482$, figure 1).

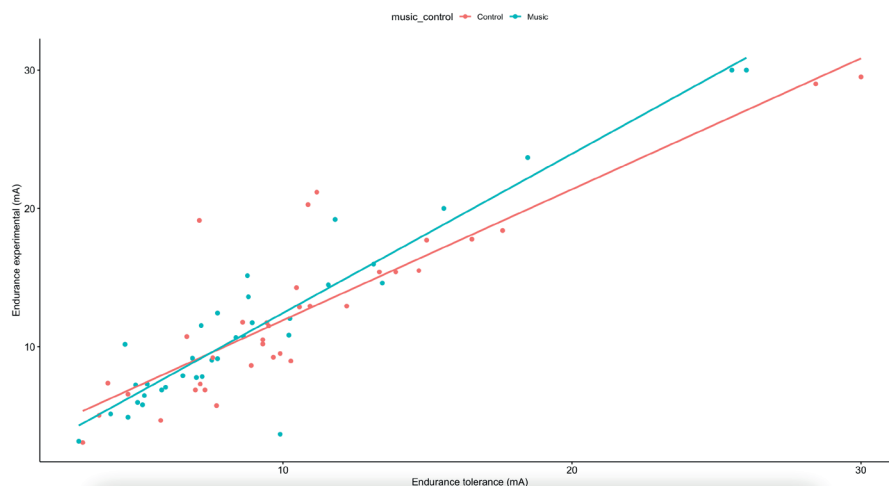


Figure 1. Primary outcome vs. music

Y axis: milliampere (mA) during experimental phase, X axis: mA during tolerance phase. Music did not increase the endurance ($p = 0.482$) during the experimental phase after correcting for the endurance during tolerance phase ($p < 0.001$) and gender ($p = 0.201$).

Detected statistical outliers showed a large variance of pain endurance between study phases and the corresponding participants were identified (Appendix C). A significant effect on endurance between the M-group and C-group was found in the subgroup analysis after excluding these identified participants (variance > 15 mA between electric stimulations, B/95%CI: 1.40/0.59;2.21, $p = 0.001$) and high skin impedance (detection threshold > 2 mA, B/95%CI: 1.60/0.36;2.85, $p = 0.013$, table 2). No significant differences between the M-group vs. C-group were apparent with regard to participants with high music importance (B/95%CI: 0.58/-0.69;1.86, $p = 0.364$) or

high adherence to the protocol (B/95%CI: 0.13/-1.40;1.66, $p = 0.865$). Jazz & Blues music had the largest effect on the primary outcome (B/95%CI 3.44; 0.08-6.80, $p = 0.045$), but this did not reach significance after pairwise comparison.

Secondary outcome parameters

See table 3 for the results of the secondary outcomes. The anxiety level (VAS-A) was not significant between the M-group and the C-group (B/95%CI: -0.16/-0.59;0.27, $p=0.456$). Cortisol decreased from baseline to 30 minutes after the experiment, but this was not different between the M-group and C-group. A non-significant increase of alpha-amylase after 10 minutes was observed in the C-group vs. the M-group (B/95%CI: -12.42/-41.29;16.45, $p=0.394$, figure 2).

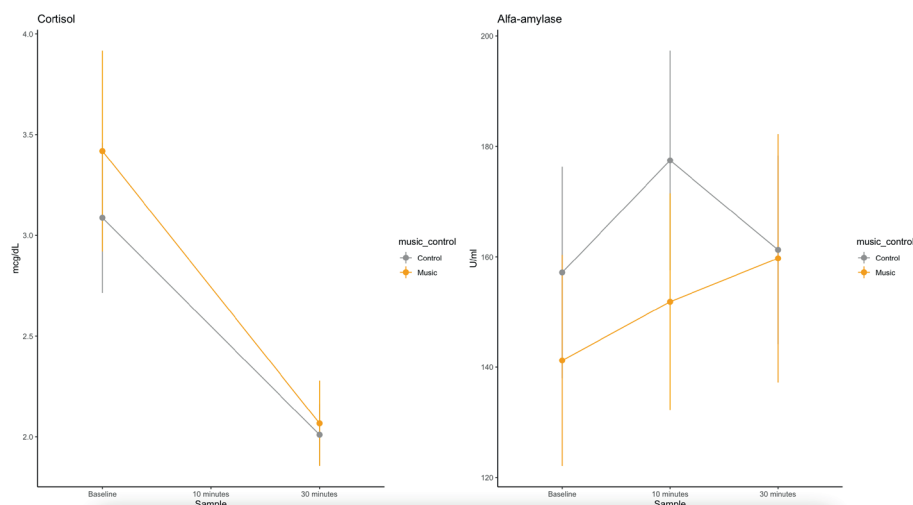


Figure 2. Cortisol and alpha amylases response to music.

X-axis: occasion 1 = baseline, occasion 2 = 10 minutes after experimental phase, occasion 3 = 30 minutes after experimental phase. Y-axis: value of sample. Left: a decrease of cortisol (mcg/dL) is seen which is not significant between groups ($p=0.866$) after correcting for baseline cortisol. Right: An increase of alpha-amylase (U/mL) is seen in the control group, as opposed to the music group, after 10 minutes which normalizes after 30 minutes. This trend was however not significantly different between groups ($p=0.394$) after correcting for baseline value ($p<0.001$).

A significantly increased HRV was observed in the M-group vs. the C-group for SDNN (B/95%CI: 13.80/2.22;25.39, $p=0.022$), RMSSD (B/95%CI:

15.97/1.64;30.31, $p=0.032$), VLF (B/95%CI: 212.08/60.49;363.67, $p=0.008$) and HF (B/95%CI:821.15/150.78;1491.52, $p=0.0190$). However, a significant decrease was found in the M-group vs. the C-group at 15, 20 and 25 minutes in the SDNN ($p = 0.015$ and 0.021 and 0.001), at 25 minutes in the RMSSD ($p = 0.019$), at 20 and 25 minutes in the VLF ($p=0.027$ and 0.027), at 25 minutes in the LF ($p = 0.049$, figure 3) and in the HF at 20 ($p=0.039$) and 25 minutes ($p=0.026$) indicating SAM activation.

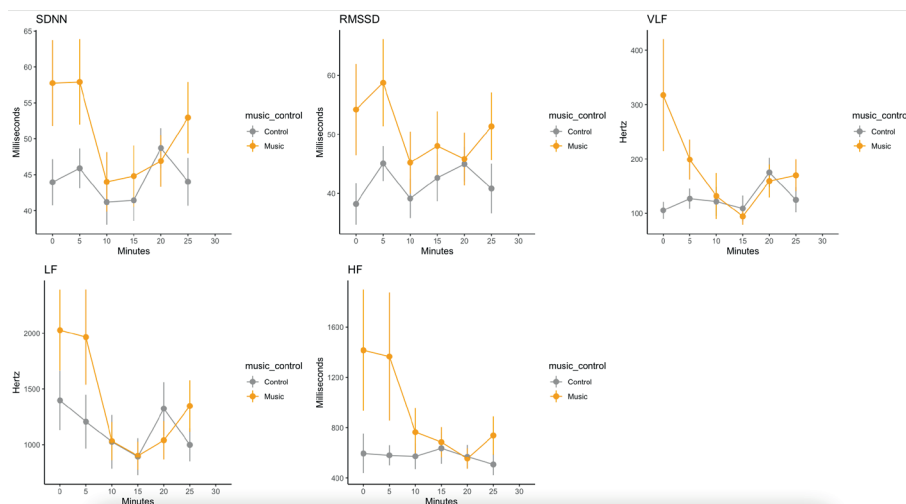


Figure 3. Heart rate variability (HRV) response to music.

Thirty-minute recording as each occasion represents a sample of 5 minutes. An increased HRV was observed in the M-group vs. the C-group for SDNN ($p=0.022$), RMSSD ($p=0.032$), and VLF ($p=0.008$) and HF ($p=0.0190$), with a significant decrease at 15 ($p=0.015$), 20 ($p=0.021$) and 25 ($p=0.001$) minutes, at 25 minutes in the RMSSD ($p = 0.019$), at 20 and 25 minutes in the VLF (both $p=0.027$), and at 25 minutes in the LF ($p = 0.049$), figure 3) and HF at 20 ($p=0.039$) and 25 minutes ($p=0.026$).

Discussion

General discussion

Our aim was to study the effect of listening to preferred music on pain endurance and the role of the autonomic and neuroendocrine responses. The intention-to-treat analysis revealed no significant effect of this intervention. However, a significant positive effect of listening to music on pain endurance was noted after excluding those participants with a high skin impedance, as a high skin impedance impedes the

electric current. This higher endurance could be explained by the parasympathetic nervous activation. Limitations and clinical implications are discussed below.

The strongest predictor for endurance during the experimental phase seemed to be the endurance during the preceding tolerance phase. This is in contrast with the available literature on pain endurance, as the literature states that the greatest predictor is to which group participants were allocated to. (21, 39) Studies on the effect of music on pain tolerance during a cold pressor test showed a significant increase in pain tolerance from pre- to post-test immersion trials, and therefore utilization of preferred music was effective in increasing pain tolerance.(12) Another study found that preferred music listening resulted in a significantly longer tolerance of painful stimulation compared to a mental arithmetic task.(13) However, these studies only evaluated thermal pain (i.e., cold pressor test) rather than electrical stimulations. The discrepancy of our results and literature could be explained by the variation in pain stimuli: painful *electrical* stimulations activate the limbic system (notably the superior caudate nucleus and posterior insula) to a greater extent than do painful *thermal* stimulations, suggesting that electrical stimuli have a stronger affective component than thermal stimuli.(40) This stronger activation could in turn influence the sensitization of the central nervous system to the nociceptive stimuli. (40) Moreover, our participants were blinded for the amount of electric stimulation they received, as opposed to the transparent duration of the cold pressor test, so that our results probably reflect a more realistic analgesic effect of music. Lastly, technical or behavioral issues and variabilities between above described the models could have contributed to the different results. With respect to these technical variabilities: skin impedance affects the strength of the electrical current through the index finger and can be influenced by multiple factors, for example sweat and grease.(41) Despite hand washing and alcohol rubbing, differences in skin impedance were observed. Analysis with the exclusion of those participants with a high skin impedance (defined as a detection threshold of $>2\text{mA}$) revealed a positive effect of music on pain endurance after).(42) With respect to the behavioral variabilities: uncertainty on the strength of electric stimulation may have induced the variation within one participant on the endurance performance, as this type of experiment was novel to all participants. Excluding these participants with a large variation between the stimuli resulted in significant effects of music on endurance performance. These results should be interpreted with caution as exclusion of outliers is not advised, because they are inherent to the natural variability of the data.(43)

The physiology of music seems to be based on up-regulation within the mesolimbic dopaminergic system, which activates the nucleus accumbens and ventral tegmental area, which are affective structures active during reward in monetary or addictive drug studies.(15, 44) Connectivity studies show interaction of these affective regions with the hypothalamus, a brain region that modulates autonomic responses through the direct SAM and the indirect HPA axis.(18, 19) The expected effect on the stress response was uncertain, as a paradox in literature on pain and cortisol is described: pain is associated with the production of cortisol but a transient stress-induced analgesia also has been proposed in which cortisol elevation reduces pain unpleasantness and increases pain tolerance and endurance.(45) In our study, listening to music prior to a standardized stressor predominantly affected the sympathetic-adrenomedullary axis activity (SAM), but did not affect the Hypothalamic-pituitary-adrenocortical (HPA) axis response. Salivary alpha-amylase (sAA) values increased in the control group, as opposed to the music group, which normalized over time. Previous studies have shown that sAA has a direct response to a stressful stimulus, shorter latency time to peak level, and no carry-over effect compared to cortisol.(46) Our results should be interpreted with caution as they did not reach significance, but do support sAA to be a potential objective non-invasive tool for pain assessments within the field of music.(47) An increased activation by music on heart rate variability (HRV) was found, which is considered a measure of the SAM. However, a decrease was observed during the music intervention, which could be explained due to the arousing effect of music, resulting in a higher heart rate and lower HRV.(47) This explanation is substantiated by the fact that the HRV returned to normal after the music intervention was completed.

Surgical studies have shown significant reduced anxiety in patients listening to music preoperatively.(6) One could hypothesize that music distracts patients from fearful and worrying thoughts about the surgical procedures, as musical information consumes attentional resources. We did not observe this effect of music on anxiety, which could be explained by the low levels of anxiety at baseline as there was no perspective of any surgical procedure.

Strengths, limitations and future studies

This is the first study evaluating the effect of music on pain using a validated experimental model, while measuring an objective outcome for pain endurance.(15) Our main analyses on endurance were non-significant, which might be caused by

our limited sample size, although our achieved power was above 80%. Moreover, participants were blinded for the primary outcome, making the measured pain endurance more reliable. Using this model makes translation towards the clinics and quantification of the analgesic effect more reliable, as this study was not confined to variation in surgical procedures, nor patient groups. (6)

We do have some limitations to discuss. First, we did not add a third arm with auditory stimulations, which could have controlled for the distractive effect of music. Second, the measured underlying effects could have been more comprehensive as we studied the effects of HPA and SAM axes, and hypothesized activation of the limbic system but did not confirm this with an electrophysiology study. Additionally, the literature shows that having lunch and/or breakfast could influence the HRV. Eating behavior could have influenced our results, as we did not correct for this. However, we conducted all experiments in the morning and assured no food consumption 30 minutes before each experiment.(48, 49) Lastly, one could argue that consecutive electric stimuli might have led to a familiarity effect. However, as patients were randomized, this ceiling effect/familiarity effect is considered similar in both groups, making the groups still comparable.

Future studies should therefore employ a more comprehensive design framework using our pain and music model, preferably with a third arm with non-music auditory signals, so to be able to assess the true analgesic effect of music stratified per type of genre. Furthermore, EEG and neurological imaging studies could be added to this model to assess the emotional-inducing effect of music evoked from the (meso-)limbic system. Lastly, eating behavior should be evaluated to assure a correct interpretation of the HRV measurements.

Conclusions

The effect of listening to preferred music on pain endurance was not statistically significant in our intention-to-treat analysis. However, subgroup analyses did reveal a significant positive effect on pain endurance after excluding those participants with a high skin impedance. Our experimental model provides a solid effect of music on pain endurance, as the outcome was objective and the patients were blinded for the primary outcome. The effect on pain endurance could be attributed to sympathetic-adrenomedullary axis activation, but this attribution should be taken with caution, as the ITT analyses were non-significant.

References

1. Kuhlmann AYR, de Rooij A, Hunink MGM, De Zeeuw CI, Jeekel J. Music Affects Rodents: A Systematic Review of Experimental Research. *Front Behav Neurosci*. 2018;12:301.
2. van der Heijden MJ, Oliai Araghi S, van Dijk M, Jeekel J, Hunink MG. The Effects of Perioperative Music Interventions in Pediatric Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PLoS One*. 2015;10(8):e0133608.
3. Fu VX, Oomens P, Klimek M, Verhofstad MHJ, Jeekel J. The Effect of Perioperative Music on Medication Requirement and Hospital Length of Stay: A Meta-analysis. *Ann Surg*. 2020;272(6):961-72.
4. Fu VX, Oomens P, Sneiders D, van den Berg SAA, Feelders RA, Wijnhoven BPL, et al. The Effect of Perioperative Music on the Stress Response to Surgery: A Meta-analysis. *J Surg Res*. 2019;244:444-55.
5. Hole J, Hirsch M, Ball E, Meads C. Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. *Lancet*. 2015;386(10004):1659-71.
6. Kuhlmann AYR, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. Meta-analysis evaluating music interventions for anxiety and pain in surgery. *Br J Surg*. 2018;105(7):773-83.
7. Joanna Briggs I. The Joanna Briggs Institute Best Practice Information Sheet: music as an intervention in hospitals. *Nurs Health Sci*. 2011;13(1):99-102.
8. de Witte M, Spruit A, van Hooren S, Moonen X, Stams GJ. Effects of music interventions on stress-related outcomes: a systematic review and two meta-analyses. *Health Psychol Rev*. 2020;14(2):294-324.
9. Nilsson U. The anxiety- and pain-reducing effects of music interventions: a systematic review. *AORN J*. 2008;87(4):780-807.
10. Lee JH. The Effects of Music on Pain: A Meta-Analysis. *J Music Ther*. 2016;53(4):430-77.
11. Garza-Villarreal EA, Pando V, Vuust P, Parsons C. Music-Induced Analgesia in Chronic Pain Conditions: A Systematic Review and Meta-Analysis. *Pain Physician*. 2017;20(7):597-610.
12. Hekmat HM HJ. Pain Attenuating Effects of Preferred Versus Non-preferred Music Interventions. *Psychology of Music*. 1993.
13. Mitchell LA, MacDonald RA, Brodie EE. A comparison of the effects of preferred music, arithmetic and humour on cold pressor pain. *Eur J Pain*. 2006;10(4):343-51.
14. Perlini AH VK. Audioanalgesia in the control of experimental pain. *Can J Behav Sci*. 1996;28(4):292.
15. Lu X, Thompson WF, Zhang L, Hu L. Music Reduces Pain Unpleasantness: Evidence from an EEG Study. *J Pain Res*. 2019;12:3331-42.
16. Blackburn-Munro G. Hypothalamo-pituitary-adrenal axis dysfunction as a contributory factor to chronic pain and depression. *Curr Pain Headache Rep*. 2004;8(2):116-24.
17. al'Absi M, Petersen KL. Blood pressure but not cortisol mediates stress effects on subsequent pain perception in healthy men and women. *Pain*. 2003;106(3):285-95.
18. Rus HM, Tiemensma J. Social media as a shield: Facebook buffers acute stress. *Physiol Behav*. 2018;185:46-54.

19. Duval F, Mokrani MC, Erb A, Gonzalez Lopera F, Danila V, Tomsa M. Neuroendocrine Assessment of Dopaminergic Function during Antidepressant Treatment in Major Depressed Patients. *Brain Sci.* 2021;11(4).
20. Ballmann CG, Cook GD, Hester ZT, Kopec TJ, Williams TD, Rogers RR. Effects of Preferred and Non-Preferred Warm-Up Music on Resistance Exercise Performance. *J Funct Morphol Kinesiol.* 2020;6(1).
21. Choi S, Park SG, Lee HH. The analgesic effect of music on cold pressor pain responses: The influence of anxiety and attitude toward pain. *PLoS One.* 2018;13(8):e0201897.
22. Tavis S. Campbell JAKAZ. *Encyclopedia of Behavioral Medicine* 2020.
23. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med.* 2010;7(3):e1000251.
24. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, Group C. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med.* 2008;148(4):295-309.
25. Reardon M, Malik M. Changes in heart rate variability with age. *Pacing Clin Electrophysiol.* 1996;19(11 Pt 2):1863-6.
26. Keil MF. Salivary cortisol: a tool for biobehavioral research in children. *J Pediatr Nurs.* 2012;27(3):287-9.
27. Hansen AM, Garde AH, Persson R. Sources of biological and methodological variation in salivary cortisol and their impact on measurement among healthy adults: a review. *Scand J Clin Lab Invest.* 2008;68(6):448-58.
28. Pud D, Golan Y, Pesta R. Hand dominance--a feature affecting sensitivity to pain. *Neurosci Lett.* 2009;467(3):237-40.
29. White JM. Effects of relaxing music on cardiac autonomic balance and anxiety after acute myocardial infarction. *Am J Crit Care.* 1999;8(4):220-30.
30. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation.* 1996;93(5):1043-65.
31. McCraty R, Shaffer F. Heart Rate Variability: New Perspectives on Physiological Mechanisms, Assessment of Self-regulatory Capacity, and Health risk. *Glob Adv Health Med.* 2015;4(1):46-61.
32. Schonfelder M, Hinterseher G, Peter P, Spitzenpfeil P. Scientific comparison of different online heart rate monitoring systems. *Int J Telemed Appl.* 2011;2011:631848.
33. Granger DA, Kivlighan KT, el-Sheikh M, Gordis EB, Stroud LR. Salivary alpha-amylase in biobehavioral research: recent developments and applications. *Ann N Y Acad Sci.* 2007;1098:122-44.
34. Bozovic D, Racic M, Ivkovic N. Salivary cortisol levels as a biological marker of stress reaction. *Med Arch.* 2013;67(5):374-7.
35. Kappen P, Jeekel J, Dirven CMF, Klimek M, Kushner S, Osse RJ, et al. Music to prevent delirium during neurosurgery (MUSYC) Clinical trial: a study protocol for a randomised controlled trial. *BMJ Open.* 2021;11(10):e048270.
36. Ellis RJ, Thayer JF. Music and Autonomic Nervous System (Dys)function. *Music Percept.* 2010;27(4):317-26.

37. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL, 3rd. Sex, gender, and pain: a review of recent clinical and experimental findings. *J Pain*. 2009;10(5):447-85.
38. Ketchum JM, Best AM, Ramakrishnan V. A Within-Subject Normal-Mixture Model with Mixed-Effects for Analyzing Heart Rate Variability. *J Biom Biostat*. 2012;Suppl 7.
39. Hsieh C, Kong J, Kirsch I, Edwards RR, Jensen KB, Kaptchuk TJ, et al. Well-loved music robustly relieves pain: a randomized, controlled trial. *PLoS One*. 2014;9(9):e107390.
40. Sean M, Coulombe-Leveque A, Bordeleau M, Vincenot M, Gendron L, Marchand S, et al. Comparison of Thermal and Electrical Modalities in the Assessment of Temporal Summation of Pain and Conditioned Pain Modulation. *Front Pain Res (Lausanne)*. 2021;2:659563.
41. Fish RM, Geddes LA. Conduction of electrical current to and through the human body: a review. *Eplasty*. 2009;9:e44.
42. Friedli WG, Fuhr P, Wiget W. Detection threshold for percutaneous electrical stimuli: asymmetry with respect to handedness. *J Neurol Neurosurg Psychiatry*. 1987;50(7):870-6.
43. Osborne JW OA. The power of outliers (and why researchers should ALWAYS check for them. *Practical Assessment, Research, and Evaluation*.9(6).
44. Alcaro A, Huber R, Panksepp J. Behavioral functions of the mesolimbic dopaminergic system: an affective neuroethological perspective. *Brain Res Rev*. 2007;56(2):283-321.
45. van Stegeren AH, Wolf OT, Kindt M. Salivary alpha amylase and cortisol responses to different stress tasks: impact of sex. *Int J Psychophysiol*. 2008;69(1):33-40.
46. Strahler J, Skoluda N, Kappert MB, Nater UM. Simultaneous measurement of salivary cortisol and alpha-amylase: Application and recommendations. *Neurosci Biobehav Rev*. 2017;83:657-77.
47. Linnemann A, Ditzen B, Strahler J, Doerr JM, Nater UM. Music listening as a means of stress reduction in daily life. *Psychoneuroendocrinology*. 2015;60:82-90.
48. Ozpelit ME, Ozpelit E. How we eat may be as important as what we eat: eating behaviour and heart rate variability. *Acta Cardiol*. 2017;72(3):299-304.
49. Okada M, Okada K, Takehashi M. Common eating habit patterns are associated with a high maximum occlusal force and pre-eating cardiac vagal tone. *PeerJ*. 2023;11:e15091.

Table 1. Baseline characteristics

	Control (N=35)	Music (N=35)	Overall (N=70)
Demographic data			
Female sex	19 (54.3%)	19 (54.3%)	38 (54.3%)
Age ¹	40.6 (14.8)	35.4 (14.1)	38.0 (14.6)
Right-handed dominance	30 (85.7%)	30 (85.7%)	60 (85.7%)
Alcohol ²	21 (60.0%)	25 (71.4%)	46 (65.7%)
BMI ³	23.5 (4.0)	23.3 (2.9)	23.4 (3.5)
High education ⁴	19 (54.3%)	18 (51.4%)	37 (52.9%)
Music data			
Plays an instrument or sings	19 (54.3%)	17 (48.6%)	36 (51.4%)
High music importance ⁵	28 (80.0%)	33 (94.3%)	61 (87.1%)
Type of music listened to			
Classical	-	6 (17.1%)	-
Electronic	-	3 (8.6%)	-
Jazz & Blues	-	5 (14.3%)	-
Pop	-	13 (37.1%)	-
R&B	-	3 (8.6%)	-
Experimental baseline data			
Detection threshold ⁶	1.75 (0.400)	1.75 (0.583)	1.75 (0.496)
Anxiety ⁷	1.31 (1.18)	1.31 (1.11)	1.31 (1.14)

1. Mean/SD age in years. 2. Reported alcohol consumption: missing in 1 (2.9%). 3. Mean (SD) Body mass index: missing 2 (5.7%) 4. In case of higher education at the middle/high school or more (VWO). 5. In case of a reported importance of 7 or above on the 10-point Likert scale. 6. Mean (SD) milli amperage until electric stimulation was 'detected'. 7. Mean (SD) baseline VAS-Anxiety.

Table 2. Primary outcome: music vs. pain endurance

	N	Control ¹	Music ¹	B (95% CI)	P-value
Main analysis²					
Overall population	70	11.8/0.467	12.3/0.466	0.47/-0.85;1.79	0.482
Subgroup analysis					
Exclusion of participants with large variance between measure points ³	65	10.9/0.367	12.2/0.344	1.40/0.59;2.21	0.001
Participants with high music importance ⁴	61	11.6/0.465	12.2/0.428	0.58/-0.69;1.86	0.364
Exclusion of participants with high skin impedance ⁵	51	10.5/0.421	12.1/0.439	1.60/0.36;2.85	0.013
Exclusion of participants with fail to protocol adherence ⁶	44	11.9/0.485	12.0/0.578	0.13/-1.40;1.66	0.865

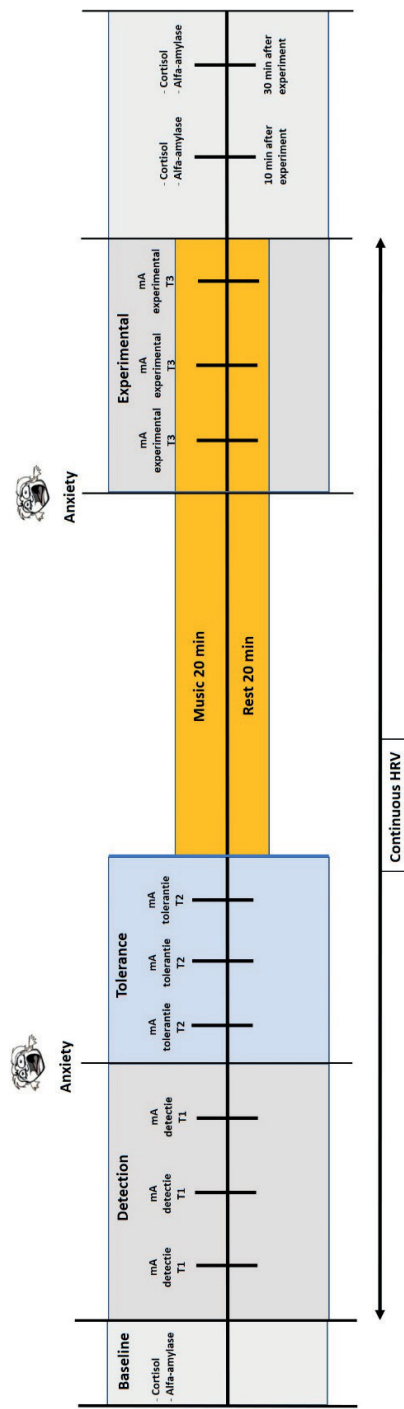
*Coefficient/95%Confidence interval (B/95%CI), corrected for endurance tolerance phase and gender. 1. Mean/SE endurance experimental phase control/music group. 2. Intention-to-treat analysis. 3. Outlier analyses revealed large variance between tolerance/experimental phase, hence patients >15mA difference between electric stimulations (n=5) were excluded. 4. Patients that reported high importance of music (7 or above on the 10-point Likert scale). 5. In case of a detection threshold of 2mA or above. 6. Adequate endurance of pain as requested to the participants: perceived pain (NRS) during tolerance/experimental of 8 or above.

Table 3. Secondary outcome measures

	Control (n = 35) ¹	Music (n = 35) ¹	B/95%CI	P-value
Anxiety ²	0.835/0.151	0.675/0.151	-0.16/-0.59;0.27	0.456
Cortisol (mcg/dL)	2.06/0.144	2.02/0.142	-0.03/-0.44;0.37	0.866
Alpha-amylase ⁴				
10 minutes	171/10.3	159/10.1	-12.42/-41.29;16.45	0.394
30 minutes	154/11.5	167/11.3	12.23/-20.03;44.49	0.452
HRV ⁵				
SDNN	44.2/3.71	50.7/3.53	13.80/2.22;25.39	0.022
RMSSD	41.8/4.35	50.6/4.14	15.97/1.64;30.31	0.032
VLF	126/45.1	178/43.0	212.08/60.49;363.67	0.008
LF	1156/213	1396/203	625.35/-123.59;1374.29	0.106

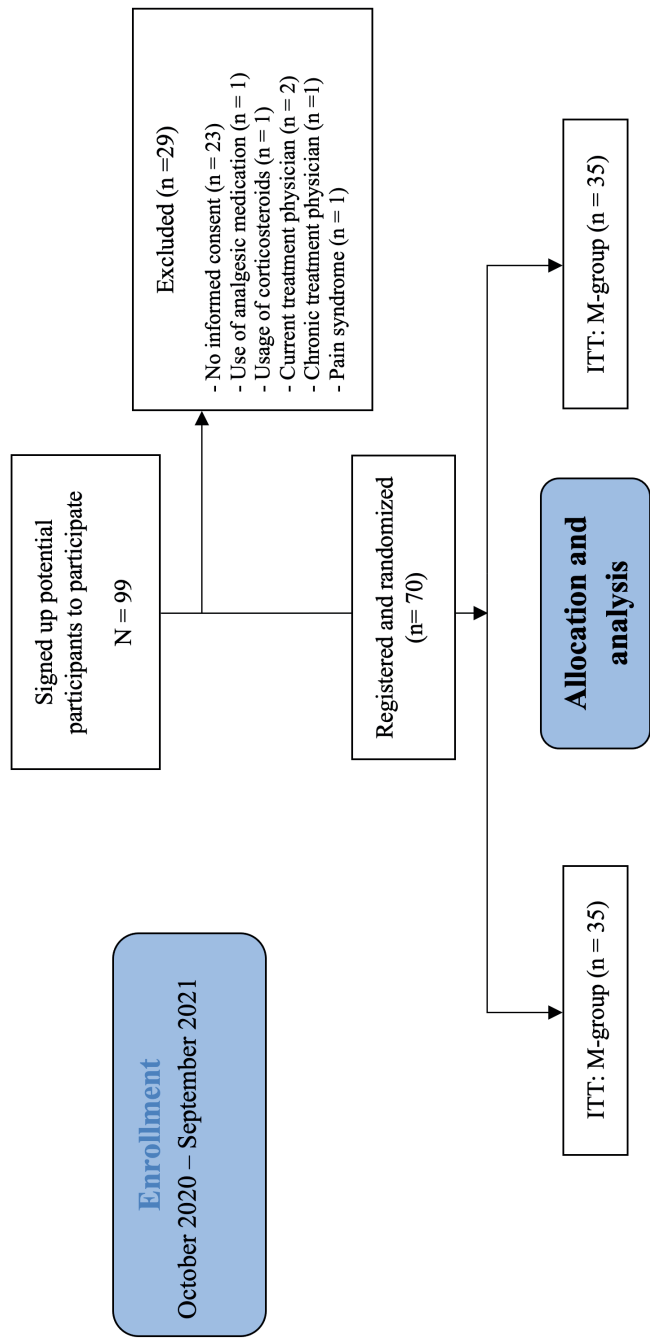
1. mean/SE corrected values per group. 2. Anxiety measures before experimental phase (VAS-A) corrected for gender and baseline anxiety. 3. Cortisol (mcg/dL) 30 minutes after experiment corrected for baseline measure. 4. Alpha amylase (U/mL) corrected for baseline measure. 5. Heart rate variability. Time domain analysis: SDNN and RMSSD. Frequency domain analysis: VLF and LF. Overall measures illustrated, corrected but not specified per occasion (in main text).

Appendix A. Study procedure

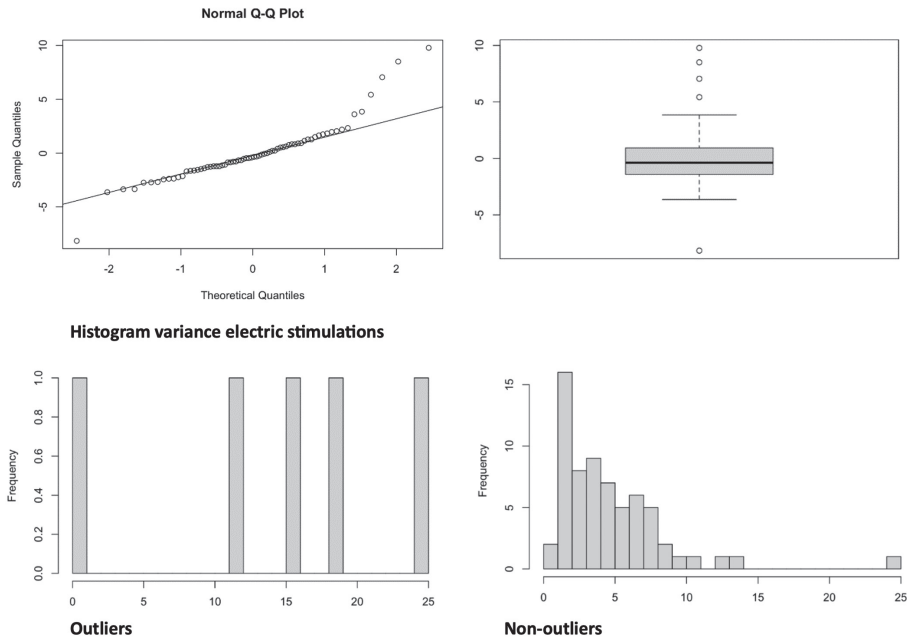


Course of the study procedure is schematically presented in this figure. This study was conducted at the outpatient of Pain Medicine of the Erasmus MC, Rotterdam. At baseline, participants were randomized (music vs. control), connected to the STIMUSOL for electric stimulation and received a HRV chest band. Moreover, salivary swap sample for alpha-amylase and cortisol measurements were taken. Detection phase was to assess the sensitivity of the participant to STIMUSOL: the participants pressed the button until an electric stimulation was 'detected', which was repeated three times. Tolerance phase was to assess the endurance towards the electrical stimulation prior to intervention; the participants pressed the button until and the electric stimulation was endured as maximum as possible (i.e. minimally pain VAS of 8), which was repeated three times. Experimental phase was to assess the endurance towards the electrical stimulation after/during to intervention: the same procedure as during the tolerance phase. Ten and thirty minutes after the experimental phase salivary swap samples were collected for alpha-amylase and cortisol measurements.

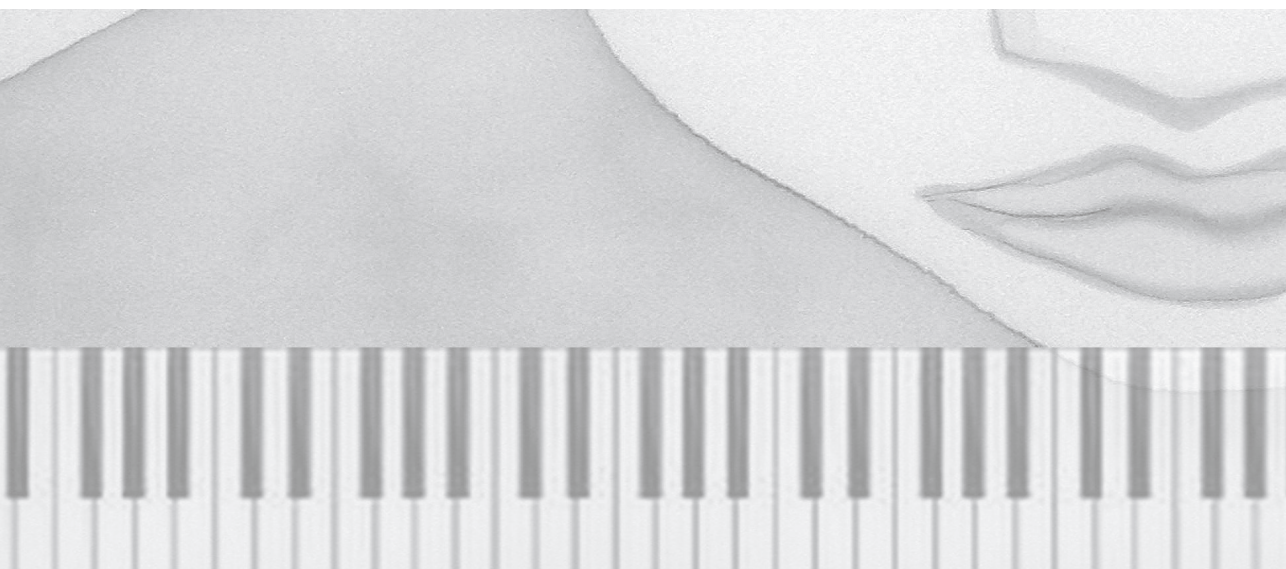
Appendix B. CONSORT flow diagram



Appendix C. Detecting outliers and motivation for subanalysis



As shown in our Q-Q and boxplot, our main analysis coped with some statistical outliers. After further analyzing we found that the distribution of variance between the non-outliers and outliers was different ($>15\text{mA}$ variance between electric stimulations in the outlier group). Hence we conducted a post hoc analysis excluding patients with large variance ($>15\text{mA}$) between the electric stimulations.

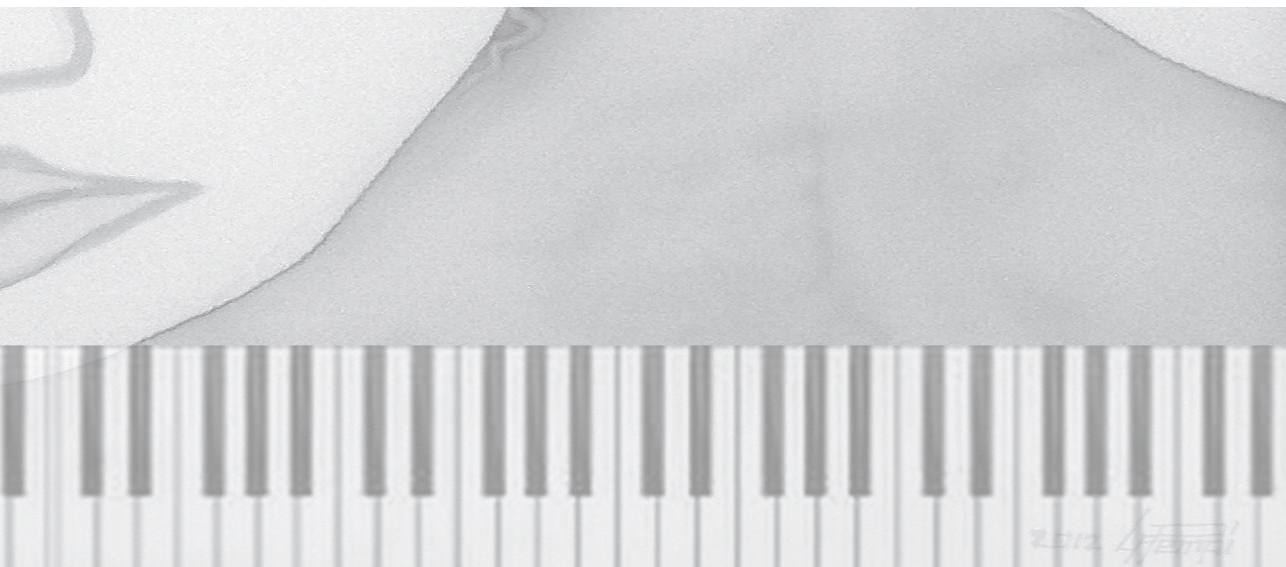


CHAPTER 5

Music to prevent deliriUm during neuroSurgerY (MUSYC) Clinical trial: a study protocol for a randomised controlled trial

P.R. Kappen, J. Jeekel, C.M.F. Dirven, M. Klimek, S.A. Kushner, R.J. Osse, M. Coesmans,
M.J. Poley, A.J.P.E. Vincent

BMJ Open, 2021



Abstract

Introduction

Delirium is a neurocognitive disorder characterized by an acute and temporary decline of mental status affecting attention, awareness, cognition, language and visuospatial ability. The underlying pathophysiology is driven by neuro-inflammation and cellular oxidative stress.

Delirium is a serious complication following neurosurgical procedures with a reported incidence varying between 4 - 44% and has been associated with increased length of hospital stay, increased amount of re-operations, increased costs and mortality.

Perioperative music has been reported to reduce pre-operative anxiety, post-operative pain and opioid usage, and attenuates stress response caused by surgery. We hypothesize that this beneficial effect of music on a combination of delirium eliciting factors might reduce delirium incidence following neurosurgery and subsequently improve clinical outcomes.

Methods

This protocol concerns a single-centered prospective randomized controlled trial with 6 months follow-up. All adult patients undergoing a craniotomy at the Erasmus MC in Rotterdam are eligible. The music group will receive recorded music through an over-ear headphone before, during and after surgery until post-operative day 3. Patients can choose from music playlists, offered based on music importance questionnaires administered at baseline. The control group will receive standard of clinical care

Delirium is assessed by the delirium observation scale (DOS) and confirmed by a delirium-expert psychiatrist according to the DSM-5 criteria. Risk factors correlated with the onset of delirium, such as cognitive function at baseline, pre-operative anxiety, peri-operative medication use, depth of anaesthesia and postoperative pain, and delirium-related health outcomes such as length of stay, daily function, quality of life (i.e. EQ-5D, EORTC questionnaires), costs and cost-effectiveness are collected.

Ethics and dissemination

This study is being conducted in accordance with the Declaration of Helsinki. The Medical Ethics Review Board of Erasmus University Medical Center Rotterdam, The Netherlands, approved this protocol. Results will be disseminated via peer-reviewed scientific journals and conference presentations.

Trial registration number

Trialregister.nl: NL8503

ClinicalTrials.gov ID: NCT04649450

Strengths and limitations of this study

- This study is the first randomized controlled trial evaluating the effects of recorded music on post-operative delirium in a neurosurgical cohort.
- To our knowledge, this is the largest study assessing the effects of music on delirium.
- Both the short-term and longer-term delirium-associated clinical outcomes will be evaluated, as either data during hospitalization and follow-up data until 6 months postoperatively, will be collected.
- Due to the nature of the intervention, blinding of the patients and data collectors was not possible, which is a limitation. However, we expect a low risk of bias in the clinical assessment, as the onset of delirium is not considered a subjective outcome.

Introduction

Delirium is characterized by an acute and temporary decline in mental status affecting attention, awareness, cognition, language and visuospatial ability.¹ This decline is caused by dysregulation of neuronal activity secondary to several pathophysiological disturbances.² Surgery within the brain parenchyma evokes an inflammatory reaction resulting in the formation of oedema and decrease of vascular permeability with impaired oxygenation of nearby tissue resulting in the generation of oxidative stress. Hypotheses describing the pathophysiology of delirium rely on neuro-inflammatory and oxidative reactions within the brain.³ Considering this, it is plausible that neurosurgical patients are in particular vulnerable to developing postoperative delirium and that the incidence of delirium in this population is high.

Incidence rates of post-operative delirium after intracranial surgery vary between 4 – 44% depending on the type of surgery, such as major neuro-vascular reporting higher incidence rates, and method of delirium assessment, such as short follow-up duration resulting in lower incidence rates.⁴⁻¹³

Delirium often causes a traumatic experience for the patient and his or her relatives. Delirium also leads to up to twice the length of hospital stay, twice the intensity of nursing hours, almost twice the amount of re-operations with extra exposure to complications, three times the costs and more than five times higher mortality risk.^{6, 7, 14} Delirium can cause in the long-term a decline in subjective memory, cognitive decline and increase the chance of developing dementia.¹⁵⁻¹⁷ These observations warrant the search for preventive therapies for post-operative delirium.

Several preventive pharmacological interventions for occurrence of post-operative delirium have been studied. Pharmacologic interventions, targeted at the psychotic symptoms such as olanzapine or haloperidol, at the sleep-wake cycle such as melatonin, or lowering sedation levels through bispectral index, were either ineffective or non-reproducible in preventing delirium after surgery.¹⁸ Furthermore, most of these drugs may have severe side effects.^{19, 20, 21}

Non-pharmacological multi-component approaches such as the Hospital Elder Life Program (HELP) or the Perioperative Optimization of Senior Health program (POSH) are promising, showing a relative reduction of delirium in 36-77%.^{22, 23} However, success of these multi-component strategies is dependent on the adherence while

implementation is challenging and not always adjusted to the feasibility for nurse or patients' needs.²⁴

Recorded music is effective in reducing pre-operative anxiety, post-operative pain and its stress response induced by surgery. Moreover, lower doses of opioids and sedatives are required when music around surgery is applied with the strongest effect of music in case of patients-own choice irrespective of own music or from pre-selected playlists.²⁵⁻³³ These positive effect on a combination of delirium-eliciting factors might contribute to a reduction of post-operative delirium.

Three studies have been published on the effect of music as a sole intervention on the occurrence of post-operative delirium. One is a 5-armed trial with a total of 126 patients (approximately 25 per arm) in which no significant effect was seen. However, this study lacked a solid power analysis.³⁴ The second trial had no delirium in either the music and control group due to their exclusion criteria and therefore no effect could be demonstrated.³⁵ The third trial randomized 22 patients and reported significant better outcome in the music group.³⁶ In none of these trials, the music selection was based on patient's preference. In conclusion, although suggestive, currently no strong evidence exists on the possible beneficial effect of music on delirium.

Furthermore, evidence on the effects of music interventions on delirium-related health-outcomes such as length of stay, daily functioning, costs, quality of life, and cost-effectiveness is lacking. This is a significant knowledge gap, as these truly represent clinically relevant outcome measures for patient and society.

Therefore, this article reports on a randomized control trial to assess the effect of music in the prevention of post-operative delirium in neurosurgical patients.

Methods and analysis

Study design

This study is a randomized controlled trial with two study arms, designed to compare the effects on postoperative delirium, of perioperative recorded music intervention in addition to standard care (intervention group) versus standard care (control group) – prior, during and after a craniotomy. Figure 1 shows the flow diagram of the progress through the trial phases of the two study groups. We will include 189 adults at the Neurosurgery department of the Erasmus Medical Center in Rotterdam. Ethical

Committee approval was obtained in April 2020, the first patient was included in July 2020 and July 2022 is the anticipated end date of inclusion. This study protocol followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see SPIRIT checklist in online supplementary material) and the Consolidated Standards of Reporting Trials (CONSORT) guidelines for non-pharmacologic treatments. This trial was registered on trialregister.nl (NL8503) and clinicaltrials.gov (NCT04649450).

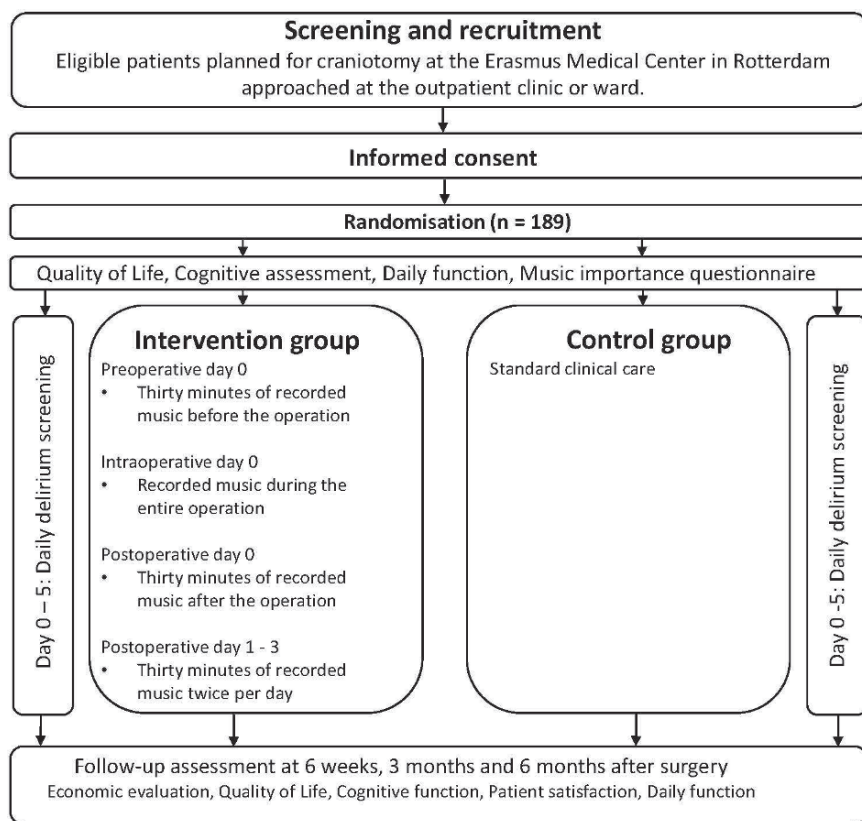


Figure 1. Flowchart

Randomisation, blinding and treatment allocation

The random allocation sequence will be computer-generated using an online software program or website (ALEA; FormVision, Abcoude, The Netherlands) ran by the executing researcher after obtaining informed consent. Randomization will be in a 1:1 ratio and stratified per type of disease characteristic (i.e. 'neuro-oncology', 'neurovascular', 'traumatic brain injury', 'infectious') and age (i.e. 'younger than 60 years', '60 years or older'). Variable block sizes will be used; in each block both groups will be represented equally. The web-based program will be secured and only members of the study staff will have login credentials.

Patients participating in the study cannot be blinded due to the nature of the treatment. Selective blinding of the clinicians and data collectors is unsecure while patients might report their experience when undergoing the (music/control) intervention. Hence, to prevent misleading conclusions an unblinded design was chosen. In our view, this is not too much of a limitation, since the primary outcome of this study (i.e., the onset of delirium) can be assessed objectively.

As the intervention is without risks and cannot be blinded, it will in no case be necessary to break the randomization code. Data collection and intervention administration (conducted by the treating nurses and consulting psychiatrist) and randomization and final analysis (conducted by the executing researcher) were separated but not masked from each other.

Interventions

Participants in the intervention group (i.e. music group) receive an over-ear headphone and a tablet with access to a platform with different music playlists. These lists are based on personal preference gathered from questionnaires at baseline assessing the role (i.e. just listening versus playing instruments), importance (i.e. through a visual analogue scale from 0 to 100) and preference of music (i.e. on genre) per patient. These pre-selected playlists are categorized based on genre (jazz, blues, classic, electronic, pop, 60s, 70s, 80s etc), country or artist, are either custom made or composed by our research group from earlier trials and have a minimum duration of 180 minutes to prevent repetition of songs within the same music session.²⁹ The first 30 minutes of music, administered by the treating nurse, is given the day of operation with the over-ear headphones while awaiting surgery. Once in the operating room they

will receive in-ear earphones after intubation, compatible with the Mayfield clamp and site of operation. The intraoperative music intervention, in accordance with the pre-operative choice of music, will be continued during the surgical procedure and discontinued just before detubation. Although patients might not remember this music session, we chose for music during general anaesthesia as a significant decrease in pain and anxiety has been reported in surgical patients when receiving intra-operative music.³³ The intra-operative music session is continuous and the duration depends on the duration of surgery and will be documented. After surgery, during recovery at the post-operative care unit (PACU) another 30 minutes of recorded music through over-ear headphones will be administered. Subsequently, participants will receive 30 minutes of recorded music twice a day for the following 3 post-operative days as music is currently investigated as preventive therapy and onset of post-operative delirium has been reported in the first 3 to 5 days after intracranial surgery.^{5, 10, 37-39}

The control group will not receive headphone music and will be treated according to standard care. We did not choose for over-ear headphone - without music or other auditory signals - in our control group as this is considered an intervention requiring another study arm, which we deemed unfeasible. It would be an interesting opportunity for future research to include other comparison and control groups (exposed to other auditory input or silence), which could also generate more options for blinding the clinicians and data collectors.

All participating subjects in this study will be requested to refrain from listening to music through headphone during the first three postoperative days, apart from the planned intervention. Music other than from the headphone (e.g. television) is allowed in either the music or control group but patient or a family member is asked to report this.

Patients in either group, besides the screening tools for our primary and secondary outcomes, will receive standard clinical care and will not be restricted from any treatments whatsoever.

Outcome parameters

The primary outcome measure is presence or absence of postoperative delirium within the first five postoperative days.^{40, 41} All participating patients on the ward will be screened daily by the treating nurse using the Delirium Observation Screening (DOS) scale, a validated 13-item delirium screening tool which is already current practice

at the Neurosurgical ward in the Erasmus MC.⁴²⁻⁴⁶ In case of raised suspicion by the DOS a psychiatrist is consulted to confirm or reject clinical diagnosis of delirium based on the DSM-5 criteria.¹

Secondary outcome parameters include risk factors and health outcomes, which substantiate the effect of music on delirium and evaluate its clinical implications for patient and society:

- Severity and duration of delirium. In case of positive delirium, its severity will be assessed using the Delirium Rating Scale-revised-98 (DRS-R-98).^{47, 48} A DOS score of lower than 3 during 24 hours will be considered as a 'faded out' delirium and number of days from onset until end will be documented.
- Pre-operative anxiety assessed with the VAS-anxiety (VAS-A). This 11-point scale, in which 0 implies no anxiety and 10 the worst anxiety possible, is easy to use, highly correlated with the State-Trait Anxiety Inventory (STAI), and is assessed while awaiting surgery. In case of visual impairment, caused by the neurologic disease, VAS will be exchanged for numeric rating scale (NRS).⁴⁹⁻⁵²
- Activation of the parasympathetic nervous system, before and after surgery, using the heart rate variability (HRV). The HRV, the variation in the time interval between adjacent heartbeats related to parasympathetic influences, is measured through ECG-recordings while awaiting and when recovering from surgery.⁵³
- Depth of anaesthesia is registered with Bispectral Index (BIS), which signals EEG brain activity displayed into numerical values. The BIS is often used to guide during anaesthesia but its feasibility and implications during neurosurgical operations is still unknown.^{54, 55}
- Peri-operative medication use, such as opioids, benzodiazepines and antipsychotic drugs will be extracted from the electronic patient files.
- Postoperative pain, assessed using the validated 11-point NRS-scale, in which 0 implies no pain and 10 the worst pain possible.⁵⁶
- Postoperative complications defined as an adverse event within two weeks after surgery resulting in prolongation of current admission, new treatment (i.e. reoperations) or death.

- Hospital length of stay in days defined as the day of admission until the actual day of discharge.
- Cognitive function assessed with the Montreal Cognitive Assessment (MoCA) tool at baseline, 3 and 6 months.⁵⁷
- Daily function, expressed in Karnofsky Performance Scale (KPS) and Modified Ranking Scale (mRS).^{58, 59, 60} This is assessed at baseline, 6 weeks, 3 and 6 months after surgery.
- Mortality and readmission rate will be evaluated during the follow-up at 6 weeks, 3 and 6 months.
- Health-related quality of life (HRQoL) with the EORTC-C30 and the EORTC-BN20 questionnaires at baseline and during the follow-up at 6 weeks, 3 and 6 months.
- Music importance (i.e. based on a visual analogue scale in which 0 implies no importance at all and 100 the most imaginable importance), preference (i.e. chosen per genre) and the role of music (i.e. just listening / active playing) is administered at baseline. Moreover patient satisfaction, whether patient received music or not, is assessed at 6 weeks after discharge.⁶¹
- Economic evaluation; see below for further details.

Eligibility criteria

Potential subjects visiting the outpatient clinic or admitted to the neurosurgical ward will be informed about our study. A member of the research team undertakes the initial screening for eligibility. In order to be eligible to participate in this study, a subject must meet all of the following inclusion criteria:

- Patients undergoing a craniotomy.
- Adult patients (i.e. age 18 years or more).
- Sufficient knowledge of the Dutch language to understand the study documents in the judgement of the attending physician or researcher.
- Provision of written informed consent by patient or legal representative.

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Impaired awareness before surgery (i.e. motoric less than 6 in the Glasgow Coma Scale)
- Planned post-operative ICU admission (i.e. with prolonged sedation and mechanical ventilation).
- Suspected delirium (defined as fluctuating awareness) before surgery.
- Current antipsychotic treatment.
- Patients undergoing surgery impeding supply of music (e.g. surgical translabrynthine approach, awake surgery).
- Severe bilateral hearing impairment, defined as no verbal communication possible.
- Known musicogenic epilepsy (i.e. seizure provoked when hearing a specific type of sound or musical stimuli)
- Current participation in other clinical trials interfering with results.

Sample size

We expect an incidence of delirium in our control group of 30%. This is based on literature documenting incidence of delirium in neurosurgical patients in a northern European population of 29-33%.^{4-6, 8-13, 62} The expected effect cannot be based on previous literature since no adequate trials exist on the effect of music on delirium. Other non-pharmacological interventions mention a relative reduction of 36-77%.^{19 22} We will therefore consider the intervention clinically relevant if a relative reduction of 60%, corresponding to an absolute reduction of 18%, is achieved. Assuming a power of 80%, a two-sided p-value of 0.05, and 1:1 randomization, a sample size of 90 patients per arm would be required. We expect a loss to follow-up of 5% and will therefore include 189 patients.

Inclusion period

We expect 50% of the craniotomy patients not to be eligible due to in- or exclusion criteria given above. This leaves 240 eligible patients each year, taking into account that approximately 480 craniotomies are conducted at the Erasmus MC in Rotterdam each year. In 30% of these cases it concerns emergency operations and we do not expect to be able to include many of these patients. Considering this, we would in theory therefore need 14 months for inclusion. Hence we would plan 24 months of inclusion time taking into account all the logistic challenges. In practice this comes down to 1 or 2 inclusions each week.

Statistical analysis

All analyses will be conducted according to the intention-to-treat (ITT) principle, i.e. patients will be analysed according to the treatment arm they were assigned to, irrespective of the treatment they actually received. The primary endpoint in a patient will be the occurrence of a DOS score 3 or higher subsequently confirmed with the DSM-5 by a psychiatrist. Those patients will be considered as event, all other patients will be considered as non-event. The proportion of patients with an event will be compared between the randomization arms using univariate and multivariate logistic regression analysis, i.e. the Odds Ratio (OR) with 95% Confidence Interval (CI) will be calculated. A two-sided p value of 0.05 or less will be considered statistically significant. All other analyses will be exploratory and therefore as hypothesis-generating only.

Economic evaluation

Taking a societal perspective, we will analyse the cost-effectiveness of the music intervention versus ‘standard care’, using the techniques of a trial-based cost-effectiveness analysis and cost-utility analysis. Established methods for economic evaluations in health care will be used.⁶³⁻⁶⁵

The analysis will include both medical and non-medical costs. Medical costs include all the costs of hospital admissions, surgeries, diagnostic imaging, laboratory findings, and consultations. The cost analysis will include costs of treating adverse consequences of delirium (such as falls and posttraumatic stress) and will extend beyond the initial hospital admission, including visits to the outpatient department, readmissions, nursing

home admissions, medications and consultations with psychiatrists. To collect data on health care use, both the hospital's electronic information system and data from the iMTA Medical Consumption Questionnaire (administered to the patients at the follow-up visits) will be used.⁶⁶ These data will then be combined with unit costs to generate patient-level costs. Non-medical costs will comprise costs of lost productivity. After all, it is expected that patients in the intervention group may resume their (paid and/or unpaid) work earlier, as the occurrence of delirium declines. Productivity losses will be measured and valued using the iMTA Productivity Cost Questionnaire (iPCQ).⁶⁷ Finally, for the patients in the intervention group, the costs of the music intervention itself (i.e., headphones, earphones and sound equipment) will be added.

To measure the effects of the intervention, the economic evaluation will consider the occurrence of delirium (as defined above) and quality-adjusted life years (QALYs). The calculation of QALYs will be based on survival data and on the EQ-5D questionnaire.⁶⁸ The EQ-5D is a generic, preference-based quality of life measure, comprising 5 dimensions of health, that allows for the calculation of QALYs. The EQ-5D will be administered at base line and at 6 weeks and 3 and 6 months follow up.

Then, incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in costs between the groups by the difference in effects, unless one treatment dominates the other (i.e., has lower costs and greater effects). The ICERs will be expressed as incremental costs per case of delirium prevented and incremental costs per QALY gained. Uncertainty in the estimation of the ICERs will be illustrated through cost-effectiveness planes (via bootstrapping). Cost-effectiveness acceptability curves (CEACs) will be calculated showing the probability of the intervention being cost-effective compared to 'standard care' as a function of society's willingness-to-pay for a QALY gained. The time horizon of the analysis will be the 6 months follow-up period. As a result, discounting of future costs and benefits will not be required. Sensitivity analysis will be performed to assess the robustness of the analysis to certain assumptions.

Patient and Public Involvement

Patients are involved in the composition of the music playlists, as these are based on their music preference, the role music plays in their life (i.e. whether they are musician / just listen to music) and the importance of music. The results of our trial will be disseminated to the participating patients through a letter after publication.

Trial monitoring

Based on the small chance of damage due to the intervention our risk is expected to be negligible (risk class A). Monitoring will be conducted for quality assurance of data, patient inflow, meeting of in- and exclusion criteria, informed consent, compliance, patient safety, study procedures and source document verification in compliance with the monitoring plan for risk class A (negligible risk).

Our Monitor will be an independent qualified researcher who completed a Good Clinical Practice (GCP) training course. Results, conclusion and advice will be recorded in the monitor report and stored for at least 15 years.

All investigators and study staff will be responsible for reporting adverse effects to the coordinating investigator. The coordinating investigator or principal investigator will report adverse events to the Medical Ethics Review Board in accordance with the ethics committee adverse event reporting procedures. The coordinating investigator and the principal investigator are responsible for adherence to all ethical committee rules and guidelines and for the accuracy and completeness of all forms, entries, and informed consent.

Data management

Data will be handled confidentially in compliance with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (Dutch: Uitvoeringswet AVG, UAVG). Each subject will receive an ID code which will be based on a random number produced by the randomization software ALEA and the database tracing towards the patients' ID will be stored separately. Any information on paper collected during this study will be placed in a research folder, which will be filed in locked cabinets in research offices at the Erasmus MC. Any electronic information acquired during the research period will be stored in Open Clinica, a secured and Erasmus MC approved storage program which tracks all the changes applied and freezes data when inclusion and data check has been done. Only the study staff will have access to the research data.

Ethics and dissemination

Ethics

The study protocol has been reviewed by the Medical Ethics Review Board of the Erasmus Medical Center in Rotterdam on 9 March 2020 and is not subject to the Medical Research Involving Human Subjects Act (Dutch: niet-WMO). This study is being conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

Benefits and risks assessment

Listening to music might be experienced as pleasant. During the informed consent process, it will be made clear that participation might not have clear direct benefits to the patient, and that refusal to participate will not have impact on the care received by any of the medical staff.

Recent meta-analysis showed no side effects of recorded music through headphones.²⁸ Hypothetically there is a chance of hearing damage – with subsequent tinnitus –, which will be minimized by setting a volume limit of 60 dB on each tablet, which is the advised loudness of a music intervention in medical care.⁶⁹ Moreover, participants might be upset of being refrained from music when allocated in the control group. Lastly, communicating at the clinician might be complicated during the music session, especially in immobile patients.

All adverse events will be documented. We expect no intervention-related serious adverse events.

Dissemination

The research team is committed to full disclosure of the results of the trial. Findings will be reported in accordance with CONSORT guidelines and we aim to publish in high-impact journals. Given the multitude of outcome parameters, results will be divided over several papers. The funder will take no role in the analysis or interpretation of results.

References

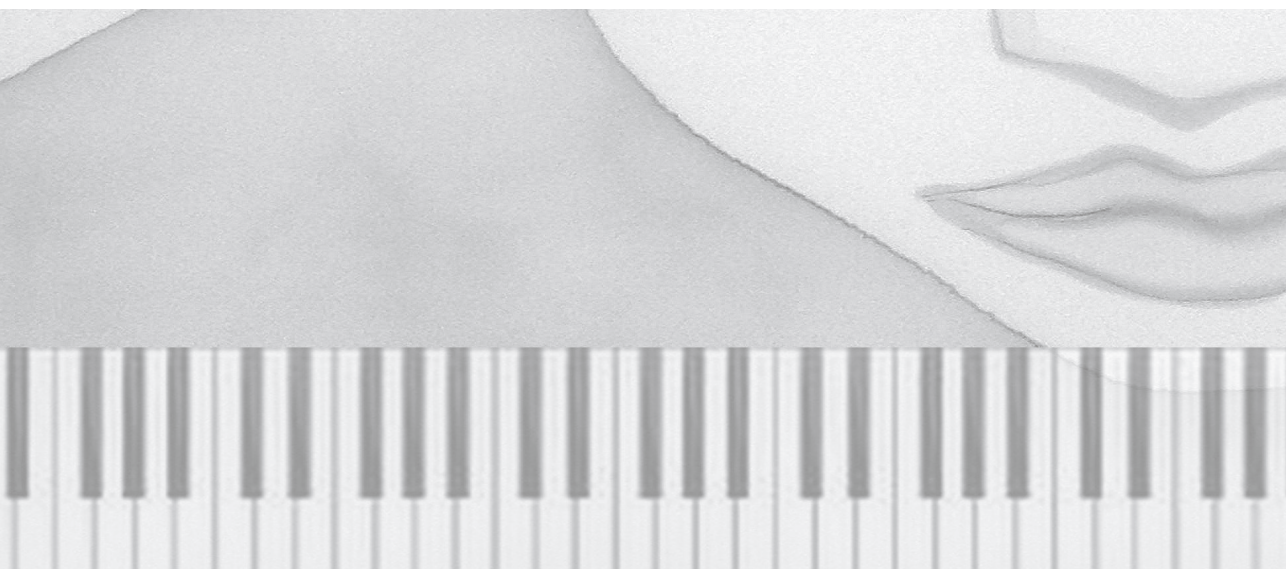
1. American Psychiatric A. American Psychiatric Association DSM-5 Task Force (2013): Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, DC: American Psychiatric Association;
2. Maldonado JR. Acute Brain Failure: Pathophysiology, Diagnosis, Management, and Sequelae of Delirium. *Crit Care Clin.* 2017;33(3):461-519.10.1016/j.ccc.2017.03.013
3. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry.* 2013;21(12):1190-222.10.1016/j.jagp.2013.09.005
4. Matano F, Mizunari T, Yamada K, Kobayashi S, Murai Y, Morita A. Environmental and Clinical Risk Factors for Delirium in a Neurosurgical Center: A Prospective Study. *World Neurosurg.* 2017;103:424-30.10.1016/j.wneu.2017.03.139
5. Wang J, Ji Y, Wang N, Chen W, Bao Y, Qin Q, et al. Risk factors for the incidence of delirium in cerebrovascular patients in a Neurosurgery Intensive Care Unit: A prospective study. *J Clin Nurs.* 2017;27(1-2):407-15.10.1111/jocn.13943
6. Zipser ZM DJ, Ernst J, Schubert M, von Känel R, Böttger S. The predisposing and precipitating risk factors for delirium in neurosurgery: a prospective cohort study of 949 patients. *Acta Neurochir.* 2019;161(7):1307-15
7. Maria Schubert RS, Soenke Boettger, David Garcia Nuñez, Urs Schwarz, Dominique Bettex, Josef Jenewein, Jasmina Bogdanovic, Marina Lynne Staehli, Rebecca Spirig and Alain Rudiger. A hospital-wide evaluation of delirium prevalence and outcomes in acute care patients - a cohort study. *BMC Health Services Research.* 2018.10.1186/s12913-018-3345-x
8. Tanaka M, Tani N, Maruo T, Oshino S, Hosomi K, Saitoh Y, et al. Risk Factors for Postoperative Delirium After Deep Brain Stimulation Surgery for Parkinson Disease. *World neurosurgery.* 2018;114:e518-e23.10.1016/j.wneu.2018.03.021
9. Chen L, Xu M, Li GY, Cai WX, Zhou JX. Incidence, Risk Factors and Consequences of Emergence Agitation in Adult Patients after Elective Craniotomy for Brain Tumor: A Prospective Cohort Study. *PLoS One.* 2014;9(12):e114239.10.1371/journal.pone.0114239
10. He Z, Cheng H, Wu H, Sun G, Yuan J. Risk factors for postoperative delirium in patients undergoing microvascular decompression. *PLoS One.* 2019;14(4):e0215374.10.1371/journal.pone.0215374
11. Flanagan PM, Jahangiri A, Weinstein D, Dayani F, Chandra A, Kanungo I, et al. Postoperative Delirium in Glioblastoma Patients: Risk Factors and Prognostic Implications. *Neurosurgery.* 2018;83(6):1161-72.10.1093/neuros/nyx606
12. Budenas A, Tamasauskas S, Sliauzys A, Navickaite I, Sidaraite M, Pranckeviciene A, et al. Incidence and clinical significance of postoperative delirium after brain tumor surgery. *Acta Neurochir (Wien).* 2018;160(12):2327-37
13. Morshed RA, Young JS, Safaee M, Sankaran S, Berger MS, McDermott MW, et al. Delirium Risk Factors and Associated Outcomes in a Neurosurgical Cohort: A Case-Control Study. *World Neurosurg.* 2019;126:930-6.10.1016/j.wneu.2019.03.012
14. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med.* 2008;168(1):27-32.10.1001/archinternmed.2007.4

15. Kat MG, Vreeswijk R, de Jonghe JF, van der Ploeg T, van Gool WA, Eikelenboom P, et al. Long-term cognitive outcome of delirium in elderly hip surgery patients. A prospective matched controlled study over two and a half years. *Dement Geriatr Cogn Disord*. 2008;26(1):1-8.10.1159/000140611
16. Bickel H, Gradingner R, Kochs E, Forstl H. High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. *Dement Geriatr Cogn Disord*. 2008;26(1):26-31.10.1159/000140804
17. Rockwood K, Cosway S, Carver D, Jarrett P, Stadnyk K, Fisk J. The risk of dementia and death after delirium. *Age Ageing*. 1999;28(6):551-6.10.1093/ageing/28.6.551
18. Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev*. 2016; 3:CD005563.10.1002/14651858.CD005563.pub3
19. Janssen TL, Alberts AR, Hooft L, Mattace-Raso F, Mosk CA, van der Laan L. Prevention of postoperative delirium in elderly patients planned for elective surgery: systematic review and meta-analysis. *Clin Interv Aging*. 2019;14:1095-117.10.2147/CIA.S201323
20. Liu Y, Li XJ, Liang Y, Kang Y. Pharmacological Prevention of Postoperative Delirium: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Evid Based Complement Alternat Med*. 2019;2019:9607129
21. Vlisides P, Avidan M. Recent Advances in Preventing and Managing Postoperative Delirium. *F1000Res*. 2019;8
22. Abraha I, Trotta F, Rimland JM, Cruz-Jentoft A, Lozano-Montoya I, Soiza RL, et al. Efficacy of Non-Pharmacological Interventions to Prevent and Treat Delirium in Older Patients: A Systematic Overview. The SENATOR project ONTOP Series. *PLoS One*. 2015;10(6):e0123090
23. Hsieh TT, Yang T, Gartaganis SL, Yue J, Inouye SK. Hospital Elder Life Program: Systematic Review and Meta-analysis of Effectiveness. *Am J Geriatr Psychiatry*. 2018;26(10):1015-33
24. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911-22.10.1016/S0140-6736(13)60688-1
25. Cerejeira J, Batista P, Nogueira V, Vaz-Serra A, Mukaetova-Ladinska EB. The stress response to surgery and postoperative delirium: evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased suppression of the GH/IGF-1 Axis. *J Geriatr Psychiatry Neurol*. 2013;26(3):185-94.10.1177/0891988713495449
26. Clegg A YJ. Which medications to avoid in people at risk of delirium: a systematic review. 2011(40:23–29)
27. Fu VX, Oomens P, Sneiders D, van den Berg SAA, Feelders RA, Wijnhoven BPL, et al. The Effect of Perioperative Music on the Stress Response to Surgery: A Meta-analysis. *J Surg Res*. 2019;244:444-55
28. Fu VX OP, Klimek M, Verhofstad MHJ, Jeekel J. The effect of perioperative music on medication requirement and hospital length of stay: a meta-analysis. *Annals of Surgery*. July 2019;272(6):961 - 72
29. Kuhlmann AYR, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. Meta-analysis evaluating music interventions for anxiety and pain in surgery. *Br J Surg*. 2018;105(7):773-83.10.1002/bjs.10853

30. Lee JH. The Effects of Music on Pain: A Meta-Analysis. *J Music Ther.* 2016;53(4):430-77.10.1093/jmt/thw012
31. Leung JM SL, Paul S. Does postoperative delirium limit the use of patient-controlled analgesia in older surgical patients? 111:625–631. 2009
32. Schor JD, Levkoff SE, Lipsitz LA, Reilly CH, Cleary PD, Rowe JW, et al. Risk factors for delirium in hospitalized elderly. *JAMA.* 1992;267(6):827-31
33. Hole J, Hirsch M, Ball E, Meads C. Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. *Lancet.* 2015;386(10004):1659-71.10.1016/S0140-6736(15)60169-6
34. Iblher P, Mahler H, Heinze H, Huppe M, Klotz KF, Eichler W. Does music harm patients after cardiac surgery? A randomized, controlled study. *Applied Cardiopulmonary Pathophysiology.* 2011;15(1):14-23
35. Johnson K, Fleury J, McClain D. Music intervention to prevent delirium among older patients admitted to a trauma intensive care unit and a trauma orthopaedic unit. *Intensive Crit Care Nurs.* 2018;47:7-14
36. McCaffrey R. The effect of music on acute confusion in older adults after hip or knee surgery. *Appl Nurs Res.* 2009;22(2):107-12.10.1016/j.apnr.2007.06.004
37. Hosoya R, Sato Y, Ishida E, Shibamoto H, Hino S, Yokote H, et al. Association between Delirium and Prehospitalization Medication in Poststroke Patients. *J Stroke Cerebrovasc Dis.* 2018;27(7):1914-20.10.1016/j.jstrokecerebrovasdis.2018.02.038
38. Mokhtari M, Farasatinasab M, Jafarpour Machian M, Yaseri M, Ghorbani M, Ramak Hashemi SM, et al. Aripiprazole for prevention of delirium in the neurosurgical intensive care unit: a double-blind, randomized, placebo-controlled study. *Eur J Clin Pharmacol.* 2020.10.1007/s00228-019-02802-1
39. Oh YS, Kim DW, Chun HJ, Yi HJ. Incidence and risk factors of acute postoperative delirium in geriatric neurosurgical patients. *J Korean Neurosurg Soc.* 2008;43(3):143-8.10.3340/jkns.2008.43.3.143
40. Robinson TN, Raeburn CD, Tran ZV, Angles EM, Brenner LA, Moss M. Postoperative delirium in the elderly: risk factors and outcomes. *Ann Surg.* 2009;249(1):173-8.10.1097/SLA.0b013e31818e4776
41. Lee H, Ju JW, Oh SY, Kim J, Jung CW, Ryu HG. Impact of timing and duration of postoperative delirium: a retrospective observational study. *Surgery.* 2018;164(1):137 - 43.10.1016/j.surg.2018.02.001
42. Association AP. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. May 2013
43. Gavinski K, Carnahan R, Weckmann M. Validation of the delirium observation screening scale in a hospitalized older population. *J Hosp Med.* 2016;11(7):494-7.10.1002/jhm.2580
44. Detroyer E, Clement PM, Baeten N, Pennemans M, Decruyenaere M, Vandenberghe J, et al. Detection of delirium in palliative care unit patients: a prospective descriptive study of the Delirium Observation Screening Scale administered by bedside nurses. *Palliat Med.* 2014;28(1):79-86.10.1177/0269216313492187
45. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. *Res Theory Nurs Pract.* 2003;17(1):31-50

46. van Velthuisen EL, Zwakhalen SM, Warnier RM, Mulder WJ, Verhey FR, Kempen GI. Psychometric properties and feasibility of instruments for the detection of delirium in older hospitalized patients: a systematic review. *Int J Geriatr Psychiatry*. 2016;31(9):974-89.10.1002/gps.4441
47. Grover S, Kate N. Assessment scales for delirium: A review. *World J Psychiatry*. 2012;2(4):58-70.10.5498/wjp.v2.i4.58
48. Trzepacz PT, Mittal D, Torres R, Canary K, Norton J, Jimerson N. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci*. 2001;13(2):229-42.10.1176/jnp.13.2.229
49. Spielberger CD GR, Lushene R, Vagg PR, Jacobs GA. Manual for the State Trait Anxiety Inventory. Consulting Psychologists Press. 1983
50. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care Res (Hoboken)*. 2011;63 Suppl 11:S467-72.10.1002/acr.20561
51. Abend R, Dan O, Maoz K, Raz S, Bar-Haim Y. Reliability, validity and sensitivity of a computerized visual analog scale measuring state anxiety. *J Behav Ther Exp Psychiatry*. 2014;45(4):447-53.10.1016/j.jbtep.2014.06.004
52. Facco E, Stellini E, Bacci C, Manani G, Pavan C, Cavallini F, et al. Validation of visual analogue scale for anxiety (VAS-A) in preanesthesia evaluation. *Minerva Anestesiol*. 2013;79(12):1389-95.R02Y9999N00A0660 [pii]
53. Camm AJ, Malik M, Bigger JT, Breithardt G, Cerutti S, Cohen RJ, et al. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996;1;93(5):1043-65.
54. Chiu CL, Ong G, Majid AA. Impact of bispectral index monitoring on propofol administration in patients undergoing cardiopulmonary bypass. *Anaesth Intensive Care*. 2007;35(3):342-7.10.1177/0310057X0703500304
55. Gan TJ, Glass PS, Windsor A, Payne F, Rosow C, Sebel P, et al. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. *Anesthesiology*. 1997;87(4):808-15.10.1097/0000542-199710000-00014
56. McCarthy M, Jr., Chang CH, Pickard AS, Giobbie-Hurder A, Price DD, Jonasson O, et al. Visual analog scales for assessing surgical pain. *J Am Coll Surg*. 2005;201(2):245-52. S1072-7515(05)00396-0 [pii]10.1016/j.jamcollsurg.2005.03.034
57. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-9
58. Verger E, Salamero M, Conill C. Can Karnofsky performance status be transformed to the Eastern Cooperative Oncology Group scoring scale and vice versa? *Eur J Cancer*. 1992;28A(8-9):1328-30.0959-8049(92)90510-9 [pii]
59. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-7.10.1161/01.str.19.5.604

60. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke*. 2007;38(3):1091-6.10.1161/01.STR.0000258355.23810.c6
61. Little CJCCYA. Music increases satisfaction in elderly outpatients undergoing cataract surgery. *Canadian Journal of Anaesthesia*. 1997;44(1):43-8
62. van den Boogaard M, Schoonhoven L, Evers AW, van der Hoeven JG, van Achterberg T, Pickkers P. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. *Crit Care Med*. 2012;40(1):112-8.10.1097/CCM.0b013e31822e9fc9
63. Institute NHC. Manual for costing research. Methods and reference prices for economic evaluations in health care. Updated edition [in Dutch]. Diemen: National Health Care Institute. 2015
64. Institute NHC. Guidelines for Economic Evaluations of Health Care [in Dutch]. Diemen: National Health Care Institute. 2015
65. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 2016;316(10):1093-103.10.1001/jama.2016.12195
66. Bouwmans C H-VRL, Koopmanschap M, Krol M, Severens H, Brouwer W. . iMTA Medical Consumption Questionnaire. Rotterdam: Institute for Medical Technology Assessment, Erasmus Universiteit Rotterdam. 2013
67. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van Roijen L. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Health*. 2015;18(6):753-8.10.1016/j.jval.2015.05.009
68. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37(1):53-72.10.1016/0168-8510(96)00822-6
69. Nilsson U. The anxiety- and pain-reducing effects of music interventions: a systematic review. *AORN J*. 2008;87(4):780-807.S0001-2092(07)00575-3 [pii] 10.1016/j.aorn.2007.09.013

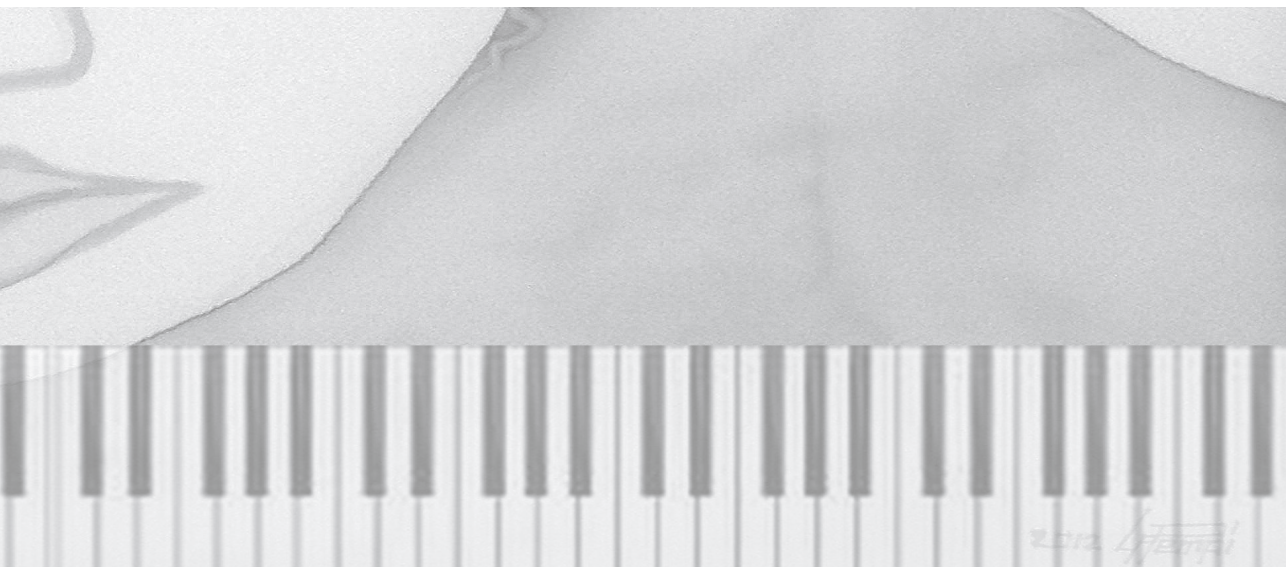


CHAPTER 6

Music to prevent delirium during neurosurgery (MUSYC): a single-centre prospective randomised controlled trial

P.R. Kappen, M.I. Mos, J. Jeekel, C.M.F. Dirven, S.A. Kushner, R.J. Osse, M. Coesmans,
M.J. Poley, M.S. van Schie, B. van der Holt, M. Klimek, A.J.P.E. Vincent

BMJ Open, 2023



Abstract

Objectives

Delirium is a serious complication following neurosurgical procedures. We hypothesize that the beneficial effect of music on a combination of delirium-eliciting factors might reduce delirium incidence following neurosurgery and subsequently improve clinical outcomes.

Design

Prospective randomized controlled trial.

Setting

Single centre, conducted at the neurosurgical department of the Erasmus MC Rotterdam, the Netherlands.

Participants

Adult patients undergoing craniotomy were eligible.

Interventions

Patients in the intervention group received preferred recorded music before, during and after the operation until day 3 after surgery. Patients in the control group were treated according to standard of clinical care.

Primary and secondary outcome measures

Primary outcome was presence or absence of postoperative delirium within the first five postoperative days measured with the Delirium Observation Screening scale (DOSS) and, in case of a daily mean score of 3 or higher, a psychiatric evaluation with the DSM-5 criteria. Secondary outcomes included anxiety, heart rate variability (HRV), depth of anaesthesia, delirium severity and duration, post-operative complications, length of stay and location of discharge.

Results

We enrolled 189 patients (music = 95, control = 94) from July 2020 through September 2021. Delirium, as assessed by the DOSS, was less common in the music ($n = 11$, 11.6%) than in the control group ($n = 21$, 22.3%, OR:0.49, $p=0.048$). However, after DSM-5 confirmation, differences in delirium were not significant (4.2% vs. 7.4%, OR:0.47, $p=0.342$). Moreover, music increased the heart rate variability (RMSSD, $p=0.012$). All other secondary outcomes were not different between groups.

Conclusion

Our results support the efficacy of music in reducing the incidence of delirium after craniotomy, as found with DOSS but not after DSM-5 confirmation, substantiated by the effect of music on pre-operative autonomic tone. Delirium screening tools should be validated and the long-term implications should be evaluated after craniotomy.

Strengths and limitations

- This is the first randomized controlled trial assessing the effect of music on delirium after craniotomy
- A variety of secondary outcomes, substantiating the onset of delirium and its clinical implications, were collected.
- Delirium was defined with the Delirium Observation Screening Score and the DSM-criteria.
- Due to the nature of the intervention, we did not blind the study, which could have influenced the outcome assessors.
- The generalizability of the results may be affected by the single-centre design of the study.

Introduction

Delirium is defined in the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as “an acute disturbance in attention and cognition which is not better explained by another neurocognitive disorder such as for example dementia”. To increase the recognition of delirium during hospital stay, a variety of delirium diagnostic screening tools have been developed, which can also be assessed by other healthcare workers. Delirium in neurosurgical patients has been reported in 4 to 44% of cases, with a large variation in definition and assessment methods. (1) The high incidence in this population is probably caused by the underlying massive neuro-inflammation which is usually induced during intracranial procedures. (2) Delirium, also in neurosurgical literature, is often multifactorial in aetiology and can be influenced by a number of predisposing (e.g. older age, cognitive impairment, multiple comorbidities) and precipitating factors (e.g. infections, operations, drugs). (3-8) The clinical relevance of delirium in neurosurgery remains difficult to assess objectively, as criteria for delirium overlap with symptoms from the primary neurologic injury. However, delirium independently predicted clinical outcomes in neurosurgical and neurocritically ill patients such as worse functional outcome (9), length of stay, costs and death. (10) These complications justify the search for preventive therapies for post-operative delirium in neurosurgical patients.

Although promising preventive approaches are emerging, pharmacological treatments have inconsistent results and are accompanied with side effects. (11, 12) Non-pharmacological multi-component approaches for primary prevention, such as reorientation, early mobilization, therapeutic activities, hydration, nutrition and sleep strategies have been shown to be effective and cost-reducing in other patient groups. However, these approaches can be labour intensive, and include the use of volunteers, or non-licensed professionals to enhance feasibility. (13)

Recorded music is an easy applicable intervention which neatly fits throughout the entire perioperative process and has been shown to be effective in the surgical population in reducing a combination of delirium-eliciting factors such as pre-operative anxiety, post-operative pain, stress response and opioid/sedation requirement. (14-21) A recent meta-analysis, evaluating six randomised pilot studies, found music potentially being effective in preventing postoperative delirium in postsurgical patients. However, these studies did not include neurosurgical patients. (22)

We therefore designed a randomized controlled trial to assess the effect of music in the prevention of post-operative delirium in neurosurgical patients.

Methods

Patient and public involvement

Patients were involved in the composition of the music playlists, as these were based on their music preference, the role music plays in their life (ie, whether they are musician/ just listen to music) and the importance of music. The results of our trial were disseminated to the participating patients through a letter after publication.

Study design

The Music to prevent deliriUm during neuroSurgerY Clinical (MUSYC) trial was a single centre, prospective randomized controlled trial conducted at the Erasmus MC Rotterdam, the Netherlands. The trial compared effects of music administered before, during and after craniotomy with standard of clinical care. The Medical Ethics Review Committee of the Erasmus Medical Center, Rotterdam (Erasmus MC), declared this study not subject to the Medical Research Involving Human Subjects Act (i.e. ‘Non-WMO’), and approved this study (MEC-2020-0064), on the 25th of February of 2020, as such.

The trial protocol was designed by neurosurgeons, psychiatrists, anaesthesiologists and neuroscientists and followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and the Consolidated Standards of Reporting Trials (CONSORT) guidelines for non-pharmacological treatments (see checklist in online supplementary material). The trial was registered (trialregister.nl: NL8503 and ClinicalTrials.gov: NCT04649450) and details of the protocol have been published previously. (23, 24)

We expected an incidence of delirium in our control group of 30%, which was based on the incidence of 24.2–32.4% documented in neurosurgical literature using the same screening tool (i.e. DOSS).(5, 7) When designing the trial, the expected effect could not be based on previous literature as no pooled effect of music on delirium was reported. Other non-pharmacological interventions mentioned a relative reduction of 36%–77% and we therefore considered the intervention clinically relevant if a relative

reduction of 60%, corresponding to an absolute reduction of 18%, was achieved.(25, 26) Assuming a loss to follow-up of 5%, we estimated that a target sample size of 189 patients would provide the trial with a power of 80%.

From July 2020 through September 2021: 189 patients were registered and randomly assigned to a trial group: 95 in the music group and 94 in the standard care group (Fig. 1). Randomization was done in a 1:1 ratio, by a secured online software program (ALEA; FormsVision BV, Abcoude, The Netherlands) and stratified per type of disease characteristic (i.e. ‘neuro-oncology’, ‘neurovascular’, ‘traumatic brain injury’, ‘infectious’) and age (i.e. ‘younger than 60 years’, ‘60 years or older’). Variable block sizes were used in which in each block both groups were represented equally.

Patients

Adult patients (i.e. age 18 years or more) undergoing craniotomy (i.e. opening the dura requiring bone flap removal) at the Erasmus MC with sufficient knowledge of the Dutch language were eligible for study participation. Exclusion criteria were: impaired awareness before surgery (i.e. motoric less than 6 in the Glasgow Coma Scale), planned post-operative intensive care unit (ICU) admission, suspected delirium (defined as fluctuating awareness) at baseline, antipsychotic treatment, undergoing surgery impeding supply of music (i.e. awake craniotomy or vestibular schwannoma surgery), bilateral hearing impairment and participation in other clinical trials interfering with results. During inclusion, one participant reported that music induced epileptic seizures (known as musicogenic epilepsy): this patient was excluded (and the exclusion criteria were adopted accordingly), as it was considered unethical to expose such a patient to music. Eligible patients were approached and written informed consent by patient or legal representative was obtained.

Intervention

All participating subjects were treated according to standard of care. Method of music intervention administration (i.e. type, frequency and duration) was applied based on previous studies.(17, 18) Participants in the intervention group (i.e. music group) received an over-ear headphone and a tablet with access to a platform with different pre-selected music playlists (i.e. jazz, blues, classic, electronic, pop, 60s, 70s, 80s etc), in which the music selection could be extended based on patients’

wishes. These patients received the first 30 minutes of music at the pre-operative holding area the day of operation (day 0) while awaiting surgery (see supplementary figure 1 for ‘Study Course MUSYC trial’) which was stopped before reaching the operation room. In the operating room, in-ear earphones after intubation, which were compatible with the Mayfield clamp and site of operation, were inserted and music was continued until just before detubation. After surgery, during recovery at the post-operative care unit (PACU), another 30 minutes of recorded music through over-ear headphones was administered. Finally, participants received 30 minutes of recorded music twice a day until post-operative day 3. Patients in the control group were asked to refrain from music listening, however this was not strictly controlled as this would influence the standard of clinical care too much. Nurses were instructed to monitor for music listening behaviour with a diary which was placed next to the music equipment. Periodically (approximately every six months) a training was given for all nurses on the ward to explain how music had to be administered and monitored.

6

Outcome measures

The primary outcome measure was presence or absence of postoperative delirium within the first five postoperative days. (27) The diagnosis of delirium required a two-step procedure; first, all participating patients were daily screened by the treating nurse using the Delirium Observation Screening scale (DOSS), a validated 13-item delirium screening tool with higher scores indicating a higher probability of delirium. Use of the DOSS was already current practice at our department and was administered by the nurse during each shift (three- 8-hour shifts per day).(28-31) Second, in case of a daily mean score of 3 or higher, which was radiologically not substantiated by a neurosurgical complication, a psychiatrist was consulted to assess the clinical diagnosis of delirium based on the DSM-5 criteria.(32) DSM-5 criteria assessment was conducted once in case of an increased mean DOS score of 3 or above. This was not standardized for a certain moment of the day, but depended on the timing of the increased mean DOSS score and the logistic of the consulting psychiatrist that specific day. We chose not to blind the assessors from the intervention, as this could not be secured which might have led to misleading results.

Secondary outcomes were assessed to substantiate the effects of music on delirium and its clinical implications. Pre-operative secondary outcomes (during the 30-minute pre-operative holding stay) included anxiety (measured with the Visual Analogue

Scale-anxiety/VAS-A) and heart rate variability (HRV), a marker of the autonomic tone reflecting parasympathetic nervous activity, measured with a 30 minutes electrocardiography (ECG) recording. The following HRV parameters were analysed: standard deviation of normal sinus beats (SDNN), root mean square of successive differences between normal heartbeats (RMSSD), the number of adjacent NN intervals that differ from each other by more than 50 ms (NN50) and the ratio of low frequency to high frequency power (HF/LF). Intra-operative secondary outcomes included depth of anaesthesia with Bispectral Index (BIS, AspectTM version 3.22) with standardized sedation dosages (propofol and remifentanyl). BIS was measured from the non-operated side, if feasible with site of resection, and the anaesthesiologist was blinded from the intra-operative BIS values, which was considered ethical as this form of monitoring is not standard of clinical care during intracranial procedures. Post-operative secondary outcomes (measured during the entire post-operative stay) were delirium severity (using the Delirium Rating Scale-revised-98/DRS-R-98) and delirium duration (onset until first day DOSS score <3), pain (Numeric Rating Scale/ NRS pain and dosages analgesic), post-operative complications, length of stay and location of discharge. Finally, patients' satisfaction of receiving music was assessed with a 100- point visual analogue scale (administered at the outpatient clinic 6 weeks after discharge).

Baseline characteristics were extracted at baseline from questionnaires or the electronic patient file consisting of age, gender, medical history, daily function (Karnofsky Performance Scale/KPS or Modified Rankin scale/MRS), quality of life (100-likert scale, EQ-5D and EORTC QLQ – BN-20), cognitive function (Montreal Cognitive assessment / MoCA), disease characteristics (i.e. neurologic deficit, type and side of intracranial pathology) and operation details (i.e. emergency grade, duration of surgery).

Statistical analysis

The main analysis was the comparison of the proportion of patients with delirium between the two arms in the Intention-to-Treat population (ITT; all registered and randomized patients) using univariate logistic regression. As sensitivity analyses the proportion of patients with delirium was also compared between the two arms in the modified ITT (m-ITT, i.e. ITT but excluding patients who were found to be ineligible after randomization) and Safety Population (i.e. all patients who underwent

craniotomy). A multivariable logistic regression analysis with the stratification factors in the ITT population was also performed as sensitivity analysis, while multivariable analyses in the m-ITT and safety population should be considered as descriptive and therefore as hypothesis-generating only. All secondary outcomes were analyses in the mITT population, and should only be considered as descriptive only.

A 2-hour recording of BIS (blinded from the anaesthesiologist between operation minute 60 to 180) was split into samples of 15 minutes as time points. A 30-minute recording of HRV was split into samples of 5 minutes as time points. Subsequently, we ran a linear mixed model with unstructured covariance for BIS and HRV, as a within subject variability was suspected, with time point and interaction group/time point as independent variables, as presented with fixed effects (β_0/β_1) and confidence intervals (95%CI). Moreover, a sensitivity analyses was conducted with possible additional confounding for depth of anaesthesia (BIS level) including age, comorbidity, type of disease, American Society of Anesthesiologists (ASA) classification and steroid use. The residual plots were visually observed and a log transformation was applied in case of heteroscedasticity.

A two-sided p value of 0.05 or less was considered statistically significant. All statistical analysis were conducted using R (version 4.1.1).

Results

A total of 309 patients were expected to be eligible after screening, of which 189 patients were registered and randomly assigned to the music (n=95) or control group (n=94). Five patients (4 in the music group and 1 in the control group) were excluded after registration due to withdrawing consent (n = 1), pre-operative use of antipsychotic treatment (n=1), or no craniotomy (n = 3, one operation cancelled, one burr-hole-biopsy and one no necessity of opening the dura). The remaining 184 patients, constituting the modified intention-to-treat population, were followed up for all the secondary outcomes.

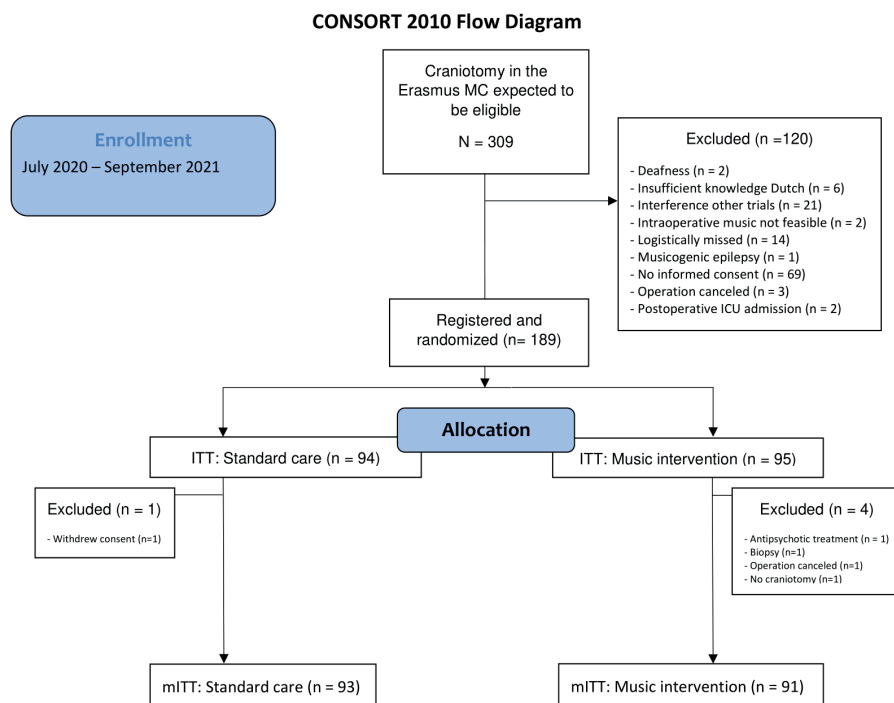


Figure 1. CONSORT Trial flowchart.

The baseline characteristics were similar in the two trial groups (ITT population), with a median age of 60 years and 44% being female (table 1). Psychiatric medical history was reported in 11%, including depression (n = 10) in most cases, pre-operative usage of possible delirium eliciting medication (i.e. antidepressants and sleep medication) in 15% and no dementia in our cohort. Baseline cognition (MoCA) was 24/20-27 (median/IQR), quality of life (QoL) was 70/55-80 (median/IQR) and no neurologic symptoms (in case of a KPS = 100 or MRS = 0) at admission were present in 23%. This cohort included mostly neuro-oncological patients (n = 161, 85%), with neurological deficit present in 38% and frontal localisation in 34%. Affection for music was reported with an importance of 8/7-8 (median/IQR), only 5% reported never to listen music in daily life. Surgical details showed duration of surgery of 220 minutes and emergency surgery (i.e. within 72 hours) in only 3%.

Table 1. Baseline characteristics

	Control (n=94)	Music (n = 95)
Pre-hospital demographics		
Age (years) *	61 (51-69)	60 (49-69)
Sex (% female)	46 (49%)	38 (40%)
Medical history (n/%)		
Somatic history ¹	79 (84%)	74 (78%)
Psychiatric history	14 (15%)	6 (6%)
Delirium prior admission	2 (2%)	5 (3%)
Dementia	0 (0%)	0 (0%)
Body mass index (kg/m ²)	26 (24-30)	26 (23-28)
Medication (n/%) ²	15 (26%)	14 (15%)
Intoxication ³		
Abuse of alcohol (n/%)	6 (6%)	1 (1%)
Abuse of drugs (n/%)	3 (3%)	3 (3%)
In-hospital demographics		
Pre-hospital functional status ⁴	80 (70-90)	80 (70-90)
KPS (100-0)	70 (18-80)	70 (45-80)
MRS (5-1)	1.0 (0.25-2.0)	1.0 (1.0-2.0)
Quality of Life (1- 100)	70 (60-79)	70 (55-80)
Cognitive function (0 - 30) ⁵	24 (19-27)	25 (21-27)
Electrolyte disturbance (n/%) ⁶	10 (11%)	9 (10%)
Disease characteristics		
Neurologic deficit (n/%)	35 (37%)	36 (38%)
Type		
Oncologic	81 (86%)	80 (84%)
Vascular	12 (13%)	14 (15%)
Other	1 (1%)	1 (1%)
Frontal disease localization (n/%)	40 (43%)	24 (25%)
Music affection		
Music importance	7.0 (6.8-8.0)	8.0 (7.0-8.0)
Frequency listening		
The whole day	29 (31%)	21 (22%)
Some hours per day	44 (47%)	54 (57%)
Some hours per week	9 (10%)	12 (13%)
Never	6 (6%)	3 (3%)
Played an instrument	20 (21%)	20 (21%)
Operation details⁷		
Operation duration (minutes)	220 (160-320)	210 (140-290)
Emergency operation (n/%) ⁸	2 (2%)	4 (4%)
Supine position (n/%)	81 (86%)	80 (84%)
Tramrail sign tension (n/%)	68 (72%)	67 (7%)

*All continuous data are presented in median/IQR. 1. Somatic history: including systematic disease (DM, hypertension) currently treated by medication and prior surgery (requiring general anesthesia on the operation room). 2. Medication known to induce delirium before admission, such as sleep medication, morphine, atropine and antidepressants 3. Reported abusive use of alcohol and/or drugs. 4. Patients' functional performance with the Karnofsky Performance Scale (ranging from 100/'No complaints' to 0/'Death') and Modified Ranking Scale (ranging from 0/'No symptoms' to 5/'Death'). 5. Cognitive function assessed with the Montreal Cognitive Assessment / MoCA 6. Electrolyte disturbance (mEq/L) in case of sodium >145 or <135 or potassium <3.5 or >5. 7. Patients in the MITT population (n=184) only. 8. Operation indication within 72 hours.

Primary outcome

In the music group, adherence to the music intervention before, during, and directly after surgery was 96%, 100%, and 74%, respectively (supplementary table 1). The following days the adherence decreased each day, from 70% on the first morning to 47% at noon on day 3. The total listening time was a median of 130 minutes (IQR, 73-230) during the five days of admission or until discharge.

A high DOSS score (i.e. 3 or higher) was observed in 32 patients. This was caused by a neurosurgical complication, as confirmed on radiology, in three patients; two patients with infarction after a vascular procedure with hemiparesis and decreased attention. The other patient had a subdural hematoma which was evacuated in the operation room. This resulted in 29 patients with possible delirium by DOSS; 21 were evaluated by the psychiatrist who diagnosed delirium in 11 patients (57%) based on the DSM-5 criteria.

According to the DOSS, a significantly higher incidence of delirium was observed in the control (n=21) vs. music (n=11) group in the ITT population for the univariable (22.3 vs. 11.6%, $p=0.048$) and multivariable (OR/95%CI: 0.49/0.20-1.00, $p=0.050$) analysis. This was not observed in the mITT ($p=0.064$) and the SP ($p=0.064$) population. The occurrence of a DSM-5 confirmed delirium, was not statistically significant between the control (n=7) vs. music (n=4) group in the ITT (7.4 vs 4.2%, OR = 0.55), the mITT (7.5 vs. 4.4%, OR = 0.57), and the SP (7.4 vs. 4.3%, OR = 0.58) population (table 2).

Of those patients with DSM-5-confirmed delirium (n = 11); severity of delirium (mean/SD) was 12.60/5.52, which was not different between the two arms ($p=0.857$). The duration of delirium (days, mean/SD) was 3.36/4.69, which was not different between the two arms ($p=0.761$).

Secondary outcome

Available ECG data (n=87) revealed that heart rate remained constant in the music group while it decreased after 15 ($\beta_1 = 2.89$, $p=0.043$), 25 ($\beta_1 = 3.36$, $p=0.05$) and 30 ($\beta_1 = 5.06$, $p=0.011$) minutes in the control group (table 3 and figure 2). A significant increase on HRV was found by music at 5 minutes on RMSSD ($\beta_1 = 55.08$, $p=0.012$). No significant effect was found on the other HRV parameters. Available depth of anaesthesia (n=70) data revealed no significant difference between the music and control group at the several analysed time points (figure 3). A trend towards less anxiety in the music group was observed ($p=0.058$, figure 4). All other secondary outcomes were not different between groups.

Table 2. Primary outcome

	Control (n/%)	Music (n/%)	Univariable analysis (OR/95%CI)*	P value ¹	Multivariable analysis (OR/95%CI)*	P value ²
Intention-to-treat analysis (ITT)						
Increased DOSS	21/22.3%	11/11.6%	0.46/0.19;1.00	0.048	0.49/0.20;1.00	0.050
Confirmed by DSM-5	7/7.4%	4/4.2%	0.55/0.14;1.96	0.342	0.57/0.16;2.07	0.39
Modified Intention-to-treat analysis (mITT)						
Increased DOSS	21/22.6%	11/12.1%	0.47/0.21;1.04	0.060	0.47/0.16;2.07	0.064
Confirmed by DSM-5	7/7.5%	4/4.4%	0.57/0.14;2.03	0.370	0.58/0.16;2.10	0.412
Safety Population (SP)						
Increased DOSS	21/22.3%	11/12.0%	0.47/0.21;1.04	0.061	0.47/0.21;1.04	0.064
Confirmed by DSM-5	7/7.4%	4/4.3%	0.58/0.14;2.03	0.370	0.58/0.16;2.11	0.414

*Odds Ratio/95%Confidence interval (OR/95%CI). 1. P values assessed with the Chi-squared test 2. Logistic regression analysis with groups, type disease and gender as independent variables.

Table 3. Secondary outcomes

	Control (n = 93)		Music (n = 91)	P value
Univariable analyses				
Anxiety difference (mean/SD) ¹	0.05/0.94		-0.25/1.49	0.058
Pain (mean/SD) ²	3.56/1.91		3.16/1.74	0.246
Naproxen mg (mean/SD)	13.6/75.4		2.75/26.2	0.103
Oxycodon mg (mean/SD)	2.03/4.35		1.61/3.31	0.828
No complications (n/%)	25 (26.9%)		21 (23.1%)	0.551
Length of stay, days (mean/SD)	7.43 (8.08)		6.74 (8.26)	0.947
Discharge home (n/%)	77 (82.8%)		76 (83.5%)	0.896
Multivariable analyses				
Heart Rate Variability/HRV (β_1 /95%CI) ⁴				
Time point ³	SDNN	RMSSD	NN50	LF/HF
5 minutes	38.84/ -2.23;79.91	55.08/13.16;97.00*	17.64/ -3.92;39.21	-0.46/-1.04;0.11
10 minutes	18.87/ -18.23;55.97	18.79/ -16.16;53.75	11.11/ -8.67;30.88	0.49/ -0.18;1.17
15 minutes	2.49/ -35.41;40.38	-3.20/ -38.60;32.19	9.14/ -11.11;29.38	0.34/ -0.28;0.96
20 minutes	-11.65/ -52.87;29.58	3.12/ -40.54;46.78	8.22/ -12.00;28.45	0.56/ -0.07;1.19
25 minutes	-15.62/ -57.24;26.00	-11.85/ -58.03;34.33	-3.56/ -27.10;19.98	0.45/ -0.26;1.16
30 minutes	7.41/ -38.04;52.87	22.20/ -17.01;61.41	-5.98/ -28.49;16.53	0.46/ -0.18;1.09
Time point ³	Depth of anesthesia/BIS (β_1 /95%CI) ⁵			P value
15 minutes	0.71/ -3.17;4.58			0.717
30 minutes	-1.44/ -3.34;0.46			0.139
45 minutes	-1.06/ -3.42;1.30			0.378
60 minutes	-2.23/ -5.34;0.89			0.162
75 minutes	-1.82/ -5.48;1.83			0.328
90 minutes	-2.46/ -6.72;1.79			0.256
105 minutes	-0.50/ -6.17;5.16			0.862
120 minutes	0.31/ -5.44;6.05			0.917

Secondary outcomes analyzed on the mITT population. 1. Anxiety differences between first and second measures with VAS-A. 2. Pain (NRS) over the first three post-operative days. 3. Time-points samples included in the linear mixed model. 4. HRV analyses; 30 minute of pre-operative ECG recordings split into 5-minute samples, all values marked with * are significant (i.e. $p < 0.05$). 5. BIS analyses: 120 minute of intra-operative BIS registration split into 15-minute samples.

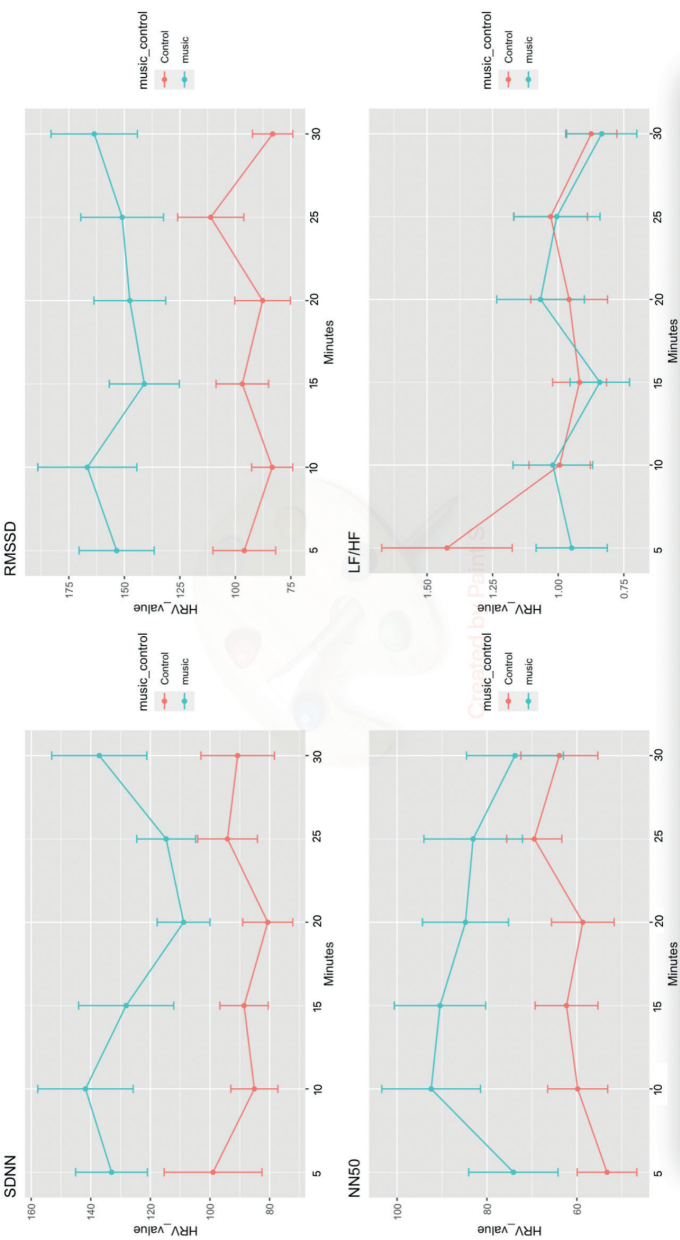


Figure 2. Pre-operative course of HRV.

Preoperative course of HRV. A 30-minute recording of HRV was split into samples of 5 min as time points and compared between groups. Heart rate remained constant in the music group while it decreased after 15 ($\beta_1=2.89, p=0.043$), 25 ($\beta_1=3.36, p=0.05$) and 30 ($\beta_1=5.06, p=0.011$) min in the control group. A significant increase on HRV was found by music at 5 min on RMSSD ($\beta_1=55.08, p=0.012$). No significant effect was found on the other HRV parameters. HRV, heart rate variability; LF/HF, ratio of low frequency to high frequency power; NN50, number of adjacent NN intervals that differ from each other by more than 50 ms; RMSSD, root mean square of successive differences between normal heartbeats; SDNN, SD of normal sinus beats.

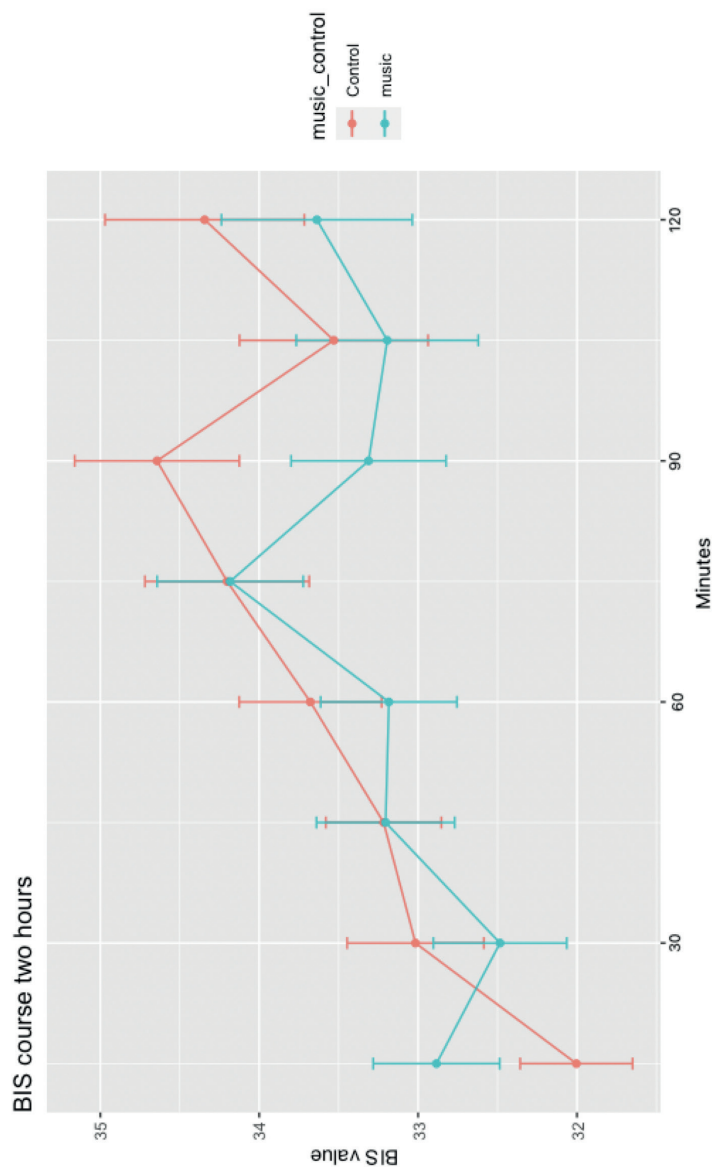


Figure 3. Intra-operative depth of anaesthesia.
Intraoperative depth of anaesthesia. A 2-hour recording of BIS was split into samples of 15 min as time points and compared between groups. Available depth of anaesthesia (n=70) data revealed no significant difference between the music and control group at the several analysed time points. BIS, Bispectral Index.

Pre-operative course anxiety

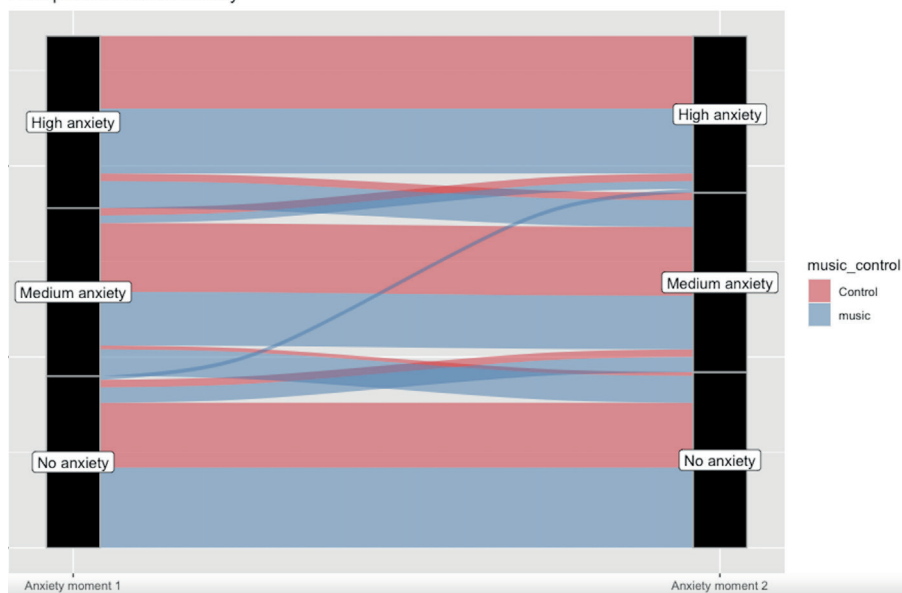


Figure 4. Anxiety Two anxiety measurements (VAS-A) were conducted before surgery and categorized in 'No anxiety' (0 – 2), 'Medium anxiety' (3-6) and 'High anxiety' (7 – 10). Most patients remained in their anxiety level, although some patients showed a decrease pre-operative anxiety when receiving music, but this difference was non-significant between groups ($p=0.058$).

Patient satisfaction (median/IQR) in the music group who filled in the questionnaire ($n = 68$), was 85/80-95, and 88% reported they would want to receive music in case of future surgery.

Discussion

We found a significant decrease on the incidence of post-operative delirium by the addition of music perioperatively using the DOSS, however this was not significant when assessed by the DSM-5 criteria. Second, music activated pre-operative heart rate variability, a marker of autonomic tone. Last, no significant effect on anxiety, depth of anesthesia, post-operative complications, length of stay and location of discharge were found. Clinical implications and limitations are discussed below.

We found a significant decrease on the incidence of post-operative delirium, defined with DOSS, by the addition of perioperative music. A recent published systematic

review conducted a meta-analysis on the preventive effect of music on delirium with six studies and found a relative reduction similar to ours (0.52 vs 0.48)(22) This meta-analysis included pilot studies which administered patient preferred music similar to our design, but varied from ours as the population considered surgical and non-surgical ICU patients and delirium was defined with the NEECHAM, CAM-ICU or own definitions. Our sample size calculation was based on other neurosurgical studies evaluating delirium in case of increased scores on delirium screening tools. (1) When handling screening tools for delirium definition by using the DOSS, we support the efficacy of music in lowering the incidence of post-operative delirium. However, although a similar trend was found, significance of results was not achieved when assessed by the DSM-5 criteria. The discrepancy between DOSS and DSM-5 may have several explanations. First, DSM-5 was evaluated by a psychiatrist *after* an increased DOSS score. Hence, delirium may have been resolved over time before the psychiatrist its assessment. Moreover, DOSS evaluation was conducted three times per day by the nurses, as opposed to DSM-5 determination which was only evaluated once. DSM-5 assessment during day-time might have missed some cases as delirium fluctuates over the course of the day, especially for the delirium-type present during night-time. Also, not all our patients with increased DOSS were evaluated by a psychiatrist due to logistics and we might have missed some patients with delirium. Second, delirium screening tools have not been validated within the neurosurgical population. (5-8, 33-37) Hence, while high diagnostic accuracies in the general population justify diagnostic usage of delirium screening tools, it is unclear whether this can be adopted to our complicated patient population, as a positive screen for delirium may be due to the underlying neurological disease or its sequelae (e.g., oedema, vasospasm, seizures, rebleeding, ischemia) leading to false-positive results.

We propose a vagal-mediated anti-inflammatory response as a candidate pathway of music on delirium, as hypotheses of delirium rely on neuro-inflammatory reactions within the brain. (2) Although we did not assess inflammatory cytokines in our study, vagal nerve activation by music was supported by the increased HRV, revealed by an increased RMSSD on ECG during the pre-operative music session. The activation of HRV by music in brain-damaged patients was proven earlier and is considered a valid marker of parasympathetic nervous activation. (38, 39) Whether HRV could be used as a marker for postoperative recovery, remains to be determined. Moreover, we observed a decreasing trend in pre-operative anxiety by music, although this did

not reach significance. This pre-operative parasympathetic activation and anxiety reduction may have induced a sedative-sparing effect, subsequently increasing cortical engagement and cognitive processing.(40) We did not find a deeper level of anesthesia in the music group. Literature is contradictory on the correlation of depth of sedation and anesthetic requirements as music listening is associated with decrease of depth of anesthesia, but no decrease of sevoflurane was achieved when pursuing constant depth of anesthesia. Future neurosurgical studies should confirm whether concentration of sedation can be reduced with music in case of standardized depth of anesthesia (BIS) levels.

We found high adherence to the music intervention before surgery. High importance of music in daily life, the number of hours listening to music in daily life and the willingness to receive music intervention in case of future surgeries was found in our cohort, which are considered important facilitators for music implementation. (41) However the adherence declined after surgery, due to pain, nausea, logistics (i.e. for MRI) or unwillingness. Absence of a near future operation prospect may have reduced the urgent necessity of music, resulting in the post-operative decline in adherence. Lack of the knowledge of the intervention is considered a barrier for implementation. Informing patients, substantiated by the results from efficacy studies such as this trial, may aid in the implementation of music in the neurosurgical population.

Although delirium is (most often) temporary and self-limiting, delirium independently predicts clinically relevant outcomes in neurologically damaged patients. (9) (10) Although a trend was observed, we did not find any significant positive effects on complications, length of admission or location of discharge. Future studies should assess the long-term implications of delirium defined with either DOSS and DSM-criteria after discharge in neurosurgical patients.

Strengths and limitations

This is the first randomized controlled trial assessing the effect of music on delirium after craniotomy and the largest assessing the effect of music against delirium. We showed that music reduced the incidence of delirium when defined with the DOSS but not after DSM-5 confirmation. Our study was subject to several limitations: first, not all our patients with increased DOSS were evaluated by a psychiatrist due to logistics and we might have missed some patients with delirium. However, we feel

that this did not affect our conclusions, because, with our low confirmation rate of suspected delirium, the study would still have been underpowered. Second, due to the nature of the intervention we did not blind the study, which could have influenced the outcome assessors. However, blinding could not be secured which might have led to misleading results. Third, the generalizability of the results may be affected by the single-centre design of the study.

Conclusion

Our results support the efficacy of music in reducing the incidence of delirium after craniotomy, as found with DOSS but not after DSM-5 confirmation. Delirium screening tools should be validated within the neurosurgical context and the long-term implications of a delirium, either defined by an increased DOSS or DSM-5, should be evaluated. This effect of music is substantiated by the effect of music on an increased pre-operative HRV. Last, although pre-operative adherence was high, this declined after surgery which should be taken into account, when considering implementation in the neurosurgical population.

References

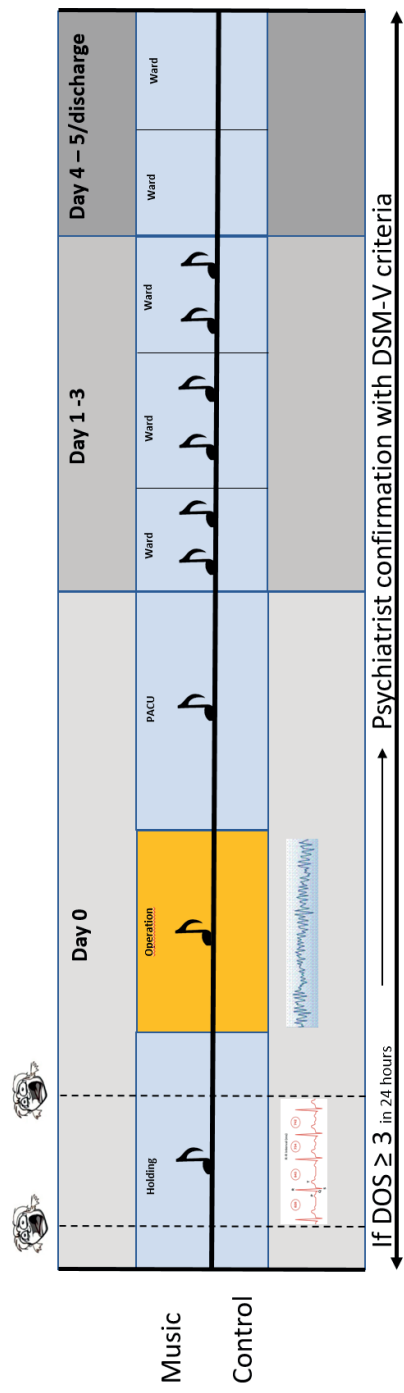
1. Kappen PR, Kakar E, Dirven CMF, van der Jagt M, Klimek M, Osse RJ, et al. Delirium in neurosurgery: a systematic review and meta-analysis. *Neurosurg Rev.* 2021;45(1):329-341.
2. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry.* 2013;21(12):1190-222.
3. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in Older Persons: Advances in Diagnosis and Treatment. *JAMA.* 2017;318(12):1161-74.
4. Flanagan PM, Jahangiri A, Weinstein D, Dayani F, Chandra A, Kanungo I, et al. Postoperative Delirium in Glioblastoma Patients: Risk Factors and Prognostic Implications. *Neurosurgery.* 2018;83(6):1161-72.
5. He Z, Cheng H, Wu H, Sun G, Yuan J. Risk factors for postoperative delirium in patients undergoing microvascular decompression. *PLoS One.* 2019;14(4):e0215374.
6. Wang CM, Huang HW, Wang YM, He X, Sun XM, Zhou YM, et al. Incidence and risk factors of postoperative delirium in patients admitted to the ICU after elective intracranial surgery: A prospective cohort study. *Eur J Anaesthesiol.* 2020;37(1):14-24.
7. Zipser Z, Deuel J, Ernst J, Schubert M, von Kanel R, Bottger S. The predisposing and precipitating risk factors for delirium in neurosurgery: a prospective cohort study of 949 patients. *Acta Neurochir (Wien).* 2019;161(7):1307-15.
8. Kappen PR, Kappen HJ, Dirven CMF, Klimek M, Jeekel J, Andrinopoulou ER, et al. Postoperative Delirium After Intracranial Surgery: A Retrospective Cohort Study. *World Neurosurgery.* 2023;(22)01838-1.
9. Budėnas A, Tamašauskas Š, Šliaužys A, Navickaitė I, Sidaraitė M, Pranckevičienė A, et al. Incidence and clinical significance of postoperative delirium after brain tumor surgery. *Acta Neurochir.* 2018;160(12):2327-37.
10. Chen H, Jiang H, Chen B, Fan L, Shi W, Jin Y, et al. The Incidence and Predictors of Postoperative Delirium After Brain Tumor Resection in Adults: A Cross-Sectional Survey. *World Neurosurg.* 2020;140:e129-e39.
11. Liu Y, Li XJ, Liang Y, Kang Y. Pharmacological Prevention of Postoperative Delirium: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Evid Based Complement Alternat Med.* 2019;2019:9607129.
12. Vlisides P, Avidan M. Recent Advances in Preventing and Managing Postoperative Delirium. *F1000Res.* 2019;8.
13. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014;383(9920):911-22.
14. Cerejeira J, Batista P, Nogueira V, Vaz-Serra A, Mukaetova-Ladinska EB. The stress response to surgery and postoperative delirium: evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased suppression of the GH/IGF-1 Axis. *J Geriatr Psychiatry Neurol.* 2013;26(3):185-94.
15. Clegg A YJ. Which medications to avoid in people at risk of delirium: a systematic review. 2011(40:23–29).
16. Fu VX, Oomens P, Sneyders D, van den Berg SAA, Feelders RA, Wijnhoven BPL, et al. The Effect of Perioperative Music on the Stress Response to Surgery: A Meta-analysis. *J Surg Res.* 2019;244:444-55.

17. Fu VX OP, Klimek M, Verhofstad MHJ, Jeekel J. The effect of perioperative music on medication requirement and hospital length of stay: a meta-analysis. *Annals of Surgery*. July 2019;272(6):961 - 72.
18. Kuhlmann AYR, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. Meta-analysis evaluating music interventions for anxiety and pain in surgery. *Br J Surg*. 2018;105(7):773-83.
19. Lee JH. The Effects of Music on Pain: A Meta-Analysis. *J Music Ther*. 2016;53(4):430-77.
20. Leung JM SL, Paul S. Does postoperative delirium limit the use of patient-controlled analgesia in older surgical patients? 111:625–631. 2009.
21. Hole J, Hirsch M, Ball E, Meads C. Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. *Lancet*. 2015;386(10004):1659-71.
22. Golubovic J, Neerland BE, Aune D, Baker FA. Music Interventions and Delirium in Adults: A Systematic Literature Review and Meta-Analysis. *Brain Sci*. 2022;12(5).
23. Kappen P, Jeekel J, Dirven CMF, Klimek M, Kushner S, Osse RJ, et al. Music to prevent deliriUm during neuroSurgerY (MUSYC) Clinical trial: a study protocol for a randomised controlled trial. *BMJ Open*. 2021;11(10):e048270.
24. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krljeza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-7.
25. Janssen TL, Alberts AR, Hooft L, Mattace-Raso F, Mosk CA, van der Laan L. Prevention of postoperative delirium in elderly patients planned for elective surgery: systematic review and meta-analysis. *Clin Interv Aging*. 2019;14:1095-117.
26. Abraha I, Trotta F, Rimland JM, Cruz-Jentoft A, Lozano-Montoya I, Soiza RL, et al. Efficacy of Non-Pharmacological Interventions to Prevent and Treat Delirium in Older Patients: A Systematic Overview. The SENATOR project ONTOP Series. *PLoS One*. 2015;10(6):e0123090.
27. Lee H, Ju JW, Oh SY, Kim J, Jung CW, Ryu HG. Impact of timing and duration of postoperative delirium: a retrospective observational study. *Surgery*. 2018;164(1):137 - 43.
28. Association AP. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. May 2013.
29. Gavinski K, Carnahan R, Weckmann M. Validation of the delirium observation screening scale in a hospitalized older population. *J Hosp Med*. 2016;11(7):494-7.
30. Detroyer E, Clement PM, Baeten N, Pennemans M, Decruyenaere M, Vandenbergh J, et al. Detection of delirium in palliative care unit patients: a prospective descriptive study of the Delirium Observation Screening Scale administered by bedside nurses. *Palliat Med*. 2014;28(1):79-86.
31. van Velthuisen EL, Zwakhalen SM, Warnier RM, Mulder WJ, Verhey FR, Kempen GI. Psychometric properties and feasibility of instruments for the detection of delirium in older hospitalized patients: a systematic review. *Int J Geriatr Psychiatry*. 2016;31(9):974-89.
32. American Psychiatric A. American Psychiatric Association DSM-5 Task Force (2013): Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, DC: American Psychiatric Association.

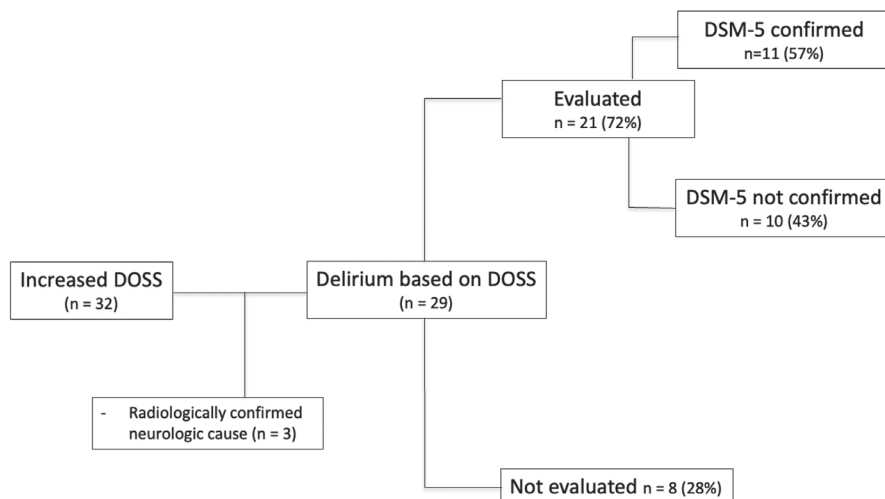
33. Chen L, Xu M, Li GY, Cai WX, Zhou JX. Incidence, Risk Factors and Consequences of Emergence Agitation in Adult Patients after Elective Craniotomy for Brain Tumor: A Prospective Cohort Study. *PLoS One*. 2014;9(12):e114239.
34. Flanigan PM, Jahangiri A, Kuang R, Truong A, Choi S, Chou A, et al. Developing an Algorithm for Optimizing Care of Elderly Patients With Glioblastoma. *Neurosurgery*. 2018;82(1):64-75.
35. Herrero S, Carrero E, Valero R, Rios J, Fabregas N. Postoperative surveillance in neurosurgical patients - usefulness of neurological assessment scores and bispectral index. *Rev Bras Anesthesiol*. 2017;67(2):153-65.
36. Matano F, Mizunari T, Yamada K, Kobayashi S, Murai Y, Morita A. Environmental and Clinical Risk Factors for Delirium in a Neurosurgical Center: A Prospective Study. *World Neurosurg*. 2017;103:424-30.
37. Wang J, Ji Y, Wang N, Chen W, Bao Y, Qin Q, et al. Establishment and validation of a delirium prediction model for neurosurgery patients in intensive care. *Int J Nurs Pract*. 2020:e12818.
38. Florez-Perdomo WA, Garcia-Ballestas E, Moscote-Salazar LR, Konar SK, Raj S, Chouksey P, et al. Heart Rate Variability as a Predictor of Mortality in Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *World Neurosurg*. 2021;148:80-9.
39. Mojtavavi H, Saghaizadeh A, Valenti VE, Rezaei N. Can music influence cardiac autonomic system? A systematic review and narrative synthesis to evaluate its impact on heart rate variability. *Complement Ther Clin Pract*. 2020;39:101162.
40. Khan SH, Wang S, Harrawood A, Martinez S, Heiderscheidt A, Chlan L, et al. Decreasing Delirium through Music (DDM) in critically ill, mechanically ventilated patients in the intensive care unit: study protocol for a pilot randomized controlled trial. *Trials*. 2017;18(1):574.
41. Kakar E, Ista E, Klimek M, Jeekel J. Implementation of music in the perioperative standard care of colorectal surgery: study protocol of the IMPROVE Study. *BMJ Open*. 2021;11(10):e051878.

Supplementary figure and tables

Supplementary figure 1. Study course MUSYC trial



Course trial: after randomization, both groups receive ECG recording and two times anxiety measures. Intra-operative BIS registration is applied for depth of anesthesia. All participating subjects are treated according to standard care and delirium is measured until day 5 or discharge. Participants in the intervention group additionally receive music intervention 30 minutes before surgery, intra-operative during the entire operation, 30 minutes after surgery and twice per day 30minutes until post-operative day 3.

Supplementary figure 2. Course delirium diagnosis

Delirium diagnosis flowchart, diagnosis of delirium required a two-step procedure. First, all participants were screened with the DOS scale. Second, in case of a daily mean score of 3 or higher (and no neurologic cause was radiologically found) a psychiatrist was consulted to assess the clinical diagnosis of delirium based on the DSM-5 criteria. In 8 patients, the psychiatrist was not consulted due to logistic issues.

Supplementary table 1. Adherence to music intervention during trial

Moment¹	Day 0			Day 1		Day 2		Day 3	
	Pre	Per	Post	Morning	Noon	Morning	Noon	Morning	Noon
N²	91	91	91	91	91	88	88	70	70
Music									
No	3	0	21	25	26	26	21	19	20
Yes	79	91	61	59	45	44	39	24	18
Unknown³	9	0	9	7	20	18	28	27	32
Adherence⁴	96%	100%	74%	70%	63%	63%	65%	56%	47%

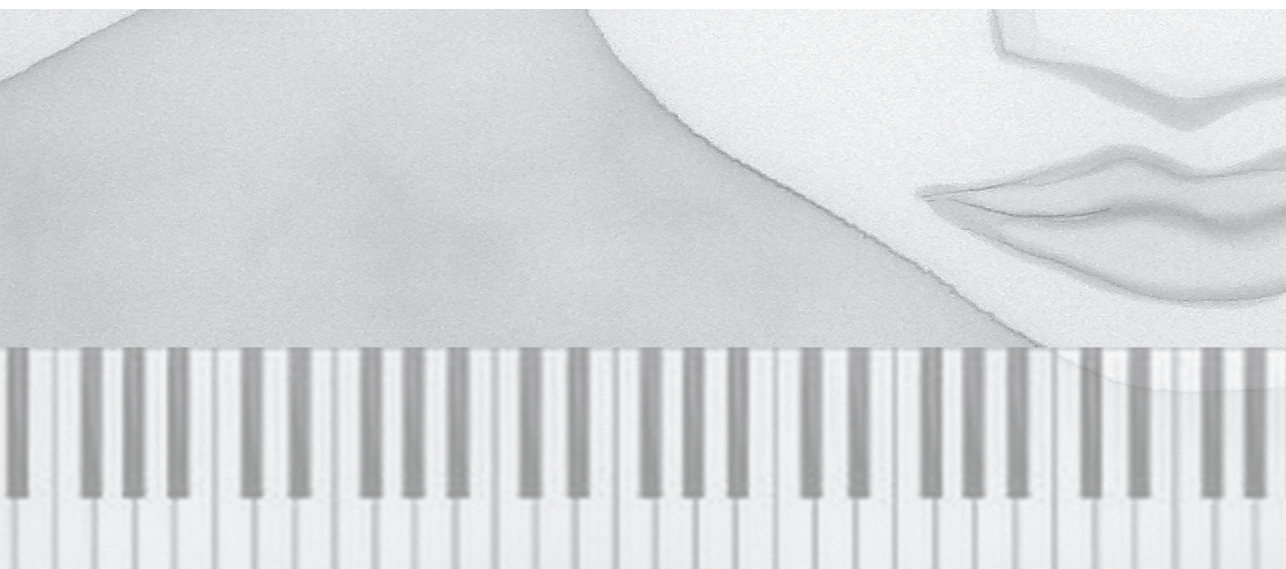
Patients in the mITT population allocated to the music group. 1. Session of 30 minutes in the morning or afternoon. 2. Amount of patients in the musical group not discharged from the ward. 3. Unregistered music session. 4. Adherence calculated from the registered patients (i.e. 'Yes'/'No' + 'Yes')



PART II

Musicality and language
in awake brain surgery



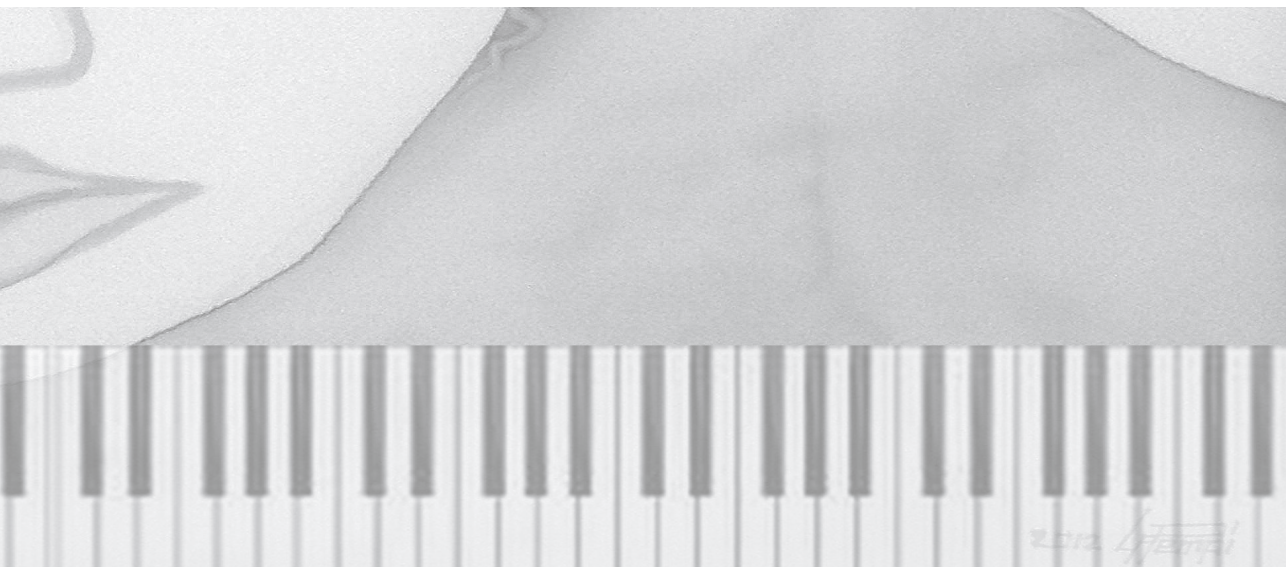


CHAPTER 7

The effect of musicality on language recovery after awake glioma surgery

P.R. Kappen, J. van den Brink, J. Jeekel, C.M.F. Dirven, M. Klimek,
M. Donders-Kamphuis, C.S. Docter-Kerkhof, S.A. Mooijman, E. Collee,
R.D.S. Nandoe Tewarie, M.L.D. Broekman, M. Smits, A.J.P.E. Vincent, D. Satoer

Frontiers in Human Neuroscience, 2022



Abstract

Awake craniotomy is increasingly used to resect intrinsic brain tumors while preserving language. The level of musical training might affect the speed and extend of postoperative language recovery, as increased white matter connectivity in the corpus callosum is described in musicians compared to non-musicians. In this cohort study, we included adult patients undergoing treatment for glioma with an awake resection procedure at two neurosurgical centers and assessed language preoperatively (T1) and postoperatively at three months (T2) and one year (T3) with the Diagnostic Instrument for Mild Aphasia (DIMA), transferred to *z*-scores. Moreover, patients' musicality was divided into three groups based on the Musical Expertise Criterion (MEC) and automated volumetric measures of the corpus callosum were conducted. We enrolled forty-six patients, between June 2015 and September 2021, and divided in: group A (non-musicians, *n*=19, 41.3%), group B (amateur musicians, *n*=17, 36.9%) and group C (trained musicians, *n*=10, 21.7%). No significant differences on postoperative language course between the three musicality groups were observed in the main analyses. However, a trend towards less deterioration of language (mean/SD *z*-scores) was observed within the first three months on the phonological domain (A:-0.425/0.951 vs. B:-0.00100/1.14 vs. C:0.0289/0.566, *p*-value=0.19) with a significant effect between non-musicians vs. instrumentalists (A:-0.425/0.951 vs. B+C:0.201/0.699, *p*=0.04). Moreover, a non-significant trend towards a larger volume (mean/SD cm³) of the corpus callosum was observed between the three musicality groups (A:6.67/1.35 vs. B:7.09/1.07 vs. C:8.30/2.30, *p*=0.13), with the largest difference of size in the anterior corpus callosum in non-musicians compared to trained musicians (A:3.28/0.621 vs. C:4.90/1.41, *p*=0.02). With first study on this topic, we support that musicality contributes to language recovery after awake glioma surgery, possibly attributed to a higher white matter connectivity at the anterior part of the corpus callosum. Our conclusion should be handled with caution and interpreted as hypothesis generating only, as most of our results were not significant. Future studies with larger sample sizes are needed to confirm our hypothesis.

Introduction

Awake craniotomy is increasingly used to resect intrinsic brain tumors (specifically for diffuse low-grade gliomas) while preserving language. This technique has improved over time, with the development of intraoperative protocols for awake tumor resection. (1) Despite these improvements, intraoperative mapping and language testing do not always ensure complete maintenance of the patient's linguistic abilities. Due to slow tumor growth, diffuse low grade glioma patients typically suffer from mild aphasia preoperatively which often temporarily deteriorates after tumor resection. (2, 3) In the year after surgery, most patients recover to their baseline level whereas others remain to suffer from this further language decline in the long term. (3) This can be attributed to differences in neuroplasticity in language networks, but it is unclear which factors and to what degree these affect postoperative language recovery. (4)

The literature suggests that musical training might affect the course of postoperative language recovery. (5) Both language and music require complex hierarchical processing systems that share features, such as pitch, rhythm, timbre, and syntactic structure. (6) Recent fMRI data suggested that some brain regions, associated with language functioning (e.g., Broca and Wernicke's areas), are also activated during music processing. (7-9)

Higher degree of organization of language structures between lobes (i.e. frontal and temporal) or hemispheres through the corpus callosum have been described in musicians. (10, 11) This has provided ground for music-induced language therapy, such as Melodic Intonation Therapy (MIT), in patients with severe aphasia. (10-12)

Some experimental studies show that musical training can improve language function (in a so-called transfer of learning) in healthy participants.(6) However, there is currently no evidence in the literature to support the hypothesis that musical training-related brain changes might also have a beneficial effect on language following brain surgery. (12)

Hence, we conducted a study in which we hypothesize a better recovery of language in musical patients after awake glioma surgery as compared to non-musical patients. Moreover, we hypothesize that this possible beneficial effect may be explained by contralateral compensation through the corpus callosum.

Methods

Study population

The consecutively included cohort consisted of adult patients, who underwent an awake resection between June 2015 and September 2021 at the Erasmus MC, University Medical Center Rotterdam (EMC) or at the Haaglanden Medisch Centrum the Hague (HMC), and received an extensive language assessment before (baseline; T1) and at least one time point after surgery (3 months; T2 and/or one year; T3). These centers consider awake surgery in case of left-sided tumors, right-sided tumors with left handedness or involvement of the sensory-motor regions or in case of prior speech deficits with or without language location confirmed by functional fMRI. Moreover, an awake craniotomy procedure is only considered if we deem this feasible for the particular patient. Patients that were operated for a recurrent glioma, non-native Dutch speakers (defined as unfamiliar with the Dutch language before the age of eight years), patients known with neurodegenerative diseases affecting language (e.g. dementia) or with a WHO grade 4 astrocytoma or glioblastoma, were excluded. Patients were additionally excluded for the volumetric analysis in case of tumor involvement in the corpus callosum.

Study design and data extraction

Data on musicality were prospectively collected through a questionnaire and retrospectively complemented with available language and clinical data.

Musicality

The Musical Expertise Criteria (MEC) are based on years of musical training and intensity and define a musician based on the “six-year rule” of training (Appendix A). (13-16) A questionnaire was developed, based on the MEC, in which points were allocated to the patient, leading to final group formation; non-musicians (group A), amateur musicians (group B), and trained musicians (group C, appendix A). Additional information on musicality was assessed such as the onset age of playing the instrument/ vocals, type of instrument and whether music was played after the operation.

Linguistic data

Language data were retrospectively extracted as language was already monitored with the Diagnostic Instrument for Mild Aphasia (DIMA) as part of standard of clinical care

at baseline (T1) and at least one time point after surgery (3 months; T2 and/or one year; T3).(17) The DIMA is a tool, developed and validated in Dutch to evaluate suspected mild aphasia in patients with glioma.(18) It consists of six subtests and assesses language production and comprehension in the following linguistic domains: phonology, semantics and (morpho-) syntax. Moreover, data from a non-linguistic cognitive test for visual attention and mental flexibility (Trail Making Test/TMT A, B and BA) were extracted.(19)

Clinical data

Clinical data were extracted consisting of demographic data (age, sex, education years and level based on the Verhage scale, handedness), disease specifications (histopathology, localization), and treatment specifications (completeness resection, complications, adjuvant treatment).(20-22)

Volumetry

To measure the size of the corpus callosum we analyzed the most recent structural brain magnetic resonance imaging (MRI: 1.5 or 3.0 Tesla GE Healthcare) before the awake craniotomy, using <1.0mm slice with T1 weighted imaging parameters. Two researchers (P.K. / J.B.), blinded for the outcome on musicality at the time of measurement, first divided the corpus callosum in 7 subregions according to the Witelson classification.(23) Afterwards, volumes (in cubic centimeters/cm³) for each subregion were measured with Brainlab's Synthetic Tissue Model (Brainlab Digital OR, Germany, München). In this model each anatomical structure is first detected and then adapted to a gray-scale image model. Tissue-class specific gray value simulation is compared with meta information from datasets and afterwards quantitatively and qualitatively validated. This software is CE marked and already widely applied for guidance during neurosurgical procedures. Sub-group analyses were conducted for sex and onset/duration of musical training, as differences in corpus callosum volumes have been described in these factors.(10, 24) For the volume lesion analysis we used the pre-operative coronal, sagittal and transversal T2 weighted FLAIR MRI images and conducted volumetric analysis with Brainlabs' smart brush (Appendix B).

Statistical analysis

The raw DIMA and TMT scores (A, B, and BA) were transferred into *z*-scores corrected for age and years of education, in order to facilitate comparisons. For each

of the corpus callosum subregions, an inter-rater agreement was calculated with the interclass correlation coefficient (ICC). Corpus callosum region volumes were compared between groups based on the raw (cm³) and corrected measurements (corpus callosum volume divided by total brain volume).

The three musicality groups and language or corpus callosum volumes were visually evaluated and statistically compared with an ANOVA in case of parametric data and a Kruskal-Wallis test in case of non-parametric data. Normality was tested with the Shapiro-Wilk test. Correlations between musical training, size of corpus callosum and course of postoperative language were conducted with the Pearson's product-moment correlation. For all analyses significance (p-value, significant in case of 0.05 or less), and for correlation coefficient (r), degrees of freedom (df) were illustrated.

We were unable to conduct a priori sample size calculation, as we were unsure which effect size was expected as this is the first study evaluating the effects of musicality on language recovery after awake glioma surgery. Hence, achieved power was computed ($1-\beta$) on post-hoc analyses in case of visually observed non-significant outcomes using G*Power version 3.1.(25) All other statistical analyses were conducted using R (version 4.1.1).

Results

Musicality and demographic data

We consecutively included 46 patients, in the period between June 2015 and September 2021, at the EMC (n = 39) and HMC (n = 7). Patients were divided into three groups based on musicality: non-musician (A: n = 19, 41.3%), amateur musician (B: n = 17, 36.9%), and trained musicians (C: n = 10, 21.7%).

The mean (SD) age at the time of craniotomy was 39.6 (12.0) years; 18 women (39.1%) and 40 (87.0%) right-handed patients (Table 1). Higher education level was observed in 24 (52.2%) patients, with mean (SD) number of years of education of 14.8 (2.47). Gross total resection of the tumor was achieved in 20 (56.5%) patients. Intra-operative complications were reported in 4 (8.7%) patients; one patient had an arterial bleeding which was coagulated and three other patients had intra-operative seizures during mapping.

Adjuvant therapy within one year was administered in 16 (65.2%) patients. Histopathology revealed WHO grade 2 glioma in 39 (84.8%) patients and tumor

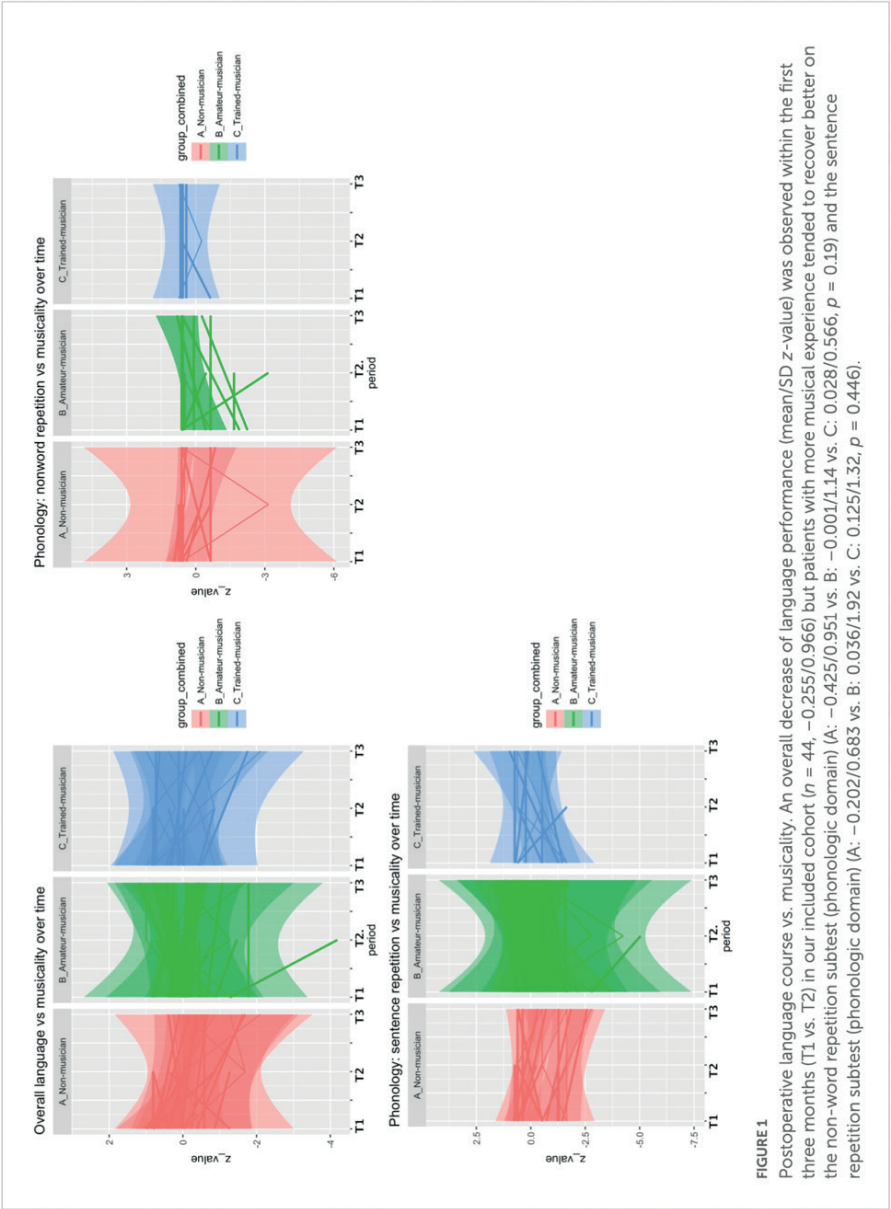
localization was right-sided in 20 (43.5%) patients. None of the baseline characteristics differed significantly among groups, except for right sided tumor localization, which was more common in group C ($p=0.02$).

TMT (mean/SD z -scores) were 0.289/1.13 - 1.00/1.62 (average to high average) and were similar between the three groups. In musical patients, the mean/SD age of starting to play an instrument was 13.1/8.44 years (group B) and 12.0/4.59 years (group C), with a mean/SD total of hours of playing music of 535/743 (group B) and 5020/3890 (group C).

Table 1. Baseline characteristics

	A. Non-musician N = 19	B. Amateur musician N = 17	C. Trained musician N = 10	P value
Demographic data				
Age (mean / SD) ¹	38.8 (11.7)	40.3 (14.3)	39.6 (9.31)	0.92
Female sex (n/%)	9 (47.4%)	6 (37.5%)	3 (27.3%)	0.61
Higher education (n/%) ²	6 (31.6%)	12 (70.6%)	6 (60.0%)	0.06
Education years (mean/SD)	14.1 (2.27)	15.1 (2.42)	15.5 (2.83)	0.17
Right handedness	16 (84.2%)	14 (82.4%)	10 (100%)	0.38
Disease and surgical specifics				
High grade tumor (n/%)	1 (5.3%)	5 (29.4%)	1 (10.0%)	0.12
Right sided localization (n/%)	5 (26.3%)	7 (41.2%)	8 (80.0%)	0.02
Lesion volume (mean/SD cm ³)	31.4 (19.2)	49.2 (31.7)	36.5 (28.0)	0.20
Gross total resection (n/%)	7 (36.8%)	8 (47.1%)	5 (50.0%)	0.74
Intra-operative complications (n/%)	1 (5.3%)	1 (5.9%)	2 (20.0%)	0.36
Adjuvant treatment (n/%) ³	5 (26.3%)	9 (52.9%)	2 (20.0%)	0.13
Cognitive function⁴				
TMT A (mean/SD)	0.889 (1.63)	1.24 (1.64)	0.810 (1.68)	0.63
TMT B (mean/SD)	0.611 (0.918)	0.318 (1.73)	0.660 (0.862)	0.97
TMT BA (mean/SD)	0.358 (1.21)	0.288 (1.19)	0.160 (0.937)	0.97
Musical specifications⁵				
Main instrument	-			
Singing		4 (23.5%)	2 (20%)	
Instrument	-	15 (88.2%)	10 (100%)	0.46
Start age main instrument (mean/SD)	-	13.1 (8.44)	12.0 (4.59)	0.78
Start instrument under 10 years (n/%)	-	10 (58.8%)	3 (30.0%)	0.15
Total hours of playing (mean/SD) ⁶	-	535 (743)	5020 (3890)	<0.001

1. Age at awake craniotomy. 2. Finished high level secondary education or university degree. 3. Received adjuvant therapy, including chemotherapy (i.e. temozolomide) or radiotherapy, until one year after surgery. 4. Trail making test; z values. 5. P values were calculated between the amateur and trained musicians. 6. Mean hours per day*years ($\times 365$) playing



Primary outcome: musicality vs. language

Our main analyses comparing musicality and postoperative course of language were not statistically significant (Figure 1, Table 2). An overall decrease of language performance (mean/SD z -value) was observed within the first three months (T1 vs T2) in our included cohort ($n = 44$, $-0.255/0.966$, Table 2), which was not different between the three groups (A: $-0.411/0.865$ vs. B: $-0.0947/1.18$ vs. C: $-0.227/0.779$, $p = 0.45$).

Within the first three months (T1 vs T2), patients with more musical experience tended to recover better in the phonologic domain on the non-word repetition subtest (A: $-0.425/0.951$ vs. B: $-0.001/1.14$ vs. C: $0.028/0.566$, $p = 0.19$, effect size: 0.233 , $1-\beta = 0.26$) and the sentence repetition subtest (A: $-0.202/0.683$ vs. B: $0.036/1.92$ vs. C: $0.125/1.32$, $p = 0.44$, effect size = 0.09 , $1-\beta = 0.08$), and recover less on the syntactic domain in the sentence completion subtest (A: $0.031/2.09$ vs. B: $-0.048/0.46$ vs. C: $-0.531/1.45$, $p = 0.86$, effect size = 0.127 , $1-\beta = 0.11$). However, these differences were not significant. In the period of three months to one year (T2 vs T3) a decrease of language performance (z -value mean/SD) was observed ($n = 27$, $-0.246/0.947$), which was not different between the groups (A: $-0.178/1.19$ vs. B: $-0.265/0.818$ vs. C: $-0.260/1.07$, $p = 0.90$), but a beneficial effect of non-musicality was found in the word repetition subtest (phonologic domain, A: $0/0$ vs. B: $0.393/2.30$ vs. C: $0.568/1.71$, $p = 0.86$, effect size = 0.19 , $1-\beta = 0.18$). Post-hoc analyses revealed a maximum achieved power ($1-\beta$) of 26%.

Sub-analyses within the musicians (B and C), comparing instrument players ($n = 21$) with singers ($n = 7$) revealed worse language performance of singers within the first three months ($0.0428/0.837$ vs. $-0.729/1.44$, $p = 0.21$), in the compound word repetition subtest (phonologic domain, $-0.248/0.776$ vs. $-1.77/2.33$, $p = 0.03$) and the semantic subtest ($0/0.968$ vs. $-0.990/0.949$, $p = 0.01$). Excluding singers from the main analyses revealed a significant effect within the first three months (T1 vs T2) on the non-word repetition subtest (phonologic domain) when comparing non-musicians vs. instrumentalist musicians (A: $-0.425/0.951$ vs. B and C: $0.201/0.699$, $p = 0.039$).

Table 2. DIMA scores vs musicality.

	Baseline (T1) vs. after 3 months (T2)				After 3 months (T2) vs. after one year (T3)			
	A. Non-musician	B. Amateur musician	C. Trained musician		A. Non-musician	B. Amateur musician	C. Trained musician	
Overall								
DIMA	-0.411 (0.865)	-0.0947 (1.18)	-0.227 (0.779)		-0.260 (1.07)	-0.265 (0.818)	-0.178 (1.19)	
Days*	68.3 (18.8)	73.6 (33.4)	67.2 (39.1)		347 (77.3)	297 (110)	353 (70.5)	
Phonology								
Word repetition	-0.293 (1.20)	-0.510 (1.86)	0 (0)		0.568 (1.71) [□]	0.393 (2.30) [□]	0 (0) [□]	
Compound repetition	-0.308 (1.83)	-0.805 (1.66)	-0.214 (0.642)		0 (1.45)	-0.224 (0.806)	0.385 (0.861)	
Non-word repetition	-0.425 (0.951) [△]	-0.00100 (1.14) [△]	0.0289 (0.566) [△]		0.279 (1.63)	0.0768 (0.582)	0.199 (0.445)	
Sentence repetition	-0.202 (0.683) [△]	0.0359 (1.92) [△]	0.125 (1.32) [△]		-0.318 (0.631)	0.426 (1.59)	0.226 (0.505)	
Semantic								
Semantic tests	-0.470 (1.32)	-0.225 (1.20)	-0.234 (0.703)		-0.234 (1.27)	0.162 (1.04)	0 (0)	
Syntaxis								
Sentence completion	0.0316 (2.09) [□]	-0.0484 (1.46) [□]	-0.531 (1.45) [□]		-1.09 (2.46)	-1.37 (1.96)	-1.01 (4.43)	

All values are mean (SD) Z scores, calculated from a healthy population ($n = 211$) based on age (cutoff 55 years) and Education years (cutoff 12 years). T1; baseline / before surgery, T2; 3 months after surgery, T3; One year after surgery. *mean (SD) days from craniotomy to T2/T3
[△]Beneficial trend observed between musicality and language [□]Detrimental trend observed between musicality and language.

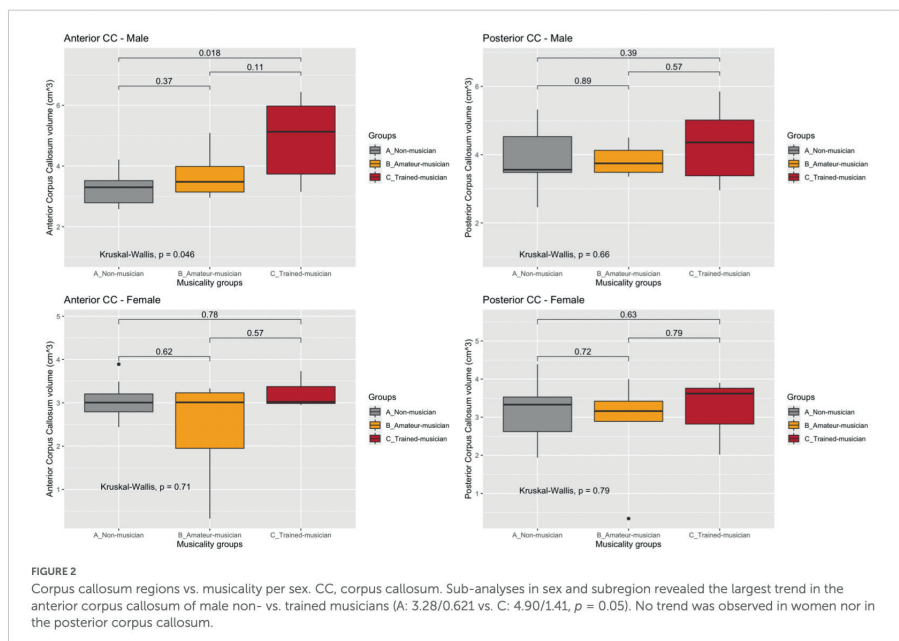
Secondary outcome: musicality vs. corpus callosum

Volumetric corpus callosum measurements were obtained from 39 patients: inter-class correlation showed good to excellent inter-observer agreement (ICC = 0.77 – 0.99) for each corpus callosum region. No statistically significant difference was observed between the musicality groups and the corpus callosum volumes (Figure 2 and Table 3).

Table 3. Corpus callosum measurements vs. musicality

	A. Non-musician N = 17	B. Amateur musician N = 13	C. Trained musician N = 9	
	Overall (n=39)			P value
Corpus callosum	6.67 (1.35)	7.09 (1.07)	8.30 (2.30)	0.13
Anterior corpus callosum	3.17 (0.551)	3.16 (1.12)	4.34 (1.41)	0.06
Posterior corpus callosum	3.49 (0.878)	3.42 (1.03)	3.93 (1.17)	0.52
	Male (n = 23)			
Corpus callosum	7.08 (1.42)	7.54 (0.995)	9.23 (2.18)	0.12
Anterior corpus callosum	3.28 (0.621)	3.66 (0.723)	4.90 (1.41)	0.05
Posterior corpus callosum	3.79 (0.905)	3.83 (0.433)	4.30 (1.13)	0.66
	Female (n=16)			
Corpus callosum	6.21 (1.19)	6.36 (0.808)	6.44 (1.26)	0.13
Anterior corpus callosum	3.05 (0.468)	2.37 (1.27)	3.23 (0.432)	0.70
Posterior corpus callosum	3.16 (0.762)	2.76 (1.41)	3.18 (1.01)	0.78

All volume measures are in mean/SD cubic centimeter (cm³). Patients with tumor involvement in the corpus callosum were excluded. Anterior corpus callosum: rostrum, genu, rostral body and anterior body. Posterior corpus callosum: posterior body, isthmus and splenium.



A trend of effect of musicality on corpus callosum volume (mean/SD cm³) was observed (A: 6.67/1.35 vs. B: 7.09/1.07 vs. C: 8.30/2.30, $p = 0.13$) which diminished after correcting for total brain volume (A: 0.756/0.128 vs. B: 0.763/0.091 vs. C: 0.837/0.221, $p = 0.63$).

Sub-analyses in sex and subregion revealed the largest difference in the anterior corpus callosum of male non- vs. trained musicians (A: 3.28/0.621 vs. C: 4.90/1.41, $p = 0.05$). No trend was observed in women nor in the posterior corpus callosum. Size of corpus callosum (mean/SD cm³) was not significantly larger in patients that started playing their instrument before their tenth life year (7.33 vs. 7.84, $p = 0.81$).

A linear correlation was visually observed, but not statistically confirmed, between volume of corpus callosum and postoperative language course (T1 vs T3, $t = 0.79$, $df = 22$, p -value = 0.43) and between the total hours of playing and corpus callosum volume ($t = 1.57$, $df = 18$, p -value = 0.13, Figure 3).

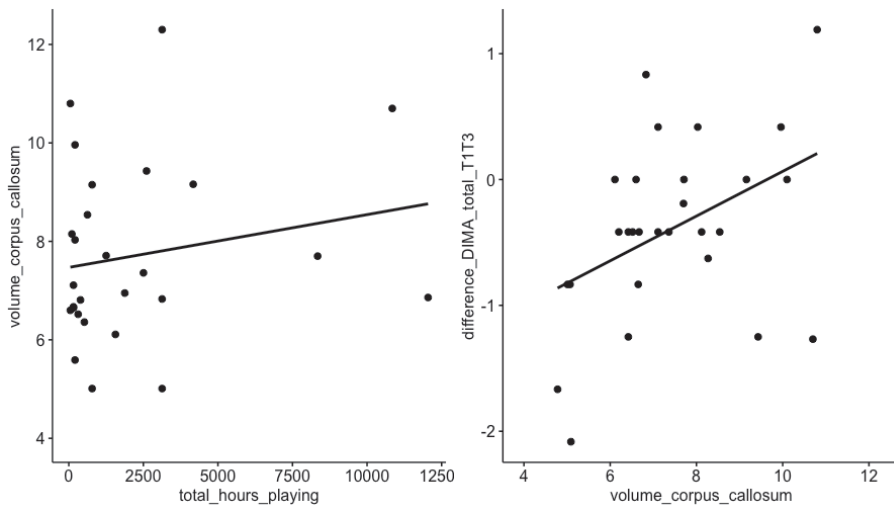


Figure 3 Correlation hours of playing vs. volume of corpus callosum vs. language.

A linear correlation was visually observed, but not statistically confirmed, between volume of corpus callosum and postoperative language course (T1 vs. T3, $t = 0.79$, $df = 22$, $p\text{-value} = 0.43$) and between the total hours of playing and corpus callosum volume ($t = 1.57$, $df = 18$, $p\text{-value} = 0.13$)

Discussion

In this cohort study, we evaluated the effect of musicality on the course of post-operative language recovery following awake glioma surgery. We did not find a significant difference between musicality, corpus callosum size and postoperative course of language performance after awake glioma surgery in our main analysis. This could point into the direction that there is no correlation between musicality and language recovery. However, the lack of evidence could also be attributed to our limited sample size, as our power ($1-\beta$) concerning possible trends did not exceed 26%. Future studies with larger sample size could confirm our findings.

Although most findings did not reach significance, we did observe a significant beneficial effect, after excluding the vocal musicians, in two phonological subtests in patients with a musical background compared to non-musicians. The observed effect in our study related to musicality and phonology is not unexpected as the phonologic system and music share a common hierarchical structure (e.g. syllabic and grouping structure, prosody and melody). In the phonological subtests existing words and non-

words had to be repeated, including a correct phonological form (including syllables and phonemes), stress patterns and pitch. Musical expertise increases sensitivity to pitch changes which allows musicians to detect subtle variations of pitch, rhythm, and harmony within musical phrases faster, and more accurately than non-musicians. (26-28) This enhanced sensitivity to acoustic features might allow musicians to construct more elaborated perceptions of the speech signal, referred to as transfer effects, than non-musicians. This transfer effect was supported by a study showing that musicians were more sensitive than non-musicians to abstract phonological representations (consonant or vowel changes; e.g., *bán/ zán*) derived from the processing of acoustic parameters. (29) This, in turn, can facilitate stages of speech processing, leading to higher scores on the phonologic language tests. (26)

As our patients were asked to focus their attention during the language test, one could argue that the beneficial results of musicians on language tests reflect a general effect of attention. However, data from a non-linguistic cognitive test for visual attention and mental flexibility (Trail Making Test) revealed average to high scores, which did not differ between groups. Moreover, electro-encephalogram studies tackled this issue by showing similar attention between both musicians and non-musicians while conducting several language tests. (30-32) Our findings on phonology are clinically relevant as its prognostic relation to the quality of verbal communication at the long run were already demonstrated in aphasic patients after stroke. (33) The phonological subtests included, among other tests, non-word and sentence repetition; these two tests are important to address as they enable us to distinguish lexical from non-lexical processes. Additional to the classic theory, in which a lesion in the arcuate fasciculus leads to conduction aphasia (34), recent studies suggest that a word-repetition impairment may be explained by a “dual-route” model: a dorsal language stream which is dedicated to phonological processing (non-lexical: ability to link sound to articulation), and a ventral stream which is dedicated to semantic processing (lexical: linking sound to meaning). (35) Therefore, it is important to monitor subtle changes in phonological production (e.g. word repetition) as an indicator for the overall quality of language processing. (36) Moreover, future language rehabilitation could be targeted at the phonological level in glioma patients with a musical background. The advantage of musicality on phonology between three months and one year was less prominent: restoration of language in the non-musical population may have reduced the beneficial effect of music induced alternative compensatory pathways for language recovery.

We did not expect the worse performance in the syntactic domain in the trained musicians compared to the non-musicians. In the literature a paradox is found on syntactic relations in music and language. Cases of dissociations have been described with impaired perception of harmonic relations in music (i.e. amusia) with no signs of aphasia or, inversely, language impairment with spared musical abilities. (37-41) On the other hand, associations have been described on neuroimaging studies showing early right anterior negativity (associated with harmonic processing) in Broca's area.(7) Patel et al. tackled this paradox by proposing the 'shared syntactic integration resource hypothesis' in which linguistic and musical syntax share certain syntactic integration processes that apply over different domain-specific syntactic representations. (42) The syntactic subtest involved completion of the sentence with words that would fit within the context, which also touches upon semantic performance. Therefore, the decrease of syntactic scores in the trained musician group may have been attributed to damage to domain-specific semantic representations rather than a problem with syntactic integration processes, which is expected to be enhanced in this sub-group.

A trend towards a larger corpus callosum, predominantly anteriorly, in trained musical patients compared to non-musical patients was observed. Anterior corpus callosum connects frontal structures; it has been suggested that the intense bimanual motor training of musicians, such as when playing a string instrument, could play an important role in the development of more and thicker myelinated transcallosal fibers.(10) This difference was mostly found in men, which confirms a prior study conducted by Lee and colleagues. (24) A pre-existing sex-based difference in brain symmetry was hypothesized by these researchers. Less brain symmetry, thus more functional lateralization, is observed in smaller corpus callosum volumes. (43) There are reports of women showing increased symmetry compared with men; the authors speculate that female musicians might not show a significant change in lateralization after repetitive bimanual motoric movement and therefore no effect on corpus callosum size.(24, 44)

A paper on musicality and corpus callosum size reported an increased size for those musicians who commenced music training prior to seven years of age, which was confirmed by a number of papers since that time. (45)(24, 46) We were not able to assess this correlation as the trained musicians in our cohort started playing their instrument at an older age. There seemed to be a trend between the hours of musical training and the size of the corpus callosum, however this was not statistically

confirmed. A longitudinal study investigating the influence of musical training on brain structure in children found a significant relationship between the amount of practice and the degree of structural change in the corpus callosum. (47) Future studies should therefore not just consider when musicians start to train, but also how long and how much they train.

We observed a linear trend between the size of the corpus callosum, hours of musical training and postoperative language recovery. Musical patients may benefit from higher white matter connectivity in the corpus callosum, contributing to functional reorganization towards the contralateral side. (14, 45, 48-53) Melodic Intonation Therapy (MIT), a rehabilitation technique using melodic intoning and rhythm to restore language, has been demonstrated to be beneficial in improved functional language in stroke patients with severe aphasia.(54) A current debate in the aphasia literature concerns whether this occurs due to contralateral hemisphere or ipsilateral perilesional compensation. (55) Presently, it is thought that contralateral activation occurs commonly in the post-acute phase, with a return to ipsilateral perilesional activation over the following months. (56) Our results create some substantiation for contralateral compensation in the (sub-)acute phase through the corpus callosum. As our results were less clear after three months post-surgery, future studies could focus on the connectivity of the ipsilateral arcuate fasciculus and the role over time between musicians and non-musicians. (14, 45, 48-53)

Strengths and limitations

This is the first study supporting that musicality contributes to language recovery after awake glioma surgery possibly due to increased neuroplastic properties in language networks. This is relevant as increased knowledge on factors contributing to language recovery can be used in clinical practice to inform the patients on their prognosis and could even aid in the final decision-making when considering surgery. There are some limitations to discuss: the first and most important issue is that most of our findings were not statistically significant, which may be due to our limited sample size as our power did not exceed 26%. Our conclusions should therefore be interpreted to generate new hypotheses. Second, patients in the musical group had a higher level of education, which could have contributed to a better cognitive reserve, also described as ‘brain reserve capacity’. According to these models, the threshold of brain damage necessary to bring about a given deficit is more quickly reached in individuals with less

cognitive training due to less brain reserve capacity. (12, 57, 58) However, we tend to tackle this by showing a similar cognitive level at baseline. Moreover, language scores were corrected for education level and age. Second, tumor in the right hemisphere was more often observed in the musical group which could be a confounding on language performance, considering that language is often lateralized in the left hemisphere. However, we argue that this does not influence our results as prior research found that hemispheric lateralization does not affect language performance on the DIMA scale in glioma patients. (18) (59)

Future studies

Future studies with a larger sample size should confirm our findings, and might be able to correct for the above-described confounding variables. Second, imaging techniques such as diffuse tensor imaging (DTI) and functional MRI (e.g., with language and musical (intonation) tests) before and after surgery could be linked to the course of postoperative language recovery to identify the role of contra- and ipsilateral compensation over time.(60) Last, quality of life questionnaires may be added to assess the true impact of subtle language differences between musical and non-musical patients after glioma surgery.

Conclusion

This is the first study supporting that musicality contributes to language recovery after awake glioma surgery due to increased neuroplastic properties in language networks, especially in instrumentalists. This may be partly attributed to a higher white matter connectivity at the anterior part of the corpus callosum developed during repetitive bimanual musical training, which might have contributed to functional reorganization towards the contralateral side. Our conclusion should be handled with caution and interpreted as hypothesis generating only, as most of our results did not reach statistical significance. Future studies with larger sample sizes are needed to confirm our hypothesis.

References

1. De Witte E, Satoer D, Robert E, Colle H, Verheyen S, Visch-Brink E, et al. The Dutch Linguistic Intraoperative Protocol: a valid linguistic approach to awake brain surgery. *Brain Lang.* 2015;140:35-48.
2. Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Lopes M, et al. Functional recovery after surgical resection of low grade gliomas in eloquent brain: hypothesis of brain compensation. *J Neurol Neurosurg Psychiatry.* 2003;74(7):901-7.
3. Satoer D, Kloet A, Vincent A, Dirven C, Visch-Brink E. Dynamic aphasia following low-grade glioma surgery near the supplementary motor area: a selective spontaneous speech deficit. *Neurocase.* 2014;20(6):704-16.
4. Kiran S, Thompson CK. Neuroplasticity of Language Networks in Aphasia: Advances, Updates, and Future Challenges. *Front Neurol.* 2019;10:295.
5. Merrett DL, Peretz I, Wilson SJ. Moderating variables of music training-induced neuroplasticity: a review and discussion. *Front Psychol.* 2013;4:606.
6. Besson M, Schön D. Comparison between Language and Music. *Annals of the New York Academy of Sciences* 2001. 930, p. 232-58.
7. Maess B, Koelsch S, Gunter TC, Friederici AD. Musical syntax is processed in Broca's area: an MEG study. *Nat Neurosci.* 2001;4(5):540-5.
8. Abrams DA, Bhatara A, Ryali S, Balaban E, Levitin DJ, Menon V. Decoding temporal structure in music and speech relies on shared brain resources but elicits different fine-scale spatial patterns. *Cereb Cortex.* 2011;21(7):1507-18.
9. Levitin DJ, Menon V. Musical structure is processed in "language" areas of the brain: a possible role for Brodmann Area 47 in temporal coherence. *Neuroimage.* 2003;20(4):2142-52.
10. Schlaug G, Jancke L, Huang Y, Steinmetz H. In vivo evidence of structural brain asymmetry in musicians. *Science.* 1995;267(5198):699-701.
11. Schlaug G, Marchina S, Norton A. Evidence for plasticity in white-matter tracts of patients with chronic Broca's aphasia undergoing intense intonation-based speech therapy. *Ann N Y Acad Sci.* 2009;1169:385-94.
12. Omigie D, Samson S. A protective effect of musical expertise on cognitive outcome following brain damage? *Neuropsychol Rev.* 2014;24(4):445-60.
13. Lamont A. *Musical identities and the school environment.* Oxford University Press ed. Hargreaves M, Macdonald, editor2002.
14. Lotze M, Scheler G, Tan HR, Braun C, Birbaumer N. The musician's brain: functional imaging of amateurs and professionals during performance and imagery. *Neuroimage.* 2003;20(3):1817-29.
15. Weijkamp J, & Sadataka, M. Attention to affective audio-visual information: Comparison between musicians and non-musicians. . *Psychology of Music.* 2017;45(2), 204-215.
16. Zhang JD, Susino, M., McPherson, G. E., & Schubert, E. . The definition of a musician in music psychology: A literature review and the six-year rule. . *Psychology of Music.* 2018.
17. Satoer D, De Witte, E., Bulte, B., Bastiaanse, R., Smits, M., Vincent, A., Mariën, P., & Visch-Brink, E. Dutch Diagnostic Instrument for Mild Aphasia (DIMA-NL): Standardisation and a first clinical application in two brain tumour patients. *Linguistics & Phonetics*, in press. 2022.

18. Satoer D, De Witte, E., Bulte, B., Bastiaanse, R., Smits, M., Vincent, A., Mariën, P., & Visch-Brink, E. . Dutch Diagnostic Instrument for Mild Aphasia (DIMA-NL): Standardisation and a first clinical application in two brain tumour patients. *Clinical Linguistics & Phonetics*, in press.
19. Llinas-Regla J, Vilalta-Franch J, Lopez-Pousa S, Calvo-Pexas L, Torrents Rodas D, Garre-Olmo J. The Trail Making Test. *Assessment*. 2017;24(2):183-96.
20. Reitan RM WD. The seashore rhythm test and brain functions. *Clinical Neuropsychologist*.1989/01/01;3(1):70-8.
21. Verhage F. Intelligentie en leeftijd: Onderzoek bij Nederlanders van 12 tot 77 jaar. . Assen, The Netherlands: Van Gorkum. 1964.
22. Verhage F. Intelligence and age: Research study in Dutch individuals aged twelve to seventy-seven. Assen, Netherlands: Van Gorkum/Prakke & Prakke. 1964.
23. Witelson SF, McCulloch PB. Premortem and postmortem measurement to study structure with function: a human brain collection. *Schizophr Bull*. 1991;17(4):583-91.
24. Lee DJ, Chen Y, Schlaug G. Corpus callosum: musician and gender effects. *Neuroreport*. 2003;14(2):205-9.
25. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods*. 2009;41(4):1149-60.
26. Besson M, Faita F, Requin J. Brain waves associated with musical incongruities differ for musicians and non-musicians. *Neurosci Lett*. 1994;168(1-2):101-5.
27. Bidelman GM, Krishnan A. Effects of reverberation on brainstem representation of speech in musicians and non-musicians. *Brain Res*. 2010;1355:112-25.
28. Koelsch S, Schmidt, B.H. and Kansok, J. . Influences of musical expertise on the ERAN: an ERP-study. *Psychophysiology* 2002;657-663(39).
29. Marie C, Magne C, Besson M. Musicians and the metric structure of words. *J Cogn Neurosci*. 2011;23(2):294-305.
30. Courchesne E, Hillyard SA, Galambos R. Stimulus novelty, task relevance and the visual evoked potential in man. *Electroencephalogr Clin Neurophysiol*. 1975;39(2):131-43.
31. Escera C, Alho K, Schroger E, Winkler I. Involuntary attention and distractibility as evaluated with event-related brain potentials. *Audiol Neurotol*. 2000;5(3-4):151-66.
32. Squires KC, Squires NK, Hillyard SA. Decision-related cortical potentials during an auditory signal detection task with cued observation intervals. *J Exp Psychol Hum Percept Perform*. 1975;1(3):268-79.
33. El Hachoui H, Lingsma HF, van de Sandt-Koenderman MW, Dippel DW, Koudstaal PJ, Visch-Brink EG. Long-term prognosis of aphasia after stroke. *J Neurol Neurosurg Psychiatry*. 2013;84(3):310-5.
34. Wernicke C. *Der Aphasische Symptomencomplex*. Breslau: Cohen and Weigert. 1874.
35. Moritz-Gasser S, Duffau H. The anatomo-functional connectivity of word repetition: insights provided by awake brain tumor surgery. *Front Hum Neurosci*. 2013;7:405.
36. Sierpowska J, Gabarras A, Fernandez-Coello A, Camins A, Castaner S, Juncadella M, et al. Words are not enough: nonword repetition as an indicator of arcuate fasciculus integrity during brain tumor resection. *J Neurosurg*. 2017;126(2):435-45.

37. Ayotte J, Peretz I, Hyde K. Congenital amusia: a group study of adults afflicted with a music-specific disorder. *Brain*. 2002;125(Pt 2):238-51.
38. Ayotte J, Peretz I, Rousseau I, Bard C, Bojanowski M. Patterns of music agnosia associated with middle cerebral artery infarcts. *Brain*. 2000;123 (Pt 9):1926-38.
39. Griffiths TD, Rees A, Witton C, Cross PM, Shakir RA, Green GG. Spatial and temporal auditory processing deficits following right hemisphere infarction. A psychophysical study. *Brain*. 1997;120 (Pt 5):785-94.
40. Peretz I, Belleville S, Fontaine S. Dissociations between music and language functions after cerebral resection: A new case of amusia without aphasia. *Canadian journal of experimental psychology*. 1997;51(4):354-68.
41. Peretz I, Champod AS, Hyde K. Varieties of musical disorders. The Montreal Battery of Evaluation of Amusia. *Ann N Y Acad Sci*. 2003;999:58-75.
42. Patel AD. Language, music, syntax and the brain. *Nat Neurosci*. 2003;6(7):674-81.
43. Keenan JP, Thangaraj V, Halpern AR, Schlaug G. Absolute pitch and planum temporale. *Neuroimage*. 2001;14(6):1402-8.
44. Dorion AA, Capron C, Duyme M. Measurement of the corpus callosum using magnetic resonance imaging: analyses of methods and techniques. *Percept Mot Skills*. 2001;92(3 Pt 2):1075-94.
45. Schlaug G, Jancke L, Huang Y, Staiger JF, Steinmetz H. Increased corpus callosum size in musicians. *Neuropsychologia*. 1995;33(8):1047-55.
46. Ozturk AH, Tascioglu B, Aktekin M, Kurtoglu Z, Erden I. Morphometric comparison of the human corpus callosum in professional musicians and non-musicians by using in vivo magnetic resonance imaging. *J Neuroradiol*. 2002;29(1):29-34.
47. Schlaug G, Norton A, Overy K, Winner E. Effects of music training on the child's brain and cognitive development. *Ann N Y Acad Sci*. 2005;1060:219-30.
48. Pantev C, Herholz SC. Plasticity of the human auditory cortex related to musical training. *Neurosci Biobehav Rev*. 2011;35(10):2140-54.
49. Amunts K, Schlaug G, Jancke L, Steinmetz H, Schleicher A, Dabringhaus A, et al. Motor cortex and hand motor skills: structural compliance in the human brain. *Hum Brain Mapp*. 1997;5(3):206-15.
50. Gaser C, Schlaug G. Brain structures differ between musicians and non-musicians. *J Neurosci*. 2003;23(27):9240-5.
51. Han Y, Yang H, Lv YT, Zhu CZ, He Y, Tang HH, et al. Gray matter density and white matter integrity in pianists' brain: a combined structural and diffusion tensor MRI study. *Neurosci Lett*. 2009;459(1):3-6.
52. Hyde KL, Lerch J, Norton A, Forgeard M, Winner E, Evans AC, et al. Musical training shapes structural brain development. *J Neurosci*. 2009;29(10):3019-25.
53. Wu J, Zhang J, Ding X, Li R, Zhou C. The effects of music on brain functional networks: a network analysis. *Neuroscience*. 2013;250:49-59.
54. Joost Hurkmans MdB, Anne M. Boonstra, Roel Jonkers, Roelien Bastiaanse, Hans Arendzen & Heleen A. Reinders-Messelink. Music in the treatment of neurological language and speech disorders: A systematic review. *Aphasiology*. 201;Volume 26, 2012 - Issue 1.

55. Van Der Meulen IJ VDS-KM, Heijenbrok MH1, Visch-Brink E2, Ribbers GM1. Melodic Intonation Therapy in Chronic Aphasia: Evidence from a Pilot Randomized Controlled Trial. *Front Hum Neurosci*. 2016;1(10):533.
56. Saur D, Lange R, Baumgaertner A, Schraknepper V, Willmes K, Rijntjes M, et al. Dynamics of language reorganization after stroke. *Brain*. 2006;129(Pt 6):1371-84.
57. Stern Y, Barulli D. Cognitive reserve. *Handb Clin Neurol*. 2019;167:181-90.
58. Gehring K, Aaronson NK, Gundy CM, Taphoorn MJ, Sitskoorn MM. Predictors of neuropsychological improvement following cognitive rehabilitation in patients with gliomas. *J Int Neuropsychol Soc*. 2011;17(2):256-66.
59. S Mooijman AV, E De Witte, E Visch-Brink, D Satoer. OS07.5A Diagnostic Instrument for Mild Aphasia (DIMA): sensitive and valuable addition to standard language assessment in glioma patients. *Neuro-Oncology*. 2021;Volume 23, Issue Supplement_2, September 2021, Pages ii10–ii11.
60. Carolina P. Mendez Orellana MEvdS-K, Emi Saliasi, Ineke van der Meulen SK, Aad van der Lugt, Marion Smits. Insight into the neurophysiological processes of melodically intoned language with functional MRI. *Brain and Behavior*. 2014;4(5):615–625.

Appendix A. Musicality classification and questionnaire

For musicality classification underlying **Table A** was filled in after telephone **questionnaire B**.

This was based on the MEC criteria which defines a musician based on years of musical training and intensity.

Table A

Definition of the group labels based on the questionnaire provided.

Group	I: Non-musicians	II: Amateur musicians (non-playing)	III: Amateur musicians (playing)	IV: Trained musicians (non-playing)	V: Trained musicians (playing)
Conditions					
Playing an instrument? ¹	No (0p)	Formerly (1p)	Yes (2p)	Formerly (1p)	Yes (2p)
Lessons?	<i>I do not play an instrument (0p)</i>	1-5 years (1p)	1-5 years (1p)	≥ 6 years (2p)	≥ 6 years (2p)
Years of playing? ²	< 1 year (0p)	1-10 years (1p)	1-10 years (1p)	≥ 11 years (2p)	≥ 11 years (2p)
Hours of playing a week?	< 0.5 hrs/wk on average (0p)	0,5-2 hrs/wk on average (1p)	0,5-2 hrs/wk on average (1p)	≥ 2,5 hrs/wk on average (2p)	≥ 2,5 hrs/wk on average (2p)
Points	0-1 points	1-5 points	2-6 points	6-7 points	7-8 points

¹ The first condition is a prerequisite for group formation.

² For singing, having received lessons or in group formation (band/choir) is a prerequisite. For instrumentalists playing an instrument without lessons is allowed.

Questionnaire B (Dutch language)

Onderstaande vragen gaan over de periode tot aan de operatie (T1)

1. Zingt u (koor, band, individueel, opleiding)?
 - a. Ja
 - b. Nee
 - c. Voorheen, maar nu niet meer
2. Bespeelt u één of meerdere instrumenten (excl. zang)?
 - a. Ja
 - b. Nee
 - c. Voorheen, maar nu niet meer

Indien tweemaal b. (groep I: non-musicians) hoeft de patiënt de volgende vragen niet meer te beantwoorden.

3. Heeft u les gehad voor de instrumenten die u bespeelt (incl. zang)?
 - a. Ja
 - b. Nee, ik ben autodidact

Indien b. hoeft de patiënt vraag 4, 11 en 12 niet meer te beantwoorden.

4. Hoelang heeft u les gehad voor de instrumenten die u bespeelt/bespeelde (incl. zangles)?
 - a. 1 tot 5 jaar
 - b. 6 jaar of langer
5. Heeft u in groepsformatie gespeeld/gezongen (band, koor), zo ja hoe lang?
 - a. Nee
 - b. 1 tot 5 jaar
 - c. 6 jaar of langer

6. Hoelang heeft u in totaal uw instrumenten bespeeld (inclusief zang)?

..... jaar

7. Hoeveel tijd heeft u gemiddeld per week besteed aan het spelen van uw instrument (inclusief zang)?

..... uur

8. Welke instrumenten bespeelt/bespeelde u (hoofdinstrument eerst)?

.....

9. Op welke leeftijd heeft u de instrumenten leren bespelen (hoofdinstrument eerst)?

.....

10. In welke periode van uw leven heeft u instrumenten bespeeld (bijv. tussen 5 en 10 jaar of tussen 25 en 33 jaar) (hoofdinstrument eerst)?

.....

11. Hoe frequent heeft u les gehad voor de instrumenten die u bespeelt/bespeelde?

- a. 3 of meer keer per week
- b. 2 keer per week
- c. 1 keer per week
- d. 1 keer per twee weken
- e. 1 keer per drie weken
- f. 1 keer per maand

12. Heeft/had u groepsles of privéles?

- a. Groepsles
- b. Privéles
- c. Een combinatie

13. Heeft u van bladmuziek leren spelen?

- a. Ja
- b. Nee

Onderstaande vragen gaan over de periode ná de operatie (T2/T3)

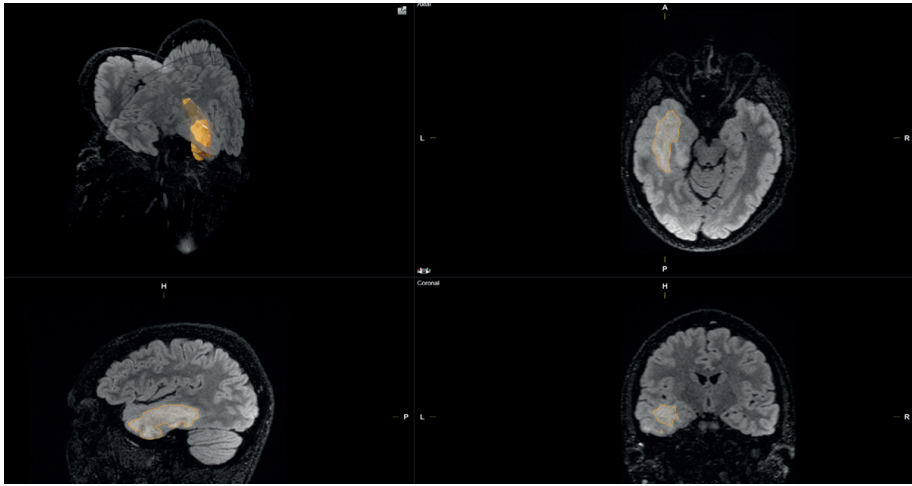
14. Wanneer bent u na de operatie weer begonnen met het spelen van uw instrument(en)/zingen?

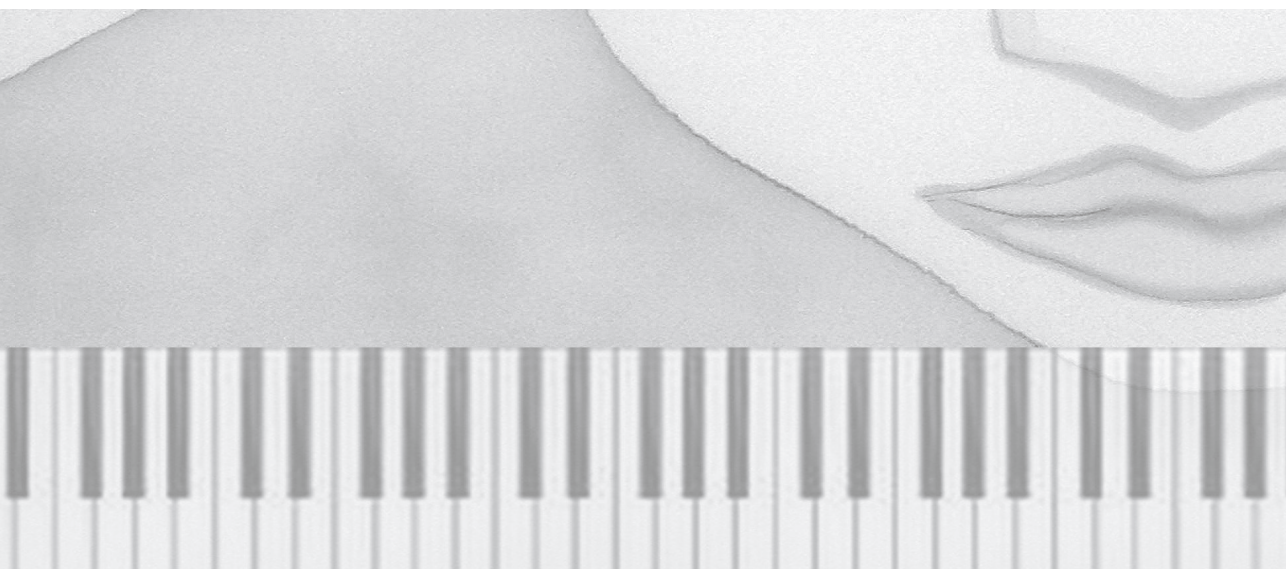
- a. Direct na de operatie
- b. Na 4 weken
- c. Na 3 maanden
- d. Na 6 maanden
- e. Na 9 maanden
- f. Na 12 maanden
- g. Ik heb niet meer gespeeld/gezongen

Indien g. hoeft de patiënt de volgende vraag niet meer te beantwoorden.

15. Hoeveel tijd heeft u in het jaar na de operatie gemiddeld per week besteedt aan het bespelen van uw instrument(en)?

[open question] uur



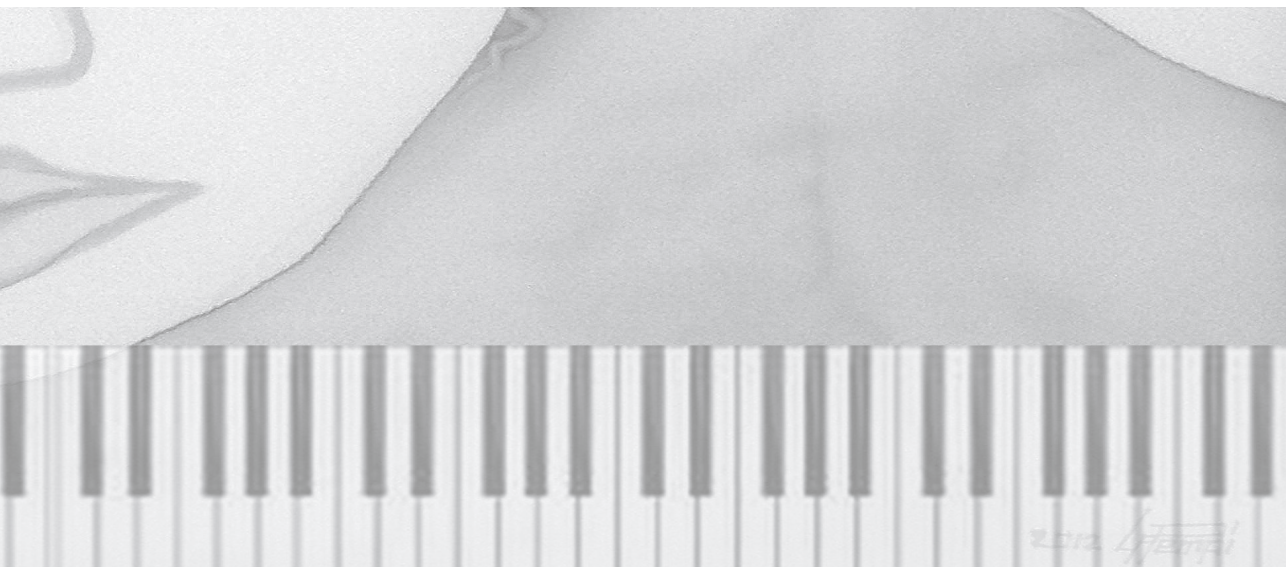


CHAPTER 8

The feasibility and added value of mapping music during awake craniotomy: a systematic review

P.R. Kappen MD, T. Beshay, A.J.P.E. Vincent MD, PhD, D. Satoer PhD,
C.M.F. Dirven MD, PhD, J. Jeekel MD, PhD, M. Klimek MD, PhD

European Journal of Neuroscience, 2022



Abstract

The value of mapping musical function during awake craniotomy is unclear. Hence, this systematic review was conducted to examine the feasibility and added value of music mapping in patients undergoing awake craniotomy. An extensive search, on the 26st of March 2021, in four electronic databases (Medline, Embase, Web of Science and Cochrane CENTRAL register of trials), using synonyms of the words “Awake Craniotomy” and “Music Performance”, was conducted. Patients performing music while undergoing awake craniotomy were independently included by two reviewers. This search resulted in ten studies and fourteen patients. Intra-operative mapping of musical function was successful in thirteen out of fourteen patients. Isolated music disruption, defined as disruption during music tasks with intact language/speech and/or motor functions, was identified in two patients in the right superior temporal gyrus (G,K), one patient in the right and one patient in the left middle frontal gyrus and one patient in the left medial temporal gyrus. Pre-operative functional MRI confirmed isolated music localizations in three patients. Assessment of post-operative musical function, only conducted in seven patients by means of standardized (57%) and non-standardized (43%) tools, report no loss of musical function. With these results we conclude that mapping music is feasible during awake craniotomy. Moreover, we identified certain brain regions relevant for music production and detected no decline during follow-up, suggesting an added value of mapping musicality during awake craniotomy. A systematic approach to map musicality should be implemented, to improve current knowledge on the added value of mapping musicality during awake craniotomy.

Introduction

Neurosurgical procedures include surgery near brain regions responsible for patients' motor, speech or language function (so called eloquent brain regions).¹ Awake craniotomy is applied when operating near these eloquent structures to safely remove tumour or epileptogenic zones, while monitoring patients' speech, language or motor functions.²

Musicians occasionally undergo awake craniotomy, during which their musical ability is at stake.³ Preservation of musical function may be of major importance for these patients as music can act as a main source of income.⁴ Furthermore, loss of musical ability may have a severe impact on their quality of life, since music can serve as an outlet for emotions and contributes to the reduction of stress and anxiety.^{4,5}

Musical function, independent of speech/language or motor function, is usually not monitored during awake craniotomy. Relevant brain regions for music production include the premotor, prefrontal and supplementary motor cortices, along with the cerebellum, basal ganglia, and the auditory superior temporal gyrus (STG) as these regions enable the auditory-motor interactions required for music production.⁶⁻⁸ Moreover, the right hemisphere, which is mainly responsible for melodic identification, and the left auditory cortex, essential for the discrimination of speech/language, are in constant dialogue with one another through the corpus callosum.⁸⁻¹³

Mapping music tasks, additional to speech/language and motor function, during awake craniotomy might be valuable, as focal damage within the right STG has shown to disrupt musical processing, without interfering with speech/language or motor functions.⁶ Furthermore, post-operative amusia (i.e. the inability to produce music) has already been described after right-sided resection of a glioma.¹⁴ Hence, several case studies and video reports on social media, summarized in a previous narrative review, report patients performing music during awake craniotomy.¹⁵⁻¹⁸

No systematic review of literature has been published addressing the feasibility and added value of intra-operative music tasks during awake craniotomy. A clear and specific overview of the intra-operative music mapping methods, the relevant brain regions and the peri-operative course of musicality could serve as a guidance in clinic and for future studies.

Methods

This systematic review follows the guideline from Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and is registered in the PROSPERO database (CRD42021261017).¹⁹

Ethics

Informed consent or approval from the local institutional review board was not required for this systematic review, as no animals or patients were involved in the process.

Search strategy and eligibility criteria

The literature search was conducted with assistance of a dedicated biomedical information specialist. The electronic databases of Medline, Embase, Web of Science and Cochrane CENTRAL register of trials were searched from the date of inception until March 26st 2021, using terms and synonyms of the words “Awake Craniotomy” and “Music Performance” (appendix A).²⁰ Cross-reference was applied in the included studies to search for additional eligible papers.

Prospective, retrospective cohort studies and case series/reports including patients performing music (i.e. humming/singing or any instrument) while undergoing awake craniotomy were included. Articles were excluded when full text was not available.

Source selection

Two independent reviewers (P.K. / T.B) screened all studies on title, abstract and full text when eligible. Discrepancies were discussed with the senior author (M.K.) until consensus was reached. Authors were not contacted to acquire additional information, since the aim of this review was to present an unmodified overview of the current literature.

Data extraction

Demographic patient data (i.e. age, sex, handedness), musicality (i.e. professional/amateur), type of musician (singer/instrumentalist), disease information (i.e. location/type/hemispheric side), course of musicality in comparison with speech/language

and motor function (i.e. standardized/non-standardized pre-and post-operative tests), specifications of the intra-operative mapping procedure (i.e. type of music/language/motor tasks, stimulation settings and mapped brain regions) and surgical details (i.e. anesthesia technique, surgical course, occurrence of complications) were independently extracted by the same two reviewers (P.K. / T.B). Full text was again accessed when differences in data between the two independent reviewers were identified.

Level of musicality was not further specified, but rather adopted as stated by the authors of the included studies, using terms as “professional” and “non-professional (e.g. hobbyist/amateur/casual player).

Successful intra-operative mapping of music was defined as performance of intra-operative music tasks, while using direct electrical stimulation for mapping purposes, without onset of task-related surgical complications.

Intra-operative findings during music mapping were categorized based on the localization of brain mapping on (sub-)lobar level and severity of the disruption classified in major (e.g. complete music arrest) and minor (e.g. changes in pitch/rhythm/melodic contour) errors. Intra-operative disruption during music tasks *without* reporting motor and/or speech/language deficits was classified as ‘isolated’. Intra-operative disruption during music tasks *with* deficits in the same region during speech/language tasks and/or observed motor deficits was classified as ‘combined’.

Assessment of pre- and post-operative musical function was defined as ‘standardized’ in case of an objective scoring system, which has been published in a scientific journal (e.g. just mentioning playing the guitar would qualify for ‘non-standardized’).

Data analysis and synthesis

Data were reported with mean +/- /standard deviation (SD) in normal distributed data (assessed with the Shapiro-Wilk test) or median and interquartile range (IQR) in non-normal distributed data.²¹

BrainVoyager EDU (Brain Innovation, Maastricht, The Netherlands) was used for the quantitative visualization of the brain regions relevant for music mapping. Only cases which sufficiently specified these regions (i.e. with illustration) were included in this figure.²²

Results

Systematic search

The literature search generated 660 studies after removal of duplications (appendix B). We excluded 642 studies after title and abstract screening, resulting in 18 studies to be assessed for full-text. We excluded nine studies after full-text screening; six studies due to a lack of intra-operative music performance,²³⁻²⁸ one conference abstract,²⁹ one case sang unexpectedly after stimulation but not for mapping purposes³⁰ and one case³¹ due to overlap with another included study.⁷ Cross-referencing led to one additional study³² resulting in ten studies (n_s) and fourteen patients (n_c) included for the final analysis.

Study and patient characteristics

Mean / SD age of the fourteen included patients was 38.57 / 16.05, of which nine male (64.3%) and twelve right-handed patients (85%, Table 1). Eight patients were singers (57%)^{15, 32, 33}, while others played either a string ($n = 4$, 29 %) ^{7, 15, 34-36} or a wind instrument ($n = 2$, 14.3%). Six out of fourteen patients were professional musicians (43%) ^{7, 35-38}

Eleven patients underwent awake craniotomy for tumor resection (79%) ^{7, 15, 17, 32, 36-38}, two for epilepsy surgery (14%)^{33, 35} and one because of a cerebral cavernous malformation (7%).³⁴ Disease localization (right hemisphere, $n = 8$) was present in the temporal ($n=5$, 36%) ^{15, 33-35, 37}, frontal ($n=7$, 50%), ^{17, 32, 36} parietal lobe ($n=1$, 7%)³⁸ and insula ($n=1$, 7%).⁷

Disease related seizures were reported in nine cases, but further no neurological deficits were described at baseline. ^{7, 15, 32-38}

Intra-operative findings

Feasibility and methods

Mapping music was successful in all but one case (93%), in whom music could not be mapped due to occurrence of a stimulation-induced generalized seizure (Table 2).³⁶ This patient continued to play the violin during surgery without use of cortical stimulation. In the other studies no surgical complications, related to the intra-operative music tasks, were reported.

Methods of music mapping were vocals (i.e. singing/humming) (n = 10, 71%)^{15, 17, 32, 33, 35, 37} or instruments (n = 4, 29%).^{7, 34, 36, 38} Patients playing instruments included the clarinet³⁸, chords on the guitar⁷, simple melodies on the keyboard³⁴ and familiar songs on the violin during surgery.³⁶

In eleven patients (71%) intra-operative speech/language tasks such as naming and reading were conducted.^{7, 17, 32-34, 37} In six cases, intra-operative motor function was explicitly reported; one case through finger tapping³⁴, one case with MEPS/SEPS³⁸ and four merely through observation.^{7, 17, 33, 36, 38}

Disruption and localization

Out of the thirteen patients in which music mapping occurred successfully; isolated disruption of musical function was identified in 5 patients (38%, table 2)^{17, 32-34, 37}, only combined with speech/language disruption in four patients (31%)^{7, 17} and with motor disruption in two patients (15%).^{17, 38} No music disruption was identified in two patients (15%).^{15, 35} See figure 1 for all the relevant brain regions with respect to the type of music disruption.

Isolated music disruption occurred in two patients, during singing, when stimulating the right posterior STG with complete music arrest (G)³⁷ and change in melodic contour (K)³³. Isolated music arrest occurred in two patients, during singing, while stimulating the middle frontal gyrus (MFG) in the left (Z)³² and right (R3)¹⁷ hemisphere. Lastly, isolated music disruption occurred during intra-operative keyboard playing while stimulating the left posterior middle temporal gyrus/ supramarginal gyrus (D, not shown in figure as the region was insufficiently specified, with lack of an illustration in the manuscript³⁴).

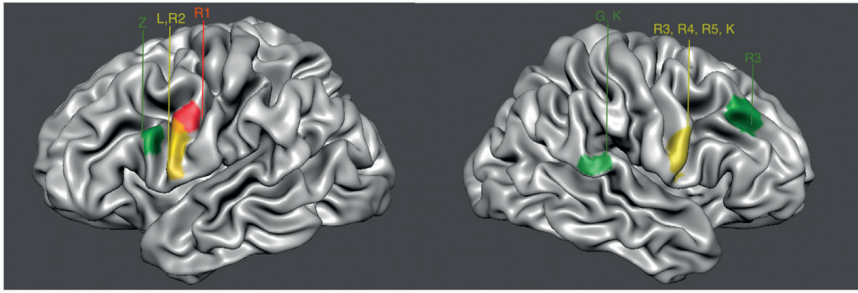


Figure 1. Stimulation sites for music production. Relevant brain regions for music production confirmed by each included case (all right-handed, except for R1). All methods of music mapping included production except Garcea et al. (G) which included music production and perception. Dziedzic et al. (D) and Scerrati et al. (S) are not shown in this figure, due to low specificity of described region and lack of an illustration. Green = brain region with isolated music deficit; confirmed in the right posterior superior temporal gyrus (pSTG) by Garcea et al. (G) and Katlowitz et al. (K), in the right middle frontal gyrus (MFG) by Roux et al. (R3) and in the left MFG (Brodmann's area) by Zhang et al. (Z). Red = brain region with music deficit combined with motor; confirmed by Roux et al. (R1) in the left precentral gyrus. Yellow = brain region with music deficit combined with speech/language, confirmed in the right precentral gyrus by Roux et al. (R3, R4, R5) and Katlowitz et al. (K) and in the left precentral gyrus by Leonard et al. (L) and Roux et al. (R2)

Music disruption only combined with speech/language occurred in four patients. Two patients in the right precentral gyrus during intra-operative singing; one left-handed patient with loss of melodic contour combined with affected speech prosody (R5) and one articulatory with naming interference (R4).¹⁷ Moreover, two patients in the left precentral gyrus; one music arrest during intra-operative guitar playing with repetition errors (L)⁷ and one articulatory during intra-operative singing with naming interference (R2).¹⁷

Music disruption only combined with motor occurred in two patients; one articulatory deficit during intra-operative singing with motor interference while stimulating the left pre-central gyrus (R1)¹⁷ and one patient while stimulating the right postcentral gyrus with music arrest and dystonic movements in the upper extremities but normal SEPs/MEPs (S, not shown in figure due to lack of illustration from original manuscript).³⁸

No music disruption was found in two patients, during intra-operative singing, while stimulating the right STG^{15,35}.

Peri-operative course of musicality

Pre-operative methods

Pre-operative musical function was assessed in ten patients (71%)^{15, 17, 32, 35-37}, of which three patients (30%) with use of standardized musical assessment tools such as the Montreal Battery of Evaluation of Amusia (MBEA)³⁹, the Seashore Rhythm Test (SRT)⁴⁰ and the Beat Alignment Test (BAT)⁴¹ (Table 3). One study assessed musical function with the MBEA, SRT and BAT³⁵ while the other two studies report using only the MBEA.^{32, 37} The non-standardized methods of music assessment (n = 7) involved rhythm and tone pitch by the music therapist in one patient¹⁵, playing familiar but complex pieces by her own instrument in another patient and one study reported the use of 'basic formal testing' in all five patients (R1-5).¹⁷ No pre-operative deficit in musical function was observed.

Pre-operative speech/language, evaluated with the use of formal tests in 13 patients (93%)^{15, 17, 32-38}, and motor function, assessed in four patients (29%),^{15, 32, 36, 38} revealed no deficits.

Pre-operative functional MRI (fMRI) for music localization was described in four patients (29%) with music tasks such as listening to music in two patients^{35, 37}, humming familiar songs in one case³² and passive and active music imagination tasks (i.e. imagining listening or singing) in another case.¹⁵ Musical dominance (i.e. increased voxel activity) was found in the right STG in one case³⁷, while bilateral STG activation was found in two other patients during music tasks.^{35, 15} Activation of the left MFG and supplementary motor area (SMA) was perceived in the fourth patient during humming, score reading and diverse speech/language tasks.³²

Pre-operative functional MRI for speech/language localization was described in four patients^{15, 36, 37}, one of which showed less voxel contrast in the right STG compared to the music-related voxel activity³⁷, left-hemispheric dominance in two patients^{15, 36} and increased voxel activation in the right anterior temporal lobe during passive word listening tasks (not shown in Table).¹⁵

Post-operative methods

Post-operative musical function was assessed in seven patients (50%), of which four patients using standardized assessment tools (Table 3); two patients tested with the

MBEA^{32, 37}, one with the SRT¹⁵ and one with the SRT, MBEA en BAT.³⁵ One patient reported improvement from 86% to 99% on the MBEA attributed to perilesional compensatory activations.³² The other three patients reported similar results compared to baseline, all within normal range.^{15, 37} The use of non-standardized methods for the assessment of musical function after surgery was reported in three patients (23%), in which authors claim that patients were able to play the piano³⁴, the violin³⁶ and the clarinet.³⁷

Post-operative speech/language was only described in two cases; one patient remained above average on the intelligence and verbal memory tests.¹⁵ The other patient scored 98% correct, concordant with baseline, on the Aphasia Battery of Chinese test 1 week and 6 months after surgery.³² Furthermore, no reports on other post-operative neurological deficits were found, except for slight dyscalculia in one case.³⁶

Discussion

This systematic review supports that mapping music during awake craniotomy is feasible. Moreover, the detection of isolated music disruption in both the right and left hemisphere and preservation of musicality in all patients indicate the additional value of this mapping technique for both hemispheres. Limitations and recommendations for future studies and clinical practice are discussed below.

Feasibility

Almost all included patients (93%) reported successful mapping while performing different music tasks during awake craniotomy. This accounts mostly for singing and humming, as this task was reported in 71% of our included patients and resembles the standard speech/language tasks.^{42, 43} Furthermore, music tasks involved variable instruments, such as the clarinet, keyboard, guitar and violin, all without the occurrence of task-related complications. While playing these instruments during awake craniotomy therefore seems feasible, generalization of the findings is limited, as different patients may require various positions on the operation table for optimal resection which might interfere with the posture and mobility needed to play for instance the violin. One case failed to map during musical tasks, due to occurrence of a stimulation-induced seizure³⁶, which was a complication not related to the music task itself. Our results on feasibility should be handled with caution since studies with negative results are often not published and publication bias cannot be ruled out.⁴⁴

Intra-operative mapping

Isolated music disruption occurred in five out of fourteen patients and was identified in the right posterior STG, in both sides the MFG and left middle temporal gyrus suggesting additional value of mapping music in these structures. Isolated music disruption was most often found in the non-dominant hemisphere ($n = 3$, 60%), but also in the dominant hemisphere ($n = 2$, 40%). This isolated music disruption in the dominant hemisphere is in contrast to the acknowledged hypothesis of Jackson and colleagues explaining that the dominant hemisphere is specialized for speech/language activity and the non-dominant hemisphere for many non-linguistic holistic functions such as music perception and production.^{45,46} The authors from our included studies that found isolated music disruption in the dominant hemisphere, clarified this with two possible explanations: first, re-organization to the contra-lateral side in younger patients combined with loss of function in the non-dominant hemisphere due to long-standing lesions.^{15,35} Second, it could be true that both hemispheres are involved in musicality. Indeed, two out of four included patients which performed pre-operative fMRI found synchronous activation in the right *and* left STG during music imagination tasks, indicating a valuable role for fMRI when operating either side.^{15,37} A fMRI study with healthy participants confirmed this, showing increased voxel activation during music listening in both the right *and* left STG.⁴⁷ Furthermore, our included studies suggest additional value of pre-operative fMRI as music localization was confirmed in three out of these four cases.^{32,35,37}

Speech/language and music errors were found in four out of fourteen patients when stimulating both the left and right precentral gyrus, suggesting a speech/language-induced musical disruption. We observed this speech/language-induced musical disruption more during intra-operative singing ($n = 3$, 75%) as opposed to playing an instrument ($n = 1$, 25%). This might be explained by the several common characteristics of speech/language and singing, such as their hierarchical structure and prosodic features (e.g. phrase-final lengthening).^{48,49} However, the small numbers limit firm conclusions on this relation. In two patients, music disruption was found combined with visible motor contractions in the right post-central gyrus and left pre-central gyrus. These regions can therefore not solely be devoted to the function of music.^{38,50} Eight cases did not explicitly mention their findings on motor mapping, so we assumed no motor deficits in these patient, as motor disruption can be determined through mere observation. Future studies should carefully describe each task per brain

region, to enable readers to understand the origin (motor, speech/language or merely music) of the deficit.

Preservation of musical function

All the included cases in this study demonstrated preserved musical function, indicative for added value of intra-operative music tasks during awake craniotomy. We do acknowledge that, in the literature, we did not find any case reports describing amusia after awake craniotomy without music tasks. However, literature describes post-operative amusia in one case after resection of the right-sided gyrus of Heschl,¹⁴ and a non-aphasic singer which lost his capacity to sing after resection of a cyst in the right MFG⁵¹. These studies, which confirm our cases which found isolated music disruption in the right MFG and STG, convince us of the added value of testing musicality during awake craniotomy. Our data on the postoperative follow-up was limited to only seven out of fourteen cases. Furthermore, while these studies reported patients playing their instrument after surgery, objective standardized tools were only used in four studies challenging comparisons between pre- and postoperative musicality.³⁹ Future studies should therefore a) report follow-up data and b) use an objective, standardized assessment tool.

Strengths and limitations

This study has several strengths and limitations. This is the first systematic review to assess the feasibility and value of music mapping during awake craniotomy. We schematically presented an overview of all the different methods, brain regions of interest and peri-operative course. Our findings are intended to be used as a guidance for clinical practice and for future studies. Our conclusions with respect to feasibility should be handled with caution, as all studies had positive outcomes (successful music mapping with preserved postoperative function) possibly indicating publication bias. Moreover, our small sample size, lack of control group, different methods of assessing musical function, and limited information concerning post-operative musical function make it difficult to draw firm conclusions on the true additional value of mapping music for preserving musicality.

Recommendations

Publication of unsuccessful case reports should be encouraged to improve insights in the feasibility of musical performance during awake craniotomy. Second, although intra-operative music tasks may vary, disruption of music should always be compared with speech/language and/or motor tasks to understand the origin (motor, speech / language or merely music) of the deficit. Third, musicality should also be assessed with a standardized objective scoring form before and after surgery allowing comparison between several moments and studies. Lastly, pre-operative fMRI with musicality related tasks is desirable in order to improve knowledge on the localization of music in neurosurgical patients and to allow for better interpretation of the intra-operative findings.

Conclusions

Successful mapping during music tasks in all but one reported patient shows the feasibility of intra-operative mapping of musical function. Moreover, isolated music disruption in both the right and left hemisphere with preservation of musicality in all patients indicate an added value of this mapping technique for both hemispheres. Future studies should use standardized protocols as described above to assess the true feasibility and added value of mapping music during awake craniotomy.

References

1. Fugate JE. Complications of Neurosurgery. *Continuum (Minneapolis)*. 2015;21(5 Neurocritical Care):1425-44.10.1212/CON.0000000000000227
2. Penfield W BE. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*. 1937;60:389-443
3. Gasenzer ER, Kanat A, Neugebauer E. The Unforgettable Neurosurgical Operations of Musicians in the Last Century. *World Neurosurg*. 2017;101:444-50.S1878-8750(16)31303-110.1016/j.wneu.2016.11.144
4. Bittman B, Berk L, Shannon M, Sharaf M, Westengard J, Guegler KJ, et al. Recreational music-making modulates the human stress response: a preliminary individualized gene expression strategy. *Med Sci Monit*. 2005;11(2):BR31-40.6567
5. de Witte M, Spruit A, van Hooren S, Moonen X, Stams GJ. Effects of music interventions on stress-related outcomes: a systematic review and two meta-analyses. *Health Psychol Rev*. 2020;14(2):294-324.10.1080/17437199.2019.1627897
6. Gaser C, Schlaug G. Brain structures differ between musicians and non-musicians. *J Neurosci*. 2003;23(27):9240-5.23/27/9240
7. Leonard MK, Desai M, Hungate D, Cai RF, Singhal NS, Knowlton RC, et al. Direct cortical stimulation of inferior frontal cortex disrupts both speech and music production in highly trained musicians. *Cognitive Neuropsychology*. 2019;36(3-4):158-66
8. Zatorre RJ, Chen JL, Penhune VB. When the brain plays music: auditory-motor interactions in music perception and production. *Nat Rev Neurosci*. 2007;8(7):547-58.nrn2152 [pii] 10.1038/nrn2152
9. Hyde KL, Lerch J, Norton A, Forgeard M, Winner E, Evans AC, et al. Musical training shapes structural brain development. *J Neurosci*. 2009;29(10):3019-25.29/10/3019 [pii] 10.1523/JNEUROSCI.5118-08.2009
10. Lee DJ, Chen Y, Schlaug G. Corpus callosum: musician and gender effects. *Neuroreport*. 2003;14(2):205-9.10.1097/00001756-200302100-00009
11. Ozturk AH, Tascioglu B, Aktekin M, Kurtoglu Z, Erden I. Morphometric comparison of the human corpus callosum in professional musicians and non-musicians by using in vivo magnetic resonance imaging. *J Neuroradiol*. 2002;29(1):29-34.MDOI-JNR-03-2002-29-1-0150-9861-101019-ART6
12. Schlaug G, Jancke L, Huang Y, Steinmetz H. In vivo evidence of structural brain asymmetry in musicians. *Science*. 1995;267(5198):699-701.10.1126/science.7839149
13. Schneider P, Sluming V, Roberts N, Bleack S, Rupp A. Structural, functional, and perceptual differences in Heschl's gyrus and musical instrument preference. *Ann N Y Acad Sci*. 2005;1060:387-94.1060/1/387 [pii] 10.1196/annals.1360.033
14. Russell SM, Golfinos JG. Amusia following resection of a Heschl gyrus glioma. Case report. *J Neurosurg*. 2003;98(5):1109-12.10.3171/jns.2003.98.5.1109
15. Bass DI, Shurtleff H, Warner M, Knott D, Poliakov A, Friedman S, et al. Awake Mapping of the Auditory Cortex during Tumor Resection in an Aspiring Musical Performer: A Case Report. *Pediatr Neurosurg*. 2021;55(6):351-8.10.1159/000509328
16. Leonardi S, Cacciola A, De Luca R, Aragona B, Andronaco V, Milardi D, et al. The role of music therapy in rehabilitation: improving aphasia and beyond. *Int J Neurosci*. 2018;128(1):90-9.10.1080/00207454.2017.1353981

17. Roux FE, Borsa S, Démonet JF. “The mute who can sing”: A cortical stimulation study on singing - Clinical article. *J Neurosurg.* 2009;110(2):282-8.10.3171/2007.9.17565
18. Scerrati A, Labanti S, Lofrese G, Mongardi L, Cavallo MA, Ricciardi L, et al. Artists playing music while undergoing brain surgery: A look into the scientific evidence and the social media perspective. *Clin Neurol Neurosurg.* 2020;196:105911.S0303-8467(20)30254-710.1016/j.clineuro.2020.105911
19. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-12.10.1016/j.jclinepi.2009.06.005
20. 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(4):510-20.10.1002/jrsm.1279
21. Shapiro SSW, M.B. . An analysis of variance test for normality (complete samples). *Biometrika.* 1965; 52 (3–4): 591–611.10.1093/biomet/52.3-4.591
22. Goebel R, Esposito F, Formisano E. Analysis of functional image analysis contest (FIAC) data with brainvoyager QX: From single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. *Hum Brain Mapp.* 2006;27(5):392-401.10.1002/hbm.20249
23. Schulz R, Horstmann S, Jokeit H, Woermann FG, Ebner A. Epilepsy surgery in professional musicians: Subjective and objective reports of three cases. *Epilepsy Behav.* 2005;7(3):552-8.10.1016/j.yebeh.2005.07.009
24. Roux FE, Lubrano V, Lotterie JA, Giussani C, Pierroux C, Démonet JF. When “Abegg” is read and (“A, B, E, G, G”) is not: A cortical stimulation study of musical score reading. *J Neurosurg.* 2007;106(6):1017-27.10.3171/jns.2007.106.6.1017
25. Riva M, Casarotti A, Comi A, Pessina F, Bello L. Brain and Music: An Intraoperative Stimulation Mapping Study of a Professional Opera Singer. *World Neurosurg.* 2016;93:486-.10.1016/j.wneu.2016.06.130
26. Gayoso García S, Herbet G, Duffau H. Vivid Mental Imagery of Biomechanically Impossible Movements Elicited by Cortical Electrostimulation of the Central Region in an Awake Patient. *Stereotact Funct Neurosurg.* 2015;93(4):250-4.10.1159/000381987
27. Gasenzer ER, Kanat A, Neugebauer EAM. First Report of Awake Craniotomy of a Famous Musician: Suprasellar Tumor Surgery of Pianist Clara Haskil in 1942. *J Neurol Surg Part A Cent Eur Neurosurg.* 2017;78(3):260-8.10.1055/s-0036-1597895
28. Suarez RO, Golby A, Whalen S, Sato S, Theodore WH, Kufta CV, et al. Contributions to singing ability by the posterior portion of the superior temporal gyrus of the non-language-dominant hemisphere: First evidence from subdural cortical stimulation, Wada testing, and fMRI. *Cortex.* 2010;46(3):343-53.10.1016/j.cortex.2009.04.010
29. Gripp DA, Aguiar PHP, Maldaun MVC, Mathias LR, Peres TAV, Verst SM, et al. Individual task specific testing associated with intra-operative mri during awake craniotomy surgery for low grade gliomas to improve extent of resection and minimize morbidity. *Neuro-Oncology.* 2017;19:iii111.10.1093/neuonc/nox036
30. Herbet G, Lafargue G, Almairac F, Moritz-Gasser S, Bonnetblanc F, Duffau H. Disrupting the right pars opercularis with electrical stimulation frees the song: Case report. *J Neurosurg.* 2015;123(6):1401-4.10.3171/2014.12.Jns141829

31. Breshears JD, Southwell DG, Chang EF. Inhibition of manual movements at speech arrest sites in the posterior inferior frontal lobe. *Clin Neurosurgery*. 2019;85(3):E496-E501.10.1093/neuros/nyy592
32. Zhang J, Lu JF, Wu JS, Yao CJ, Zhuang DX, Qiu TM, et al. A unique case of Chinese language and music dissociation with tumor located in Broca's area: multimodal mapping for tumor resection and functional preservation. *Clin Neurol Neurosurg*. 2013;115(10):2230-3.10.1016/j.clineuro.2013.07.011
33. Katlowitz KA, Oya H, Howard MA, Greenlee JDW, Long MA. Paradoxical vocal changes in a trained singer by focally cooling the right superior temporal gyrus. *Cortex*. 2017;89:111-9.10.1016/j.cortex.2017.01.024
34. Dziedzic TA, Bala A, Podgórska A, Piwowarska J, Marchel A. Awake intraoperative mapping to identify cortical regions related to music performance: Technical note. *J Clin Neurosci*. 2020.10.1016/j.jocn.2020.11.027
35. Hegde S, Bharath RD, Rao MB, Shiva K, Arimappamagan A, Sinha S, et al. Preservation of cognitive and musical abilities of a musician following surgery for chronic drug-resistant temporal lobe epilepsy: a case report. *Neurocase*. 2016;22(6):512-7
36. Piai V, Vos SH, Idelberger R, Gans P, Doorduyn J, Ter Laan M. Awake Surgery for a Violin Player: Monitoring Motor and Music Performance, A Case Report. *Arch Clin Neuropsychol*. 2019;34(1):132-7.10.1093/arclin/acy009
37. Garcea FE, Chernoff BL, Diamond B, Lewis W, Sims MH, Tomlinson SB, et al. Direct Electrical Stimulation in the Human Brain Disrupts Melody Processing. *Curr Biol*. 2017;27(17):2684-91.10.1016/j.cub.2017.07.051
38. Scerrati A, Mongardi L, Cavallo MA, Labanti S, Simioni V, Ricciardi L, et al. Awake surgery for skills preservation during a sensory area tumor resection in a clarinet player. *Acta Neurol Belg*. 2020.10.1007/s13760-020-01368-5
39. Nunes-Silva M, Haase VG. Montreal Battery of Evaluation of Amusia: Validity evidence and norms for adolescents in Belo Horizonte, Minas Gerais, Brazil. *Dement Neuropsychol*. 2012;6(4):244-52.10.1590/S1980-57642012DN06040008
40. Reitan RM WD. The seashore rhythm test and brain functions. *Clinical Neuropsychologist*. 1989/01/01;3(1):70-8.
41. Harrison PMC, Mullensiefen D. Development and Validation of the Computerised Adaptive Beat Alignment Test (CA-BAT). *Sci Rep*. 2018;8(1):12395.10.1038/s41598-018-30318-8.10.1038/s41598-018-30318-8
42. Hall S KS, Sadek A-R, et al. Awake craniotomy for tumour resection: The safety and feasibility of a simple technique. *Interdisciplinary Neurosurgery* 2021;06/01;24:101070.
43. Kanno A, Mikuni N. Evaluation of Language Function under Awake Craniotomy. *Neurol Med Chir (Tokyo)*. 2015;55(5):367-73.10.2176/nmc.ra.2014-0395
44. Montori VM, Smieja M, Guyatt GH. Publication bias: a brief review for clinicians. *Mayo Clin Proc*. 2000;75(12):1284-8.S0025-6196(11)63030-9 [pii]10.4065/75.12.1284
45. Bever TG, Chiarello RJ. Cerebral dominance in musicians and nonmusicians. *Science*. 1974;185(4150):537-9.10.1126/science.185.4150.537
46. Taylor J. *Selected Writings of John Highlings Jackson*. Hodder & Stoughton, London. 1932

47. Angulo-Perkins A, Aube W, Peretz I, Barrios FA, Armony JL, Concha L. Music listening engages specific cortical regions within the temporal lobes: differences between musicians and non-musicians. *Cortex*. 2014;59:126-37.S0010-9452(14)00244-5 [pii] 10.1016/j.cortex.2014.07.013
48. Heffner CC, Slevc LR. Prosodic Structure as a Parallel to Musical Structure. *Front Psychol*. 2015;6:1962.10.3389/fpsyg.2015.01962
49. Patel AD. Language, music, syntax and the brain. *Nat Neurosci*. 2003;6(7):674-81.10.1038/nn1082nn1082
50. DiGiuseppi J, Tadi P. Neuroanatomy, Postcentral Gyrus. 2021.(Bookversion) NBK549825
51. L M. Casuistische Beiträge zur Hirnchirurgie und Hirnlokalisation. *Msschr Psychiat Neurol* 4:369, 1898

Table 1: Demographic patient data

Authors	Case code	Gender ¹	Age	Handness ²	Disease ³	Side	Disease location ⁴	Professional ⁵	Instrument
Bass, 2020	B	F	19	R-H	Glioneural	Right	Temporal	No	Singer
Dziedziec, 2021	D	F	19	R-H	Cavernous Malformation	Left	Temporal	No	Pianist
Garcea, 2017	G	M	26	R-H	Tumour	Right	STG/MTG	Yes	Saxophonist
Hegde, 2016	H	M	16	R-H	Epilepsy	Right	MTG	Yes	Violinist and Singer
Katlowitz, 2017	K	M	41	R-H	Epilepsy	Right	Temporal	Yes	Singer
Leonard, 2019	L	M	25	R-H	Astrocytoma	Left	Insula	Yes	Guitarist
Piai, 2019	P	NR ⁶	35 – 40	L-H	Oligodendroglioma	Left	SMA	Yes	Violinist
Roux, 2009 (1)	R1	M	37 – 68	L-H	Tumour	Right	Frontal	No	Singer
Roux, 2009 (2)	R2	M	37 – 68	R-H	Tumour	Right	Frontal	No	Singer
Roux, 2009 (3)	R3	M	70	R-H	Metastasis	Right	Frontal	No	Singer
Roux, 2009 (4)	R4	M	37 – 68	R-H	Tumour	Left	Frontal	No	Singer
Roux, 2009 (5)	R5	M	37	R-H	Astrocytoma	Left	SMA	No	Singer
Scerrati, 2020	S	F	52	R-H	GBM	Right	Parietal Rolandic	Yes	Clarinetist
Zhang, 2013	Z	F	19	R-H	GBM	Left	MFG	No	Singer

1. M; male, F; female 2. R-H; Right-handed, L-H; Left-handed 3. GBM: Glioblastoma Multiforme 4. STG; Superior Temporal Gyrus, MTG; Middle Temporal Gyrus, SMA; Supplementary Motor Area 5. Level of musicality (i.e. professional vs. amateur) was adopted from the included studies 6. Not reported

Table 2. Intra-operative mapping during music tasks

Authors	Method ¹	Type music task ²	Additional mapping ³	Location ³	Music disruption	Type of disruption	Combined vs isolated
Bass, 2020	Sing	Production and perception	-	Right pSTG	No	-	-
Dziedzic, 2021	Keyboard	Production	Motor + Speech / Language	Left posterior MTG + supramarginal gyrus	Yes	Music arrest	Isolated
Garcea, 2017	Sing	Production and perception	Speech / Language	1) Right STG 2) Right MTG	1) Yes 2) No	1) Music arrest + pitch, rhythm and contour errors 2) No errors	1) Isolated 2) -
Hegde, 2016	Sing	Production, perception and reading	-	Right STG	No	-	-
Katlowitz, 2017	Sing	Production	Motor and Speech / Language	1) Right precentral gyrus 2) Right pSTG	Yes	1) Music arrest 2) No errors	1) Combined with speech / language 2) -
Leonard, 2019	Guitar	Production	Motor and Speech / Language	1) left lateral frontal / parietal 2) left ventral pre-central gyrus	1) No 2) Yes	1) No errors 2) Music arrest	1) - 2) Combined with speech / language
Piai, 2019	Violin*	Production	Motor and Speech / Language	Left SMA	No	-	-
Roux, 2009 (1)	Sing	Production	Speech / Language	1) Left precentral gyrus 2) Left Broca region 3) Left opercular ramus 4) Left supramarginal gyrus	1) Yes 2) No 3) No 4) No	1) Articulatory 2) No errors 3) No errors 4) No errors	1) Combined with speech / language 2) - 3) - 4) -
Roux, 2009 (2)	Sing	Production	Speech / Language	1) Left precentral gyrus 2) Left Broca region 3) Left opercular ramus	1) Yes 2) No 3) No	1) Articulatory 2) No errors 3) No errors	1) Isolated 2) - 3) -

Authors	Method ¹	Type music task ²	Additional mapping ³	Location ³	Music disruption	Type of disruption	Combined vs isolated
Roux, 2009 (3)	Sing	Production	Motor and Speech / Language	1) Right precentral gyrus 2) Right middle frontal gyrus	1) Yes 2) Yes	1) Articulatory 2) Music arrest	1) Isolated 2) Isolated
Roux, 2009 (4)	Sing	Production	Speech / Language	1) Right precentral gyrus 2) Right supramarginal, middle or inferior frontal gyrus	1) Yes 2) No	1) Articulatory 2) No errors	1) Isolated 2) -
Roux, 2009 (5)	Sing	Production	Speech / Language	1) Right precentral gyrus 2) Right supramarginal, middle or inferior frontal gyrus	1) Yes 2) No	1) Loss melodic contour 2) No errors	1) Combined with speech / language 2) -
Sceratti, 2020	Clarinet	Production	Motor	Right postcentral gyrus	Yes	Music arrest	Combined with motor
Zhang, 2013	Sing	Production	Speech / Language	Left middle frontal gyrus	Yes	Music arrest	Isolated

1. Music tasks during mapping. 2. Production; producing music / playing instrument / active singing, Perception; listening to music. Reading; reading music notes 2. Explicit reporting of other non-music tasks 3. Brain regions mapped during music tasks, pSTG; posterior superior temporal, MTC; Medial Temporal Gyrus, SMA; Supplementary Motor Area *Mapping not successful due to stimulation-induced seizure.

Table 3. Peri-operative course of musical function

Authors	Pre-operative assessment			Post-operative assessment		
	Assessed	Method ¹	Standardized Outcome	Localisation ²	Assessed Method ¹	Standardized Outcome
Bass, 2020	Yes	1. fMRI with passive (A) and active (B) music imagination 2. Neuropsychological rhythm and tonal discrimination 3. Rhythm, tone and pitch test by music therapist	No	1. (A) Right STG (B) and Left STG 2. - 3. -	Yes 1. Pitch recognition 2. Playing guitar 3. SRT	1) consistent with baseline 2) "Able to play" 3) Within normal range
Dziedzic, 2021	No	-	-	-	Yes 1. Playing piano	"Able to play"
Garcea, 2017	Yes	1. fMRI with (A) passive piano listening and (B) humming 2. MBEA	Yes	1. (A) lateral surface right STG and (B) right posterior Sylvian fissure 2. -	Yes 1) Play saxophone upon closure dura 2) MBEA	1) "flawless" 2) 175 / 180 (97%)
Hegde, 2016	Yes	1. MBEA 2. SRT 3. BAT 4. Song recognition* 5. fMRI while listening familiar (Indian) music	Yes	1. 88 – 100% 2. 100% 3. 100% 4. No deficit 5. Voxel activity	Yes 1. MBEA 2. SRT 3. BAT 4. Song recognition 5. fMRI in rest	1. 90 – 100% 2. 100% 3. 100% 4. "No adverse changes compared to pre-operative" 5. Enhanced connectivity IFG, MTG, ITG

Pre-operative assessment				Post-operative assessment		
Authors	Assessed Method ¹	Standardized Outcome	Localisation ²	Assessed Method ¹	Standardized Outcome	Outcome
Katlowitz, 2017	No	-	-	No	-	-
Leonard, 2019	No	-	-	No	-	-
Piai, 2019	Yes	1. Violin / keyboard: major scale and arpeggio 2. Solfege 3. Two easy pieces 4. Reading difficult piece 5. play familiar but complex piece 6. fMRI: complex motor tasks**	1. No deficit 2. No deficit 3. No deficit 4. No deficit 5. No deficit 6. No deficit	1. - 2. - 3. - 4. - 5. - 6. expected pre-/postcentral gyrus	Yes - - - - - No	- - - - - - "Patient resumed playing the violin with orchestra, assuming preservation of musical function"
Roux, 2009 (1)	Yes	1. "basic testing"	No	No	1. -	-
Roux, 2009 (2)	Yes	1. "basic testing"	No	No	1. -	-
Roux, 2009 (3)	Yes	1. "basic testing"	No	No	1. -	-
Roux, 2009 (4)	Yes	1. "basic testing"	No	No	1. -	-
Roux, 2009 (5)	Yes	1. "basic testing"	No	No	1. -	-
Sceratti, 2020	No	-	-	Yes	-	No
						"Resumed playing clarinet in the next 10 months after surgery"
Zhang, 2013	Yes	1. MBEA 2. fMRI (A) humming familiar popular Chinese lyrics and (B) reading notations	Yes	Yes	1. MBEA 2. Left MFG and SMA	Yes 1. 99%

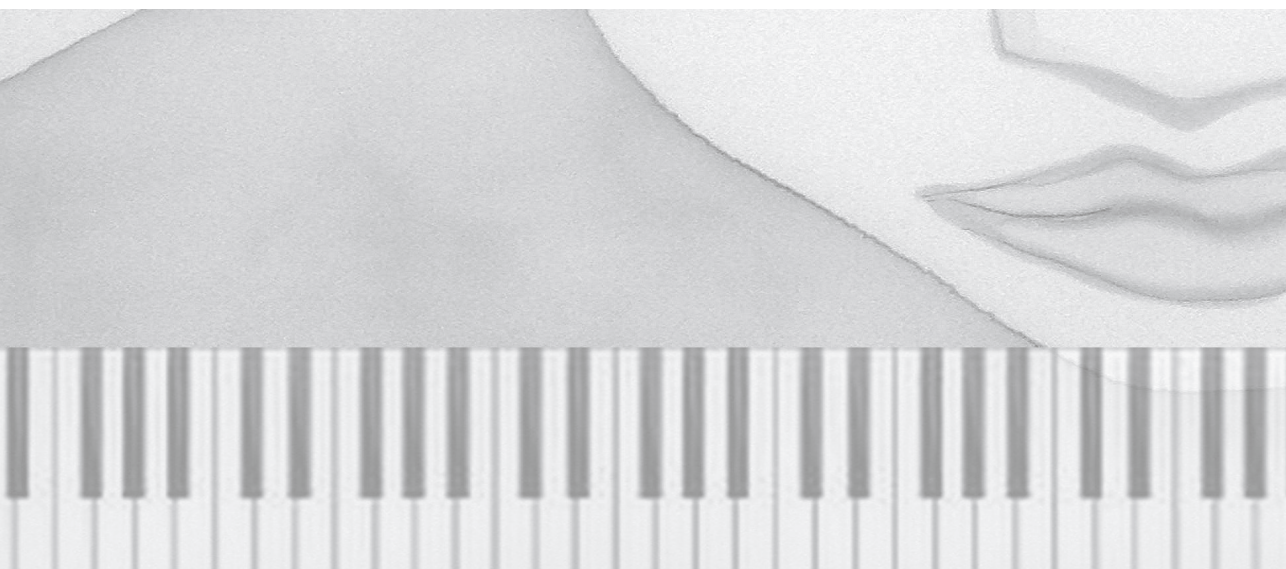
1. fMRI: functional magnetic resonance imaging, MBEA: Montreal Battery Evaluation of Amusia, SRT: Seashore Rhythm Test, BAT: Beat Alignment Test 2. Pre-operative music localization determination, STG: Superior Temporal Gyrus, MFG: Medial Frontal Gyrus, SMA: Supplementary Motor Area **No music tasks were conducted during the fMRI



PART III

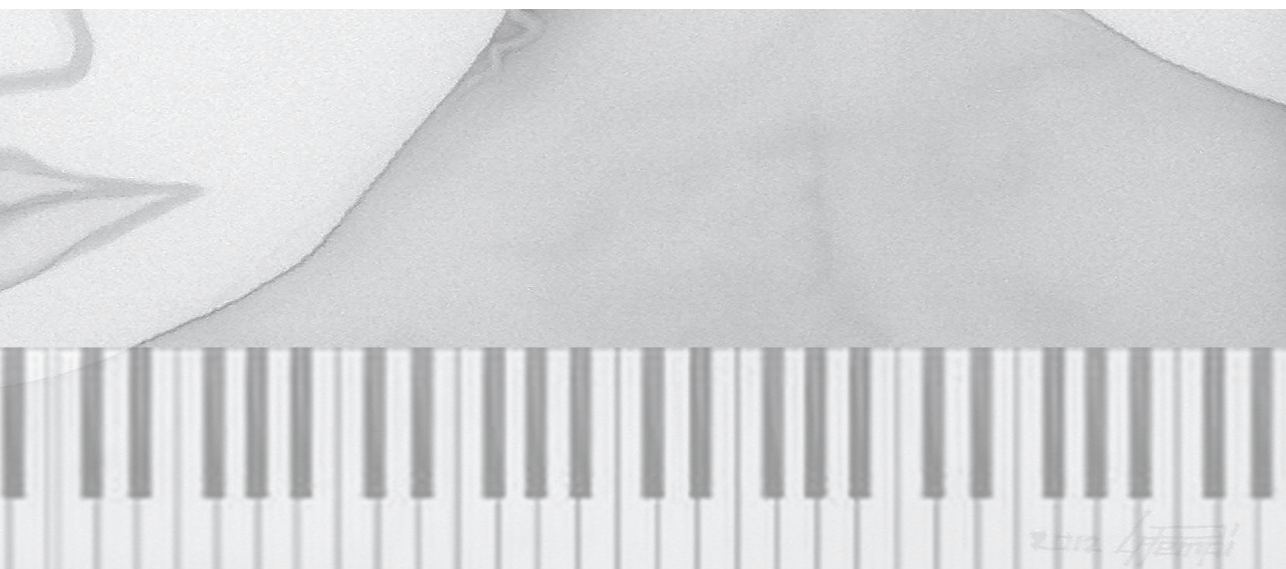
General discussion
and summary





CHAPTER 9

General discussion



This thesis aims to evaluate the effects of music and musicality on the post-operative neurosurgical course. In this general discussion, the definition and impact of delirium following brain surgery will be discussed. Subsequently, the studied effects of music on the prevention of delirium and its hypothesized mechanism will be evaluated. Moreover, we elaborate on musicality as a brain function with respect to intra-operative mapping possibilities but also as a protective factor for post-operative language decline after brain tumor surgery. The discussion is concluded with prospects for future scientific efforts.

The definition and impact of delirium on recovery following brain surgery

The recovery of a patient after brain surgery can be negatively influenced by delirium. Delirium is a psychiatric disease, defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and its diagnosis currently relies on clinical evaluation of experts in the field being a psychiatrist or geriatrician. To increase the recognition of delirium during hospital stay, a variety of delirium diagnostic screening tools have been developed, which can also be assessed by other healthcare workers. Delirium is defined in the latest DSM as “an acute disturbance in attention and cognition which is not better explained by another neurocognitive disorder such as for example dementia”. These criteria overlap with certain commonly occurring symptoms specific to the neurosurgical patient, which also may cause disturbances in attention and or cognition. The diagnostic accuracy of delirium screening tools in this population is therefore questionable. In our review it was not possible to investigate which delirium assessment tool was most suitable for the neurosurgical population, since diagnostic accuracy of the screening tools was not validated against the DSM-criteria in any study. The Confusion Assessment Method (CAM) was mostly used as a screening tool, which is considered a reliable assessment instrument for delirium in postsurgical patients. The second most used assessment tool in this review was the ICDSC, a tool primarily developed for the Intensive Care Unit (ICU). A considerable proportion of the studies in our review were retrospective studies using non-validated tools describing the ‘occurrence of hallucinations’ or ‘episodes of confusion’, which was all based on ‘positive’ symptoms. These tools risk missing delirium cases, as these assessments might fail to recognizing delirium, especially the hypoactive type which compromises 26–58% of delirium in this population. (1-11) Not only did we observe a

variation in type of screening tools, but also on frequency (one to three times per day) and follow-up duration (24 hours to 30 days postoperatively). Our analyses indicate that future studies should assess delirium at several moments per day and within at least the first five post-operative days.

The fact that the symptoms of delirium overlap with the primary neurological symptoms after brain surgery, stresses the importance of identifying delirium in this population. What is the use of investigating delirium-like symptoms, if they are temporary and perhaps inherent to the post-neurosurgical course? We addressed these issues by comparing patients with and without delirium presentation, as defined by an increased Delirium Observation Screening Score (DOSS), which is a delirium screening tool validated in the Dutch population and currently common practice at our department. By analyzing the largest retrospective cohort until present on this topic, we found an incidence of 19.3%, which was in line with the pooled estimate of our systematic review. (12) Onset of delirium did not independently correlate with hospitalization length or mortality in our cohort after controlling for gender, age and obesity. Although many studies suggest an increased mortality in patients with delirium, this is not found when controlling for pre-specified confounders in either the neurosurgical or non-neurosurgical literature. (12, 13) However, we found that patients with delirium were more often discharged towards residential care instead of home and were more often admitted to the ICU indicating a negative effect on their recovery. The fact that these patients are more often discharged towards residential care implies that delirium patients are incapable of sufficient self-care, meaning that they mostly have Karnofsky Performance Scales (KPS) of 60 or lower. In our clinic and many others a KPS of at least 70 is required to be indicated for adjuvant chemotherapy in case of high grade glioma or brain metastases, as literature indicates that the effect of adjuvant chemotherapy is minimal for patients with lower KPS. (14) Hence, onset of delirium therefore independently may lower the chance of receiving life prolonging therapy, although this did not affect the overall survival as analyzed from our retrospective cohort data.

Previous mentioned numbers suggesting high impact of delirium in neurosurgery, motivated us to search for effective preventive therapies to lower the incidence of delirium and improve patients' outcome following brain surgery.

Delirium after brain surgery: predicting onset and therapeutic targets

Current management of post-operative delirium (POD) is focused on pre-operative counseling and preventive therapies, as currently no effective treatment exists for POD in any surgical population. (15) Hence, predicting delirium and shedding light on which factors contribute to this clinical presentation could aid in the pre-operative prevention, decision-making, in informing the patient on the expected postoperative course and create targets for future intervention studies. (16) Our prediction models were able to correctly identify which patients develop POD in 65 – 78% of the cases, but these results should be validated on an external cohort to assess its true predictive value. Risk factors included older age and memory problems which was not surprising as older age with degeneration associated neuro-inflammatory processes, is associated with less cognitive resilience. (17) Moreover, admission from residential care and needing daily assistance before admission were independent risk factors for delirium. This was expected, as early mobilization has proven to decrease the onset of delirium on the ICU and is currently an element in advised multi-component strategies. (18) However, these risk factors are non-modifiable but still of interest as the treating physician could take this into account when informing the patient on its expected post-operative course. Moreover, the physician could take preventive measures, targeted at modifiable risk factors, in patients prone to the development of delirium.

Modifiable risk factors included use of dexamethasone, which is known to cause neuropsychiatric side effects. On the other hand, steroid-induced psychiatric symptoms after craniotomy have only been described in case reports and no cohort studies had supported this assertion until present. (19, 20) Also poor nutritional status, represented as low pre-operative potassium and lower body mass index, predicted higher chance of delirium and could be a potential preventive target. (21) Furthermore, the administration of post-operative use of opioids was independently associated with onset of POD. This could be attributed to the anticholinergic properties of morphine itself or opioid administration could be an epiphenomenon of more postoperative pain. Just removing the opioids may not fit, as an increase in pain also contributes to delirium development in non-neurosurgical populations. (22) Therefore, other analgesic treatments, such as local scalp-blocks or non-pharmacologic alternatives, may be considered for the prevention of post-operative delirium after intracranial surgery. (23, 24)

Music to endure pain in an experimental setting

Our Erasmus MC affiliated research group (“Muziek als Medicijn”) found listening to recorded music to be effective in reducing preoperative anxiety, postoperative pain and its stress response induced by surgery. (25) Moreover, lower doses of opioids and sedatives were required when music around surgery was applied (not in this thesis) (26) However, clinical studies hinder a firm conclusion on the quantitative analgesic effect of music. Also, it is unclear whether this decrease in pain perception leads to better endurance, and by which underlying mechanisms. This was tackled in an experimental study, as the amount of pain could be controlled. The “effect of recorded music on pain endurance (CRESCENDO)-trial” was a two-armed randomized controlled trial, comparing preferred recorded music with rest, performed on healthy participants which all received increasing electric stimuli while blinded for the amperage outcome. Although, the effect of listening to preferred music on pain endurance was not statistically significant in our intention-to-treat analysis, we did find an effect after excluding those participants with a high skin impedance. This effect on pain endurance could have been attributed to sympathetic-adrenomedullary axis activation, as an increased activation by music on heart rate variability (HRV) was found. Moreover, salivary alpha-amylase (sAA) values increased in the control group, as opposed to the music group, which normalized over time. Our results should be interpreted with caution as they did not reach significance, but do support sAA to be a potential objective non-invasive tool for pain assessments within the field of music. (27) Our experimental model provides a solid effect of music on pain endurance, as the outcome was objective and the patients were blinded for the primary outcome. Clarifying the quantitative analgesic effect of music and underlying mechanisms, such as in the CRESCENDO-trial, might expand the indications for music around certain painful procedures in hospital care.

Music to improve delirium after brain surgery

As pain, anxiety and stress promote the occurrence of delirium, we were interested to study the effect of music on the occurrence of delirium in our neurosurgical patients. Moreover, we suspected good feasibility of this intervention, as recorded music was described as an easy to apply intervention. The Music to prevent deliriUm during neuroSurgerY Clinical-trial (MUSYC) was a single center, randomized trial that compared standard of clinical care with recorded music administered before, during

and after craniotomy including 189 patients in 2 arms. We found a significant decrease of post-operative delirium, defined with DOSS, in the treatment arm receiving perioperative music. A recent published systematic review conducted a meta-analysis on the preventive effect of music on delirium with six studies and found a relative reduction (RR; 0.52) similar to ours (RR; 0.48). (28) Our results fit well within the current literature and support the implementation of music for the prevention of delirium within the neurosurgical population. Although a similar trend was found, significance of results was not achieved between the music and control groups on the onset of delirium, when assessed by the DSM-5 criteria. One of the reasons for not reaching statistical significance in our study may have been under powering, as suspicion of delirium after increased DOSS was not confirmed by the psychiatrist in almost half of the cases, resulting in a lower incidence of delirium diagnosis in our patient cohort than expected on forehand. Our sample size calculation was based on other neurosurgical studies evaluating incidence of delirium solely assessed by increased scores on delirium screening tools such as the CAM(-ICU), ICDSC, NEECHAM, Nu-DESC or DOSS. (12) In settings such as the general medical or surgical populations, diagnostic usage of these tools may be justified, as high diagnostic accuracy rates are reported.(29) However, it is unclear whether this can be adopted to our complicated patient population, as a positive screen for delirium may be confounded by underlying neurological disease symptoms or its sequelae (e.g., oedema, vasospasm, seizures, rebleeding, ischemia).

Music activates the mesolimbic system, besides the auditory cortex, resulting in an increase in parasympathetic activity. (30) As causes of delirium rely on neuro-inflammatory reactions within the brain we propose that this parasympathetic, vagal mediated anti-inflammatory response, may be a candidate pathway on which music has preventive effects for delirium. (17, 31) Although we did not assess inflammatory cytokine levels in our study, music very likely induced parasympathetic nervous activation. This was reflected by the significant increase in heart rate variability (HRV) during the first pre-operative music session, confirming the HRV results from the CRESCENDO-trial. This parasympathetic activation may have induced a sedative-sparing effect, subsequently increasing cortical engagement and cognitive processing. (32) This sedative-sparing effect was not found in the MUSYC-trial, but a deeper level of sedation level during neurosurgery in the music group was achieved with standardized sedation dosages.

We reported high adherence to the music intervention before surgery. Patients in our study reported high importance of music in daily life, high number of hours listening to music in daily life and the willingness to receive music intervention in case of future surgeries. These are considered important facilitators and should be taken into consideration for future music implementation. (33) However, after surgery the patients were less adherent to the music intervention. They might have felt less urgency to listen to the music, after the procedure was performed. Lack of the knowledge of the intervention is considered a barrier for implementation. Informing patients, substantiated by the results from efficacy studies such as the MUSYC-trial, may aid in the implementation in the neurosurgical population.

In conclusion, our results support the efficacy of music in preventing delirium after craniotomy, as found with delirium detection by the DOSS but not with DSM criteria. This effect of music was substantiated by the positive effect of music on pre-operative autonomic tone and depth of anesthesia. What are the implications with respect to patient recovery? In line with our retrospective cohort this should lead to less discharge towards residential care and in theory more patients fit enough to tolerate the life prolonging adjuvant therapy. The long-term effects of music in brain surgery after discharge are currently being analyzed.

Preserving musicality and language function during awake craniotomy

To better secure brain functions while resecting more tumor tissue, neurosurgeons may use ‘mapping’ techniques, such as the awake craniotomy to preserve functions important for patients’ daily life: an important function being language.

There is currently some suggestion in the literature that musically training-related brain changes might have a beneficial effect on language recovery following awake glioma surgery. (34) We assessed the background of musical training in patients in a cohort from two neurosurgical centers and compared this with the pre- and post-operative language scores. We found less language impairment in the musically trained patients on the language tasks assessing pitch and sound, referred to as phonology. It is known that musicians detect subtle variations of pitch within musical phrases faster, and more accurately than non-musicians. (35-37) This seemed plausible as phonology shares a common hierarchical structure between speaking and singing. Moreover, our

results support the hypothesis of musicality induced contralateral compensation in the (sub-) acute phase through the corpus callosum as we found a correlative trend between the increase of the volume of the corpus callosum, number of hours of musical training and extent of postoperative language recovery. We found a stronger effect in instrumentalists compared to singing musicians, which could have been attributed to their intense bimanual motor training resulting in more interhemispheric communication and better language scores.

We addressed musicality as a sole brain function and whether it can be protected during awake craniotomy by schematically presenting an overview of all the different methods, mapped brain regions of interest and the peri-operative course as mentioned in the current literature. We found that mapping music during awake craniotomy is feasible, as almost all included patients reported successful mapping while performing different musical tasks during awake craniotomy. (38) Moreover, isolated music disruption during electric stimulation in the temporal and frontal regions was found with preserved post-operative musical function, suggesting additional value of mapping music in these structures. We do acknowledge that, in the literature, we did not find any case reports describing amusia after awake craniotomy without music tasks which could be a counter argument for adding music mapping to language/motor tasks during awake craniotomy. Clear conclusions are challenging, since a control group is difficult to add in this type of research. However, literature describes post-operative amusia in cases after operating under general surgery on the right frontal and temporal lobe which confirms our localization with isolated music disruption. (39, 40) These arguments justify addition of music tasks, as no complications related to these tasks were found, and quality of life may have been preserved for these patients.

Future scientific efforts and perspectives

Our prediction model for delirium should be validated on an external cohort to assess its true predictive value. Other modifiable risk factors could be targeted for decreasing delirium incidence such as lowering dexamethasone dosages. As dexamethasone is applied to attenuate neurologic deficit, the advantage of delirium should be compared with the disadvantage of impeding dexamethasone administration. Pre-operative potassium and improving nutritional status could be targeted, which may be challenging as the indication for most brain operations are within a couple of weeks. Prospective studies need to assess the long-term implications of delirium, as

defined with DOSS and DSM, after discharge to underpin the true clinical relevance of delirium in the neurosurgical cohort.

The CRESCENDO-trial should be replicated with a more comprehensive design framework using our pain and music model, preferably with a third arm with non-music auditory signals, to assess the true analgesic effect of music stratified per type of genre. The measured underlying effects could have been more comprehensive as we studied the effects of HPA and SAM axes, and hypothesized activation of the limbic system, but did not confirm this with an electrophysiology study. Therefore, EEG and neurological imaging studies could be added to this model to assess the emotional-inducing effect of music evoked from the (meso-)limbic system.

The results of the MUSYC-trial are promising, as a reduction of delirium was achieved with music when defined with the DOSS. Our results fit well in current literature and support the implementation of music for the prevention of delirium within the neurosurgical population. Further efficacy studies are needed to analyze which subgroups mostly benefit from music and what optimal dosage needs to be applied to prevent delirium after craniotomy. Although the pre-operative adherence to music listening was high, this declined after surgery which should be taken into account, when considering for implementation in the neurosurgical population. Informing patients, substantiated by the results from efficacy studies such as the MUSYC-trial, may aid in the implementation in the neurosurgical population. The results of our study were limited by the issue on delirium definition, as the beneficial effect of music was not statistically confirmed in case of handling the DSM-5 diagnosis. The definition of delirium should be re-defined within the neurological population to create clear ‘Gold Standards’ for diagnostic studies of screening instruments. Furthermore, future studies should validate the current existing screening tools as certain symptoms specific to the neurosurgical patient overlap with diagnostic criteria of delirium.

To confirm our findings on the effects of musicality on post-operative language recovery, larger sample sizes are needed, which enables to correct for the confounding variables described in this study. Second, imaging techniques such as diffuse tensor imaging (DTI) and functional MRI (i.e. with MIT protocol) before surgery and after surgery could be linked to the course of postoperative language recovery to identify the role of contra- and ipsilateral compensation over time. Third, future language rehabilitation could be targeted at the phonologic level in glioma patients with

musical background. Last, quality of life questionnaires may be added to assess the true impact of subtle language differences between musical and non-musical patients after glioma surgery.

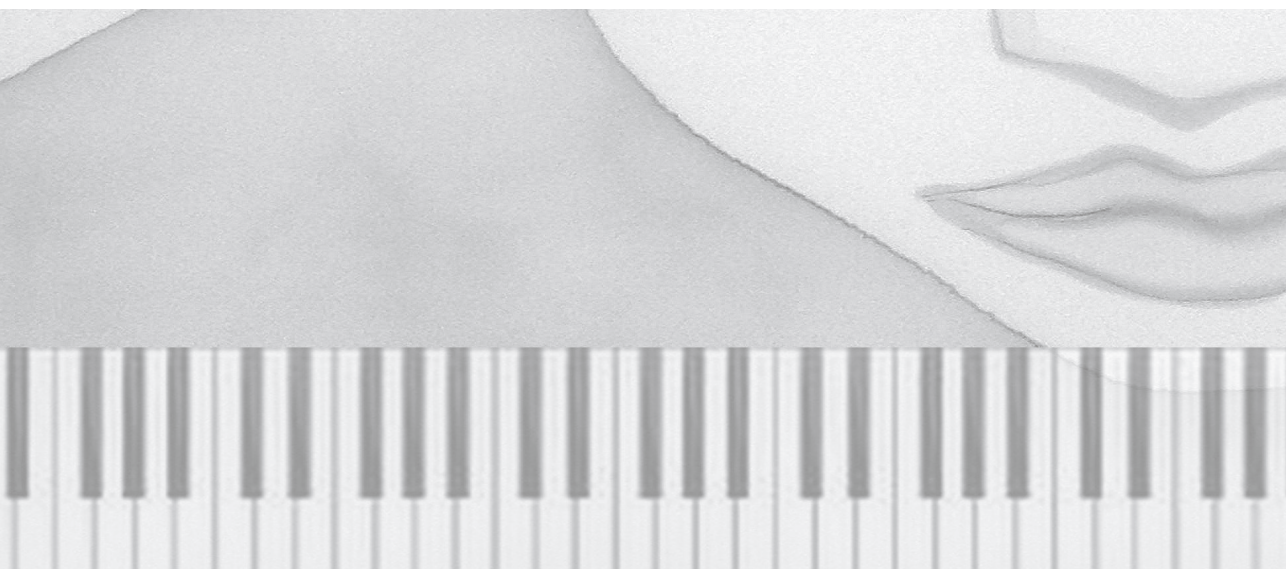
To improve insights on the feasibility of musical performance during awake craniotomy, unsuccessful case reports should be published. Secondly, although intra-operative music tasks may vary, disruption of music should always be compared with speech/language and/or motor tasks to understand the origin (motor, speech/language or merely music) of the deficit. Third, musicality should also be assessed with a standardized objective scoring form before and after surgery allowing comparison between several moments and studies. Last, pre-operative fMRI with musicality related tasks is desirable to allow for better interpretation of the intra-operative findings.

References

1. Flanigan PM, Jahangiri A, Kuang R, Truong A, Choi S, Chou A, et al. Developing an Algorithm for Optimizing Care of Elderly Patients With Glioblastoma. *Neurosurgery*. 2018;82(1):64-75.
2. Wang CM, Huang HW, Wang YM, He X, Sun XM, Zhou YM, et al. Incidence and risk factors of postoperative delirium in patients admitted to the ICU after elective intracranial surgery: A prospective cohort study. *Eur J Anaesthesiol*. 2020;37(1):14-24.
3. Wang J, Ji Y, Wang N, Chen W, Bao Y, Qin Q, et al. Risk factors for the incidence of delirium in cerebrovascular patients in a Neurosurgery Intensive Care Unit: A prospective study. *J Clin Nurs*. 2017;27(1-2):407-15.
4. Flanigan PM, Jahangiri A, Weinstein D, Dayani F, Chandra A, Kanungo I, et al. Postoperative Delirium in Glioblastoma Patients: Risk Factors and Prognostic Implications. *Neurosurgery*. 2018;83(6):1161-72.
5. Brown EG, Josephson SA, Anderson N, Reid M, Lee M, Douglas VC. Evaluation of a multicomponent pathway to address inpatient delirium on a neurosciences ward. *BMC Health Serv Res*. 2018;18(1):106.
6. Carlson JD, Neumiller JJ, Swain LDW, Mark J, McLeod P, Hirschauer J. Postoperative delirium in Parkinson's disease patients following deep brain stimulation surgery. *J Clin Neurosci*. 2014;21(7):1192-5.
7. Lange M, Zech N, Seemann M, Janzen A, Halbing D, Zeman F, et al. Anesthesiologic regimen and intraoperative delirium in deep brain stimulation surgery for Parkinson's disease. *J Neurol Sci*. 2015;355(1-2):168-73.
8. Maneewong J, Maneeton B, Maneeton N, Vaniyapong T, Traisathit P, Sricharoen N, et al. Delirium after a traumatic brain injury: predictors and symptom patterns. *Neuropsychiatr Dis Treat*. 2017;13(1):459-65.
9. Ogasawara K, Ogawa A, Okuguchi T, Kobayashi M, Suzuki M, Yoshimoto T, et al. Postoperative hyperperfusion syndrome in elderly patients with chronic subdural hematoma. *Surg Neurol*. 2000;54(2):155-9.
10. Oh YS, Kim DW, Chun HJ, Yi HJ. Incidence and risk factors of acute postoperative delirium in geriatric neurosurgical patients. *J Korean Neurosurg Soc*. 2008;43(3):143-8.
11. Tanaka M, Tani N, Maruo T, Oshino S, Hosomi K, Saitoh Y, et al. Risk Factors for Postoperative Delirium After Deep Brain Stimulation Surgery for Parkinson Disease. *World neurosurgery*. 2018;114:518-23.
12. Kappen PR, Kakar E, Dirven CMF, van der Jagt M, Klimek M, Osse RJ, et al. Delirium in neurosurgery: a systematic review and meta-analysis. *Neurosurg Rev*. 2021;45(1):329-41.
13. Hamilton GM, Wheeler K, Di Michele J, Lalu MM, McIsaac DI. A Systematic Review and Meta-analysis Examining the Impact of Incident Postoperative Delirium on Mortality. *Anesthesiology*. 2017;127(1):78-88.
14. Golden DW, Lamborn KR, McDermott MW, Kunwar S, Wara WM, Nakamura JL, et al. Prognostic factors and grading systems for overall survival in patients treated with radiosurgery for brain metastases: variation by primary site. *J Neurosurg*. 2008;109:77-86.
15. Siddiqi N, Stockdale R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. *Cochrane Database Syst Rev*. 2007(2):CD005563.

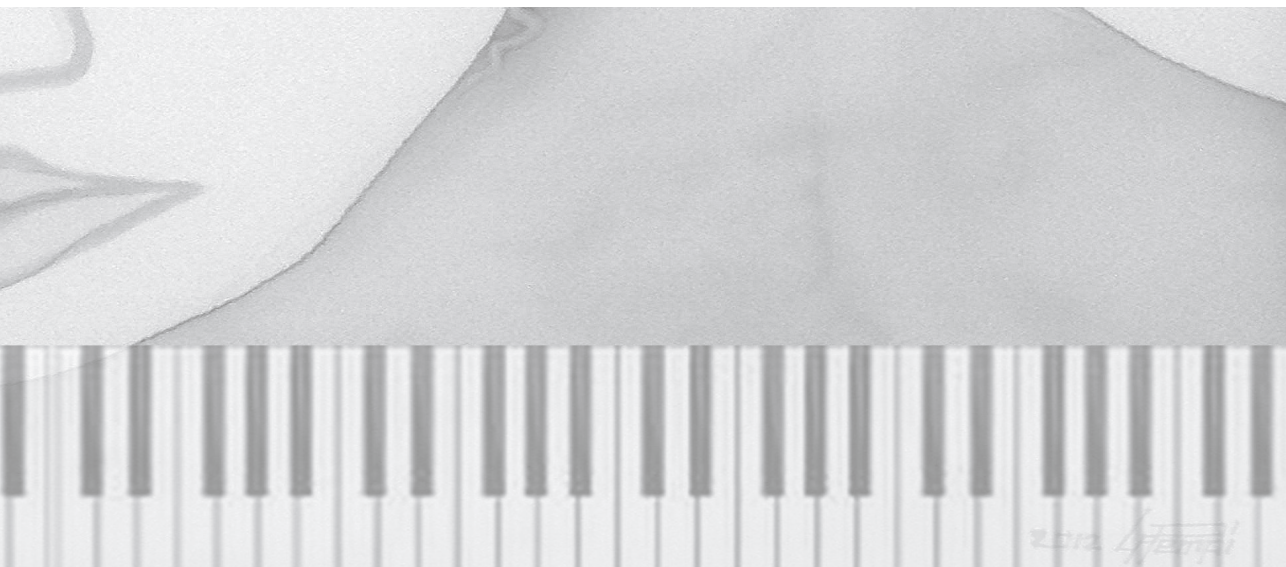
16. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *Int J Geriatr Psychiatry*. 2018;33(11):1428-57.
17. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry*. 2013;21(12):1190-222.
18. Hsieh TT, Yue J, Oh E, Puelle M, Dowal S, Trivison T, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA Intern Med*. 2015;175(4):512-20.
19. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. *J Affect Disord*. 1983;5(4):319-32.
20. Marcantonio ER, Juarez G, Goldman L, Mangione CM, Ludwig LE, Lind L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA*. 1994;272(19):1518-22.
21. Setti SE, Littlefield AM, Johnson SW, Kohman RA. Diet-induced obesity attenuates endotoxin-induced cognitive deficits. *Physiol Behav*. 2015;141:1-8.
22. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: the importance of pain and pain management. *Anesth Analg*. 2006;102(4):1267-73.
23. Swart LM, van der Zanden V, Spies PE, de Rooij SE, van Munster BC. The Comparative Risk of Delirium with Different Opioids: A Systematic Review. *Drugs Aging*. 2017;34(6):437-43.
24. Darmawikarta D, Sourour M, Couban R, Kamath S, Reddy KK, Shanthanna H. Opioid-Free Analgesia for Supratentorial Craniotomies: A Systematic Review. *Can J Neurol Sci*. 2019;46(4):415-22.
25. Kuhlmann AYR, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. Meta-analysis evaluating music interventions for anxiety and pain in surgery. *Br J Surg*. 2018;105(7):773-83.
26. Fu VX OP, Klimek M, Verhofstad MHJ, Jeekel J. The effect of perioperative music on medication requirement and hospital length of stay: a meta-analysis. *Annals of Surgery*. July 2019;272(6):961 - 72.
27. Linnemann A, Ditzen B, Strahler J, Doerr JM, Nater UM. Music listening as a means of stress reduction in daily life. *Psychoneuroendocrinology*. 2015;60:82-90.
28. Golubovic J, Neerland BE, Aune D, Baker FA. Music Interventions and Delirium in Adults: A Systematic Literature Review and Meta-Analysis. *Brain Sci*. 2022;12(5).
29. Inouye SK. Delirium in older persons. *N Engl J Med*. 2006;354(11):1157-65.
30. Koelsch S. Brain correlates of music-evoked emotions. *Nat Rev Neurosci*. 2014;15(3):170-80.
31. Tracey KJ. Reflex control of immunity. *Nat Rev Immunol*. 2009;9(6):418-28.
32. Khan SH, Wang S, Harrawood A, Martinez S, Heiderscheid A, Chlan L, et al. Decreasing Delirium through Music (DDM) in critically ill, mechanically ventilated patients in the intensive care unit: study protocol for a pilot randomized controlled trial. *Trials*. 2017;18(1):574.
33. Kakar E, Ista E, Klimek M, Jeekel J. Implementation of music in the perioperative standard care of colorectal surgery: study protocol of the IMPROVE Study. *BMJ Open*. 2021;11(10):e051878.

34. Omigie D, Samson S. A protective effect of musical expertise on cognitive outcome following brain damage? *Neuropsychol Rev.* 2014;24(4):445-60.
35. Besson M, Faita F, Requin J. Brain waves associated with musical incongruities differ for musicians and non-musicians. *Neurosci Lett.* 1994;168(1-2):101-5.
36. Bidelman GM, Krishnan A. Effects of reverberation on brainstem representation of speech in musicians and non-musicians. *Brain Res.* 2010;1355:112-25.
37. Koelsch S, Schmidt, B.H. and Kansok, J. . Influences of musical expertise on the ERAN: an ERP-study. *Psychophysiology* 2002;657-663(39).
38. Montori VM, Smieja M, Guyatt GH. Publication bias: a brief review for clinicians. *Mayo Clin Proc.* 2000;75(12):1284-8.
39. Russell SM, Golfinos JG. Amusia following resection of a Heschl gyrus glioma. Case report. *J Neurosurg.* 2003;98(5):1109-12.
40. Mann L. Casuistische Beiträge zur Hirnchirurgie und Hirnlocalisation. *Monatsschr Psychiatr Neurol.* 1898;4:369-78.



CHAPTER 10

Summary / Samenvatting



Summary

The effect of music on delirium after brain surgery

Delirium is a neuropsychiatric clinical syndrome with overlapping symptoms with the neurologic primary disease. This is why delirium is such a difficult and under-exposed topic in neurosurgical literature. Delirium is a complication which might affect recovery after brain surgery, hence we describe in **Chapter 2** a systematic review which focuses on how delirium is defined in the neurosurgical literature. We included twenty-four studies (5589 patients) and found no validation studies of screening instruments in neurosurgical papers. Delirium screening instruments, validated in other cohorts, were used in 70% of the studies, consisting of the Confusion Assessment Method (- Intensive Care Unit) (45%), Delirium Observation Screening Scale (5%), Intensive Care Delirium Screening Checklist (10%), Neelon and Champagne Confusion Scale (5%), and Nursing Delirium Screening Scale (5%). Incidence of post-operative delirium after intracranial surgery was 19%, ranging from 12 – 26% caused by variation in clinical features and delirium assessment methods. Our review highlighted the need of future research on delirium in neurosurgery, which should focus on optimizing diagnosis, and assessing prognostic significance and management.

It is unclear what the impact of delirium is on the recovery after brain surgery, as delirium is often a self-limiting and temporary complication. In **Chapter 3** we therefore investigated the impact of delirium, by means of incidence and health outcomes, and identified independent risk factors by including 2901 intracranial surgical procedures. We found that delirium was present in 19.4% with an average onset (mean/SD) within 2.62/1.22 days and associated with more Intensive Care Unit (ICU) admissions and more discharge towards residential care. These numbers confirm the impact of delirium with its incidence rates, which were in line with our previous systematic review, and significant health-related outcomes. We identified several independent non-modifiable risk factors such as age, pre-existing memory problems, emergency operations, and modifiable risk factors such as low pre-operative potassium and opioid and dexamethasone administration, which shed light on the pathophysiologic mechanisms of POD in this cohort and could be targeted for future intervention studies.

As listening to recorded music has been proven to lower delirium-eliciting factors in the surgical population, such as pain, we were interested in the size of analgesic effect and its underlying mechanism before applying this into our clinical setting. In **Chapter 4** we describe the results of a two-armed experimental randomized controlled trial in which 70 participants received increasing electric stimuli through their non-dominant index finger. This study was conducted within a unique pain model as participants were blinded for the outcome. Participants in the music group received a 20-minute music intervention and participants in the control group a 20-minute resting period. Although the effect of the music intervention on pain endurance was not statistically significant in our intention-to-treat analysis ($p = 0.482$, CI -0.85; 1.79), the subgroup analyses revealed an increase in pain endurance in the music group after correcting for technical uncertainties ($p = 0.013$, CI 0.35; 2.85). This effect on pain endurance could be attributed to increased parasympathetic activation, as an increased Heart Rate Variability (HRV) was observed in the music vs. the control group ($p=0.008;0.032$).

As our prior chapters increased our knowledge on the significance of delirium on the post-operative recovery after brain surgery and the possible beneficial effects of music, we decided to design a randomized controlled trial. In **Chapter 5** we describe the protocol and in **Chapter 6** we describe the results of this single-centered randomized controlled trial. In this trial we included 189 patients undergoing craniotomy and compared the effects of music administered before, during and after craniotomy with standard of clinical care. The primary endpoint delirium was assessed by the delirium observation screening scale (DOSS) and confirmed by a psychiatrist according to DSM-5 criteria. A variety of secondary outcomes were assessed to substantiate the effects of music on delirium and its clinical implications. Our results support the efficacy of music in preventing delirium after craniotomy, as found with DOSS (OR:0.49, $p=0.048$) but not after DSM-5 confirmation (OR:0.47, $p=0.342$). This possible beneficial effect is substantiated by the effect of music on pre-operative autonomic tone, measured with HRV ($p=0.021;0.025$), and depth of anesthesia ($p<0.001;0.022$). Our results fit well within the current literature and support the implementation of music for the prevention of delirium within the neurosurgical population. However, delirium screening tools should be validated and the long-term implications should be evaluated after craniotomy to assess the true impact of music after brain surgery.

Musicality and language in awake brain surgery

In the second part of this thesis, the focus shifts towards maintaining musicality and language functions around awake craniotomy. Intra-operative mapping of language does not ensure complete maintenance which mostly deteriorates after tumor resection. Most patients recover to their baseline whereas other remain to suffer from aphasia affecting their quality of life. The level of musical training might affect the speed and extend of postoperative language recovery, as increased white matter connectivity in the corpus callosum is described in musicians compared to non-musicians. Hence, in **Chapter 7** we evaluate the effect of musicality on language recovery after awake glioma surgery in a cohort study of forty-six patients. We divided the patients into three groups based on the musicality and compared the language scores between these groups. With the first study on this topic, we support that musicality protects against language decline after awake glioma surgery, as a trend towards less deterioration of language was observed within the first three months on the phonological domain ($p = 0.04$). This seemed plausible as phonology shares a common hierarchical structure between language and singing. Moreover, our results support the hypothesis of musicality induced contralateral compensation in the (sub-) acute phase through the corpus callosum as the largest difference of size was found in the anterior corpus callosum in non- musicians compared to trained musicians ($p = 0.02$).

In **Chapter 8** we addressed musicality as a sole brain function and whether it can be protected during awake craniotomy in a systematic review consisting of ten studies and fourteen patients. Isolated music disruption, defined as disruption during music tasks with intact language/speech and/or motor functions, was identified in two patients in the right superior temporal gyrus, one patient in the right and one patient in the left middle frontal gyrus and one patient in the left medial temporal gyrus. Pre-operative functional MRI confirmed these localizations in three patients. Assessment of post-operative musical function, only conducted in seven patients by means of standardized (57%) and non-standardized (43%) tools, report no loss of musical function. With these results we concluded that mapping music is feasible during awake craniotomy. Moreover, we identified certain brain regions relevant for music production and detected no decline during follow-up, suggesting an added value of mapping musicality during awake craniotomy. A systematic approach to map musicality should be implemented, to improve current knowledge on the added value of mapping musicality during awake craniotomy.

Samenvatting

Het effect van muziek op het delier na een hersenoperatie

Het delier is een neuropsychiatrisch klinisch syndroom met overlappende symptomen met de neurologische primaire ziekte. Hierom is het delier zo'n moeilijk en onderbelicht onderwerp in de neurochirurgische literatuur. Het delier is een complicatie die het herstel na een hersenoperatie kan beïnvloeden, vandaar dat wij ons in Hoofdstuk 2 op het delier hebben gericht door een systematische review uit te voeren op de wijze waarop het delier in de neurochirurgische literatuur wordt gedefinieerd. Wij includeerden vierentwintig studies (5589 patiënten) en vonden geen validatiestudies van screeningsinstrumenten in neurochirurgische artikelen. Delirium screeningsinstrumenten, gevalideerd in andere cohorten, werden gebruikt in 70% van de studies, bestaande uit de Confusion Assessment Method (- Intensive Care Unit) (45%), Delirium Observation Screening Scale (5%), Intensive Care Delirium Screening Checklist (10%), Neelon and Champagne Confusion Scale (5%), en Nursing Delirium Screening Scale (5%). Incidentie van postoperatief delier na intracraniele chirurgie was 19%, variërend van 12 - 26% veroorzaakt door variatie in klinische kenmerken en delierbeoordelingsmethoden. Ons overzicht benadrukte de noodzaak van toekomstig onderzoek naar delirium bij neurochirurgie, dat zich moet richten op het optimaliseren van de diagnose en het beoordelen van de prognostische betekenis.

Het is onduidelijk wat de impact van een delier is op het herstel na een hersenoperatie, aangezien een delier vaak een zelfbeperkende en tijdelijke complicatie is. In Hoofdstuk 3 onderzochten wij daarom de impact van het delier, door middel van incidentie en gezondheidsuitkomsten, en identificeerden wij onafhankelijke risicofactoren door 2901 intracraniele chirurgische procedures te analyseren. Wij vonden dat een delier aanwezig was in 19,4% met een gemiddeld (SD) ontstaan binnen 2,62 (1,22) dagen na de operatie en geassocieerd met meer opnames op de Intensive Care Unit (ICU) en meer ontslag naar verpleeghuizen. Deze incidentie cijfers bevestigen de impact van het delier, die overeenkwamen met onze systematische review, en significante gezondheidsgerelateerde uitkomsten. Wij identificeerden een aantal niet-modificeerbare risicofactoren zoals leeftijd, reeds bestaande geheugenproblemen, spoedoperaties, en modificeerbare risicofactoren zoals laag preoperatief kalium en toediening van opioïden en dexamethason, die inzicht geven in de pathofysiologische mechanismen van delirium in dit cohort en die aangegrepen kunnen worden in toekomstige interventiestudies.

Eerder is aangetoond dat het luisteren naar muziek de pijnbeleving kan verlagen in de chirurgische populatie. Wij waren geïnteresseerd in de omvang van het pijnstillende effect en het onderliggende mechanisme van muziek aangezien pijn een uitlokkende factor voor het delirium is. In Hoofdstuk 4 beschrijven wij de resultaten van een experimenteel 2-armig gerandomiseerd onderzoek waarbij 70 deelnemers toenemende elektrische prikkels kregen via hun niet-dominante wijsvinger. Deze studie werd uitgevoerd binnen een uniek pijnmodel, aangezien de deelnemers geblindeerd waren voor de uitkomst. Deelnemers in de muziekgroep kregen een muziekinterventie van 20 minuten en deelnemers in de controlegroep een rustperiode van 20 minuten. Hoewel het effect van de muziekinterventie op het uithouden van pijn niet statistisch significant was in onze primaire analyse ($p = 0,482$), lieten de subgroep analyses, na correctie voor technische onzekerheden, een toename van het uithouden van pijn in de muziekgroep zien ($p = 0,013$). Dit effect zou kunnen worden toegeschreven aan een verhoogde parasympathische activering, aangezien een verhoogde hartslagvariabiliteit (HRV) werd waargenomen in de muziek- vs. de controlegroep ($p=0,008$).

Aangezien onze eerdere hoofdstukken de impact van het delirium na hersenchirurgie en de mogelijke gunstige effecten van muziek lieten zien, besloten wij een gerandomiseerde studie te ontwerpen. In Hoofdstuk 5 beschrijven we het protocol en in Hoofdstuk 6 beschrijven we de resultaten van deze single-centered gerandomiseerde trial. In dit onderzoek onderzochten we 189 patiënten die een craniotomie ondergingen en vergeleken we de effecten van muziek voor, tijdens en na de craniotomie met de standaard klinische zorg. Het primaire eindpunt delirium werd gedefinieerd met de delirium observation screening scale (DOSS) en bevestigd door een psychiater middels de DSM-5 criteria. Een scala aan secundaire uitkomsten werd onderzocht om de onderliggende mechanismen van muziek op het delier te achterhalen en de klinische implicaties ervan te onderbouwen. Onze resultaten ondersteunen de effectiviteit van muziek in de preventie van een delier na craniotomie, zoals gevonden met DOSS (OR:0,49, $p=0,048$) maar niet na DSM-5 bevestiging (OR:0,47, $p=0,342$). Dit mogelijke gunstige effect werd toegeschreven door het effect van muziek op het preoperatieve parasympathische zenuwstelsel, gemeten met HRV ($p=0,021;0,025$), en diepte van de anesthesie ($p<0,001;0,022$). Onze resultaten passen goed binnen de huidige literatuur en ondersteunen de implementatie van muziek ter preventie van delirium binnen de neurochirurgische populatie. De instrumenten voor de screening van het delier moeten echter worden gevalideerd en de gevolgen op lange termijn

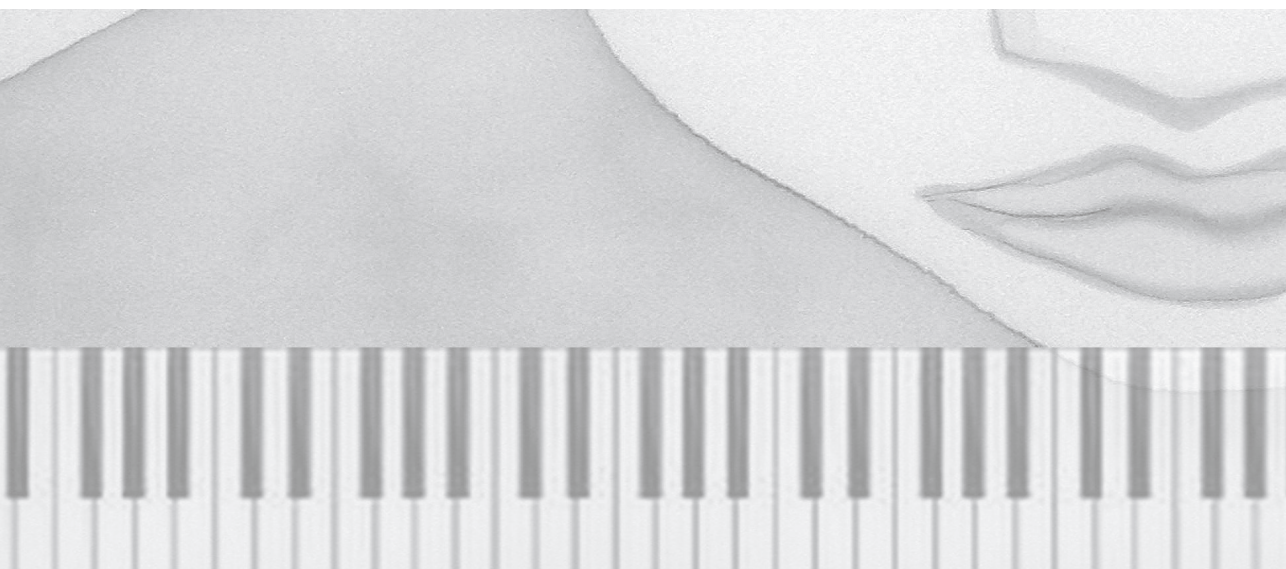
moeten worden geëvalueerd na een craniotomie om de werkelijke impact van muziek na hersenchirurgie te beoordelen.

Muziek- en taal functie in wakkere hersenchirurgie

In het tweede deel van dit proefschrift verschuift de aandacht naar het behoud van muziek- en taalfuncties rondom wakkere hersenoperaties. Intra-operatief in kaart brengen van taal, gedurende een wakkere ingreep, is geen garantie voor volledig behoud van taal, welke meestal verslechtert na tumorresectie. De meeste patiënten herstellen tot hun basisniveau, terwijl andere blijven lijden aan afasie, wat hun levenskwaliteit aantast. Het niveau van muzikale training zou de snelheid en omvang van het postoperatieve taalherstel kunnen beïnvloeden, aangezien een verhoogde witte stof connectiviteit in het corpus callosum is beschreven bij musici in vergelijking met niet-musici. Daarom evalueren wij in Hoofdstuk 7 het effect van muziek maken op jongere leeftijd op taalherstel na wakkere gliomchirurgie in een cohortstudie van zesenvierentwintig patiënten. Wij verdeelden de patiënten in drie groepen op basis van hun muzikale achtergrond en vergeleken de taalscores tussen deze groepen. Met de eerste studie over dit onderwerp ondersteunen wij dat een muzikale achtergrond beschermend werkt tegen taal achteruitgang na wakkere gliomchirurgie. Een trend naar minder taalverslechtering werd waargenomen binnen de eerste drie maanden op het fonologische domein ($p = 0,04$). Dit is aannemelijk aangezien fonologie een gemeenschappelijke eigenschap is tussen taal en zang. Bovendien ondersteunen onze resultaten de hypothese dat een muzikale achtergrond de contralaterale hemisfeer activeert via het corpus callosum. Het grootste verschil in grootte werd hierbij gevonden in het voorste corpus callosum bij niet-musici in vergelijking met getrainde musici ($p = 0,02$).

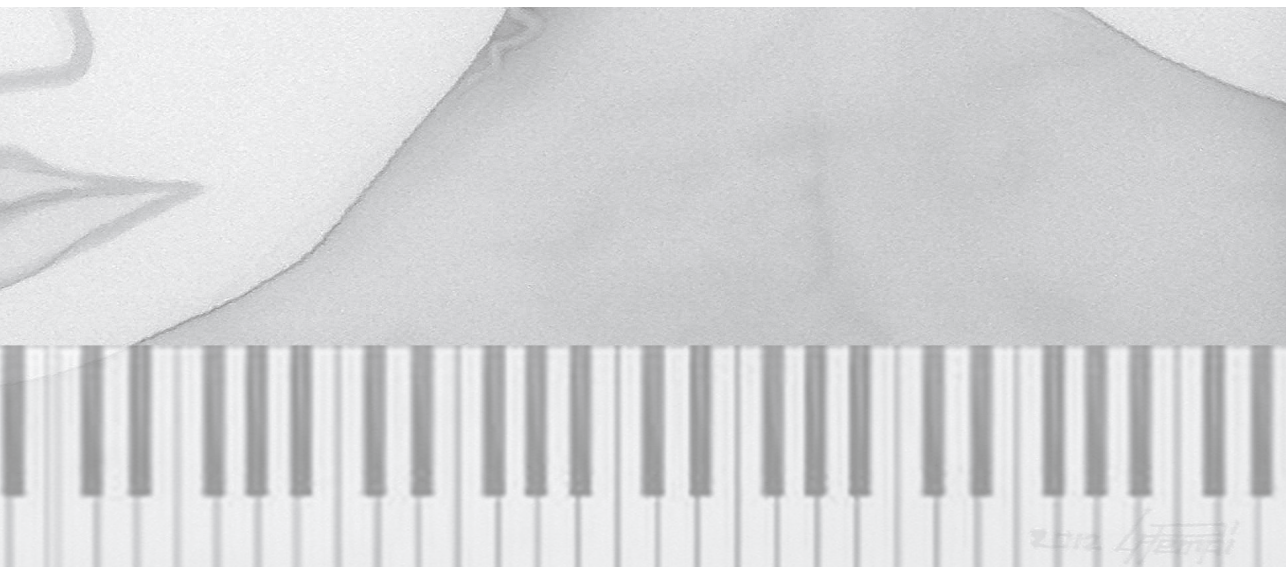
In Hoofdstuk 8 onderzochten we muziek als hersenfunctie en of deze beschermd kan worden tijdens wakkere craniotomie in een systematische review bestaande uit tien studies en veertien patiënten. Geïsoleerde muziekverstoring, gedefinieerd als verstoring tijdens muziektaken met intacte taal/spraak en/of motorische functies, werd vastgesteld bij twee patiënten in de rechter superieure temporale gyrus, één patiënt in de rechter middelste frontale gyrus, één patiënt in de linker middelste frontale gyrus en één patiënt in de linker mediale temporale gyrus. Pre-operatieve functionele MRI bevestigde deze lokalisaties bij drie patiënten. Beoordeling van de postoperatieve muzikale functie, alleen uitgevoerd bij zeven patiënten door middel

van gestandaardiseerde (57%) en niet-gestandaardiseerde (43%) instrumenten, rapporteren geen verlies van muzikale functie. Met deze resultaten concluderen wij dat het in kaart brengen van muziek mogelijk is tijdens een wakkere hersenoperatie. Bovendien identificeerden we bepaalde hersengebieden die relevant zijn voor muziekproductie en constateerden we geen achteruitgang tijdens de follow-up, wat een toegevoegde waarde suggereert van het in kaart brengen van muzikaliteit tijdens wakkere craniotomie. Een systematische implementatie voor het in kaart brengen van muzikaliteit rondom hersenoperaties is noodzakelijk om de kennis hierover te verbeteren.



APPENDICES

Dankwoord
PhD Portfolio
List of Publications
Curriculum Vitae



Dankwoord

Graag zou ik dit proefschrift willen afsluiten met het bedanken van hen die, op welke manier dan ook, belangrijk zijn geweest voor het tot stand komen van dit proefschrift. Zonder hen was het mij op geen enkele manier gelukt om dit project tot een succesvol einde te brengen.

Prof. dr. Johannes Jeekel, in het Erasmus Medisch Centrum heeft u direct uw volle vertrouwen in mij getoond na een eenmalig gesprek. Die onvoorwaardelijke kracht en dat vertrouwen van u, gaven mij de energie, wilskracht en motivatie om met volle inzet te beginnen en niet meer te stoppen tot de laatste letter van dit proefschrift was getypt. Daarnaast bent u, met uw positieve energie, buiten de gebaande paden denkend en met uw verbindende rol echt een voorbeeld voor mij. Hiervoor wil ik u bijzonder bedanken.

Prof. dr. Clemens Dirven, als afdelingshoofd en promotor gaat mijn dank eveneens zeer naar u uit. U heeft u mij altijd ten volle gesteund om dit project tot een succesvol einde te brengen. De gesprekken die we op reguliere basis hadden en waar u ruimschoots de tijd voor nam ondanks uw drukke agenda, heb ik altijd erg gewaardeerd. Ik mis ze nog steeds na mijn promotieperiode. Uw verbindende rol binnen de neurochirurgische groep, tussen zowel assistenten als stafleden, uw luisterend oor maar ook de pragmatische manier waarop u naar oplossingen zoekt, hebben mij geïnspireerd in mijn vroege ontwikkeling als arts en onderzoeker.

Prof. dr. Arnaud Vincent, ook u wil ik bedanken. Zodra u begon over de auriculaire aftakkingen die mogelijk als onderliggend mechanisme van muziek zou kunnen spelen bij delier, was ik verkocht. De manier waarop u met hoge snelheid maar met onvermoeibare nieuwsgierigheid tot vragen en oplossingen weet te komen en de leuke gesprekken die we hebben gehad heb ik erg gewaardeerd. Op een dag zullen we het mysterie van het parasympatisch zenuwstelsel en de nervus vagus samen ontrafelen!

Dr. Markus Klimek, voor mij ben je van onschatbare waarde geweest voor het tot stand komen van dit proefschrift. Ik heb weinig supervisors meegemaakt die zo snel reageerden. U wist dan ook bijna altijd eerder dan ik als er weer een paper was geaccepteerd. Niet alleen de vele adviezen die te maken hadden met mijn promotietraject, maar ook de algemene levenslessen die ik van je heb gehad, pas ik nog steeds toe in mijn dagelijks leven. Bedankt dat je mijn co-promotor wilde zijn.

Leden van de kleine commissie: prof. Dr. B. van Leeuwen, prof. dr. Van der Zwan en prof. dr. Hoogendijk, hartelijk dank voor de bereidheid van u allen om dit proefschrift te beoordelen en zitting te nemen in de kleine commissie.

Leden van de grote commissie: prof. dr. A.R. Absalom, dr. M.L.D. Broekman hartelijk dank dat u wilt opponeren op deze, voor mij zo belangrijke, dag.

Dr. Djaina Satoer, ook jou wil ik graag apart bedanken voor de afgelopen jaren. Ik genoot vaak enorm van onze lange gesprekken over mogelijke onderzoeksplannen die we samen hadden. Daarnaast zijn we natuurlijke trotse bandgenoten van de ‘The Craniotomies’. Onze gezamenlijke passie voor onderzoek en muziek hebben geleid tot een tweetal publicaties over wakkere hersenoperaties bij muzikanten. Daar ben ik trots op. Kers op de taart was onze gezamenlijke congresreis, samen met Marike, Saskia en Ellen naar Bordeaux en Wenen. Op heel veel vlakken hebben wij overeenkomsten en hierom hoop ik dat onze paden, zowel academisch als persoonlijk, zich in de toekomst nog eens zullen kruisen.

Mede MAM genoten, Thomas, Roos, Ryan, Victor, Ellaha en nu ook Jorrit, Antonia en Emy. Eenmaal MAM, altijd MAM in je hart. De wekelijkse onderzoeksmeetings op woensdagochtend mis ik nog elke dag. Hoe we elkaar, zowel binnen als buiten het ziekenhuis, als collega’s maar ook als vrienden konden begroeten is een bijzonder gegeven. Ongeacht waar we later terecht komen durf ik met een gerust hart te zeggen dat weinig dokters hun carrière hebben mogen starten met zo’n warme onderzoeksgroep. Blijf in jezelf geloven en dan komt alles vanzelf goed! Paul, Fyke en Pien: jullie inzet en betrokkenheid is altijd van onschatbare waarde geweest.

Mede Na-21 Wendy, Dana, Ellen, Sepehr en Rahman. Iedere keer was het weer een verrassing wie ik zou aantreffen als ik er op de 21^e zat. De gesprekken over van alles en nog wat, de nationale en internationale frietendag en het gezamenlijk aanhoren van de chirurgieassistenten verderop waren iedere dag weer de hoogtepunten op de Na21. Anja, aan jou nog een bijzondere dank voor je snelle oplossingen en luisterend oor op ieder moment van de dag.

Neurochirurgie collega’s, alle assistenten en PA’s. Ontzettend bedankt dat jullie een rol hebben gespeeld in mijn eerste fase in mijn ontwikkeling tot arts. De toewijding en dagelijkse energie, ondanks de zeer acute en complexe pathologie, is noemenswaardig en een springplank voor iedere carrièrestap die hierna gezet moet worden. Dank voor

jullie geduld, vertrouwen en toewijding in mij. Speciaal dank aan alle hardwerkende en lieve verpleegkundigen op de afdeling. Zonder jullie steun was mijn onderzoek absoluut geen succes geworden.

Mijn naaste vrienden, zonder ieder bij naam te benoemen weten jullie wie ik bedoel. Met jullie in mijn omgeving, vanaf de basisschool tot aan nu, heb ik mij kunnen ontwikkelen tot wie ik nu ben. Het grootste deel van mijn persoonlijkheid op dit moment, heb ik ontwikkeld met jullie aan mijn zijde. Daarnaast heb ik dankzij jullie, een uitlaatklep gehad in de weekenden. Dat heeft ervoor gezorgd dat ik op maandag met frisse tegenzin weer aan de bak kon gaan. Bedankt dat jullie deze rit, het leven, met mij delen.

Mijn paranimfen, Rutger en Casper. Jullie hebben allebei op jullie eigen manier een belangrijke bijdrage gehad in mijn leven. Bedankt dat jullie op deze belangrijke dag mij willen ondersteunen.

Bert, lieve paps. Al sinds ik een jochie ben vraag ik je de oren van het lijf. Het maximaal aantal vragen van 10 per uur worden nog steeds overschreden. Je geduld tijdens het uitleggen van middelbare schoolmaterie, het wekelijks langs de zijlijn staan tijdens hockey, samen pianospelen, het sparren over de carrièrekeuzes en je actieve hulp hierbij en onze gezamenlijke wandelingen waarin we eindeloos over diepe (maar gelukkig ook oppervlakkige) dingen praten: het zijn deze dingen die ik zeer waardeer aan onze relatie. Natuurlijk zijn we allebei uniek maar ik ben juist enorm trots op onze gemeenschappelijke eigenschappen.

Marta, ola mamá. También quería darte las gracias por separado en esta tesis. Estoy muy orgulloso de tener una madre como tú. Aún no he conocido a nadie con tu inteligencia de comprender tan bien a la gente a tu alrededor. Pase lo que pase, sigues teniendo una fuerza interior, una alegría y un fuego que nunca se apaga. Incluso los momentos que no estamos juntos, siento tu presencia cerca, e intento tomar decisiones desde tu perspectiva.

Clara en Teresa, lieve zusjes. Wat ben ik blij jullie aan mijn zijde te hebben. We spraken laatst met verbazing naar elkaar toe dat we iedere stap van elkaar vanaf de eerste rij zullen volgen. Ik word heel gelukkig van deze gedachte. Jullie steun als het me tegenzit, en de gezelligheid als we samen zijn, zullen we nooit kwijtraken. Ik ben erg trots op de vrouwen die jullie zijn geworden.

Evert, Jacomien en Hermen, mijn nieuwe familie. Sinds ik met Willemijn ben heb ik er een gratis familie bij gekregen, en wat voor een. Ik heb altijd erg genoten van jullie nuchterheid en warmte. Over de afgelopen jaren, met een boost in Nieuw-Zeeland, zijn we naar elkaar toe gegroeid en voelen jullie ook echt als familie. Ook jullie wil ik heel erg bedanken.

Willemijn, mijn vrouw. Ook jou wil ik specifiek heel erg bedanken voor het tot stand komen van dit proefschrift. Al vanaf het begin was je enthousiast over dit project, zag je hierin de potenties en heb je mij laten floreren in mijn kracht. Naast dat je mijn partner bent, ben je dagelijks mijn coach en sparringpartner geweest. Naast jouw liefde heb ik ook van jouw intelligentie kunnen profiteren. Die heeft er mede voor gezorgd dat ik dit project in korte tijd succesvol heb kunnen afronden.

PhD portfolio

DATE	Training activiteit	EC
CURSUSSEN		
MEI 2019	BROK cursus	1.50
MEI 2019	Endnote cursus	2.00
JULI 2019	Wetenschappelijke integriteit	0.30
NOVEMBER 2019	Systematic review (Pubmed/Embase)	1.00
DECEMBER 2019	Wetenschappelijk schrijven	2.00
FEBRUARI 2020	Biomedical English writing	2.00
MEI 2020	Open Clinica	0.80
MEI 2020	Basis Cursus R	1.80
MEI 2020	Cursus R	1.80
MEI 2020	Powerpoint cursus	0.30
SEPTEMBER 2021	Castor EDC	1.00
MEI 2022	Basis Cursus SPSS	1.00
CONGRESSEN		
MEI 2019	Keppel Stichting: Music as Medicine: platform presentatie	1.0
NOVEMBER 2019	NvvN: platform presentatie	1.0
NOVEMBER 2019	Miracles of music Congress	1.0
FEBRUARY 2020	Themater Isala Theater: Music as Medicine. Platform presentatie	1.0
SEPTEMBER 2020	Opleidings- en Onderwijsregio Zuidwest: Music as Medicine. Presentatie	1.0
OKTOBER 2020	EANS: poster presentatie	2.0
APRIL 2021	Nvva. Platform presentatie	1.0
MEI 2021	Muziek & Gezondheid Lustrum MFAS: Music as Medicine. Platform presentatie	1.0
OKTOBER 2021	EANS DONE: Virtuele orale presentatie	2.0
SEPTEMBER 2021	EANO DONE: virtuele orale presentatie	2.0
NOVEMBER 2021	NvvN platform presentatie	1.0
SEPTEMBER 2022	EANO (Wenen) SING studie: poster presentatie	2.0
SEPTEMBER 2022	Science of Aphasia (Bordeaux): SING. Poster presentatie	2.0
SUPERVISION		
JUNI 2020 - DECEMBER 2020	Supervision Master Student Tim Lafleur	5.0
OCTOBER 2020 – JUNE 2021	Supervision 2 nd year bachelor student Tobia Beshay	3.0
MARCH 2021 UNTIL OCTOBER 2021	Supervision 3 rd year bachelor student Sepehr Mohadammian	3.0
JUNE 2021 UNTIL DECEMBER 2021	Supervision Master Student Max Mos	5.0
SEPTEMBER 2021 UNTIL NOVEMBER 2021	Supervision Clinical Technology Master Student Merel van der Maarel	3.0
NOVEMBER 2021 UNTIL JANUARY 2022	Supervision Clinical Technology Master Student Tamir Themans	3.0
GRANT APPLICATIONS		
AUGUSTUS 2019	Grant Application Mrace Erasmus Medical Center	5.0
TOTAL		56,8

List of publications

R.J. Billar, **P.R. Kappen**, S. Mohammadian, C. van den Berg, Y.B. de Rijke, E.L.T. van den Akker, J. van Rosmalen, J.M. Schnater, A.J.P.E. Vincent, C.M.F. Dirven, M. Klimek, R.M.H. Wijnen, J. Jeekel, F.J.P.M. Huygen, J. Tiemensma ‘*The effect of recorded music on pain endurance (CRESCENDO) – a randomized controlled trial.*’ *Complementary Therapies in Medicine* (2023)

P.R. Kappen, M.I. Mos, J. Jeekel, C.M.F. Dirven, S.A. Kushner, R.J. Osse, M. Coesmans, M.J. Poley, M. van Schie, B. van der Holt, M. Klimek, A.J.P.E. Vincent ‘*Music to prevent delirium during neurosurgery (MUSYC): a single-centre prospective randomised controlled trial.*’ *BMJ Open* (2023)

P.R. Kappen, H.J. Kappen, C.M.F. Dirven, M. Klimek, J. Jeekel, E.R. Andrinopoulou, R.J. Osse, A.J.P.E. Vincent ‘*Post-operative Delirium after Intracranial Surgery: a retrospective cohort study.*’ *World Neurosurgery* (2023)

P.R. Kappen, J. van den Brink, J. Jeekel, C.M.F. Dirven, M. Klimek, M. Donders-Kamphuis, C.S. Docter-Kerkhof, S.A. Mooijman, E. Collee, R.D.S. Nandoe Tewarie, M.L.D. Broekman, M. Smits, A.J.P.E. Vincent, D. Satoer ‘*The effect of musicality on language recovery after awake glioma surgery.*’ *Frontiers in Human Neuroscience* (2023)

P.R. Kappen, T. Beshay, A.J.P.E. Vincent, D. Satoer, C.M.F. Dirven, J. Jeekel, M. Klimek ‘*The feasibility and added value of mapping music during awake craniotomy: a systematic review.*’ *European Journal of Neuroscience* (2022)

P.R. Kappen, E. Kakar, C.M.F. Dirven, M. van der Jagt, M. Klimek, R.J. Osse, A.J.P.E. Vincent ‘*Delirium in Neurosurgery: a systematic review and meta-analysis.*’ *Neurosurgical Review* (2022)

P.R. Kappen, C.M.F. Dirven, M. Poley, M. Coesmans, S. Kushner, R. Osse, A.P.J.E. Vincent ‘*Music to prevent delirium in neurosurgery (MUSYC): a protocol for a randomized controlled trial*’ *BMJ Open* (2021)

P.R. Kappen, C. Eltze, M. Tisdall, J.H. Cross, R. Thornton, F. Moeller ‘*Stereo-EEG exploration in the insula/opercula in paediatric patients with refractory epilepsy.*’ *Seizure* (2020)

Curriculum Vitae – Pablo R. Kappen

PERSONALIA

Naam: Pablo Ramon Kappen (Pablo)
Adres: Twijnstraat aan de Werf 9D
Utrecht, Nederland
Telefoonnummer: +31 617226531
E-mailadres: p.r.kappen-2@umcutrecht.nl
Geboorteplaats: Nijmegen, Nederland
Geboortedatum: 20-06-1992
Nationaliteit: Nederlands



WERKERVARING

05/2023—heden **Arts-assistent (ANIOS)** Afdeling Neurologie, Universitair Medisch Centrum, Utrecht

04/2019 – 08/2022 **Arts-onderzoeker (PhD student)** *Afdeling Neurochirurgie, Erasmus Medisch Centrum Rotterdam (Verdediging ‘Muziek en muzikaliteit in hersenchirurgie: het effect op delier en taal’ in 2023)*

04/2018 – 04/2023 **Arts-assistent (ANIOS)** Afdeling Neurochirurgie, Erasmus Medisch Centrum Rotterdam

09/2008 – 09/2010 **Docent piano** *wekelijkse privélessen gegeven*

09/2008 – 06/2009 **Docent Spaans** *wekelijks privélessen gegeven*

OPLEIDING

09/2014 – 04/2018 **Master of Science Geneeskunde** *Universiteit van Utrecht (Afgestudeerd in april 2018)*

09/2010 - 09/2014 **Bachelor of Science Geneeskunde** *Universiteit van Utrecht*

- 09/2007 - 09/2010 **Voorbereidend Wetenschappelijk Onderwijs - VWO Profiel Natuur en Gezondheid** *Nijmeegse Scholengemeenschap Groenewoud, Nijmegen*
- 09/2007 - 09/2009 **Externe vooropleiding Jazz & Pop** *NSG i.s.m. conservatorium Arnhem ArtEZ*
- 01/2005 - 05/2005 **Middle School** *St. Jerome Catholic School, Berkeley, California*

BEURZEN

- 11/2019 **Erasmus MC Doelmatigheidsonderzoek ‘Music to prevent delirium in neurosurgery (MUSYC): a randomized controlled trial’** beurs twv 150.000 euro voor financiering van eigen PhD positie.
- 11/2017 **Internationalization Committee grant for strategic network development** – *Onderzoeksbeurs ter bevordering samenwerking UMC Utrecht met Great Ormond Street Children Hospital, Londen* (*‘Stereo-EEG exploration in the insula/opercula in paediatric patients with refractory epilepsy’*)
- 10/2017 **Utrechts Universiteitsfonds Beurs** – *Beurs voor congres bezoek American Epilepsy Society Washington D.C.* (*‘The added diagnostic value of MEG on localizing the epileptogenic zone in candidates for epilepsy surgery’*)
- 03/2015 – 07/2015 **USC Scholarship Foundation** – *Beurs voor onderzoeksproject ‘Tuberculosis in Indigenous’, Paraguay*

TALENKENNIS

Nederlands	Moedertaal
Spaans	Moedertaal
Engels	Uitstekend

