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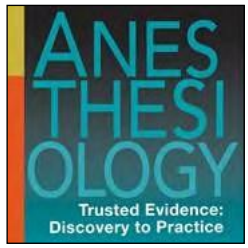

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DOI: https://doi.org/10.1097/ALN.0000000000004929

To appear in: Anesthesiology

Submitted for publication: July 21, 2023

Accepted for publication: January 19, 2024

Please cite this article as: Pollak M, Leroy S, Röhr V, Brown EN, Spies C, Koch S: EEG biomarkers from anesthesia induction to identify vulnerable patients at risk for postoperative delirium. Anesthesiology. 2024; https://doi.org/10.1097/ALN.0000000000004929

Anesthesiology Publish Ahead of Print

DOI: 10.1097/ALN.0000000000004929

EEG biomarkers from anesthesia induction to identify vulnerable patients at risk for postoperative delirium

Marie Pollak[1]*, Sophie Leroy[1]*, Vera Röhr[2], Emery Neal Brown[3-4], Claudia Spies[1], Susanne Koch[1,5]

[1]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Anesthesiology and Operative Intensive Care Medicine, Berlin, Germany

[2]Neurotechnology Group, Technische Universität Berlin, Berlin, Germany

[3]Harvard-MIT Health Sciences and Technology Program, Massachusetts Institute of Technology, Cambridge, MA 02139

[4]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114

[5]University of Southern Denmark (SDU) Odense, Region Sjælland - Nykøbing F. Sygehus, Department of Anesthesia, Denmark

*both first authors contributed equally to the manuscript

Correspondence: Assoc. Prof. Dr. Susanne Koch Department of Anaesthesiology and Intensive Care Medicine Charité - Universitätsmedizin Berlin, Campus Charité Mitte and Virchow-Klinikum Augustenburger Platz 1, D-13353 Berlin, Germany ORCID ID 0000-0001-5663-7447 e-mail: susanne.koch@charite.de

Funding: The research leading to these results was supported by the German Research Society – Project number KO 4249/3-1 and Charité – Universitätsmedizin Berlin.

The article processing charge was funded by Charité Research Support.

Conflicts of Interests/Financial Disclosures:

Marie Pollak: None.

Sophie Leroy: None.

Vera Röhr: None.

Emery Neal Brown: holds patents on anesthetic state monitoring and control. E.N.B. holds a founding interest in PASCALL, a start-up developing physiological monitoring systems; receives royalties from intellectual property through Massachusetts General Hospital licensed to Masimo. The interests of E.N.B. were reviewed and are managed by Massachusetts General Hospital and Mass General Brigham in accordance with their conflict-of-interest policies.

Claudia Spies: is an inventor on patents, she reports grants during the conduct of a study from European Commission, from Aridis Pharmaceutical Inc., B. Braun Melsung, Drägerwerk AG & Co. KGaA, German Research Society, German Aerospace Center, Einstein Foundation Berlin, European Society of Anesthesiology, Federal Joint committee and Inner University grants. Grants promoting Science and Education from WHOCC, Baxter Deutschland GmbH, Cytosorbents Europe GmbH, Edwars Lifesciences Germany GmbH, Fresenius Medical Care, Grünenthal GmbH, Masimo Europe Ltd. Phizer Pharma PFE GmbH. Personal fees from Georg Thieme Verlag, Dr. F. Köhler Chemie GmbH, Sintetica GmbH, European commission, Stifterverband für die deutsche Wissenschaft e.V. / Philips, Stiftung Charite, AGUETTANT Deutschland GmbH, AbbVie Deutschland GmbH & Co. KG, Amomed Pharma GmbH, Touch Health, Copra System GmbH, Correvio GmbH, Max-Planck-Gesellschaft zur Förderung der Wissenschaft e.V., Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin (DGAI), Medtronic, Philips Electronics Nederland BV, BMG and BMBF.

Susanne Koch: was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Society) – Project number KO 4249/3-1). S.K. is an inventor on patents, sold to Medtronic. S.K. received speakers' fee from Medtronic, and personal fees from Georg Thieme Verlag.

Abstract

Background: Postoperative delirium (POD) is a common complication in elderly patients undergoing anesthesia. Even though it is increasingly recognized as an important health issue, the early detection of patients at risk for POD remains a challenge. This study aims to identify predictors of POD by analyzing frontal electroencephalogram (EEG) at propofol induced loss of consciousness (LOC).

Methods: In this prospective, observational single-center study, we included patients over 70 years undergoing general anesthesia for a planned surgery. Frontal EEG was recorded on the day before surgery (baseline), and during anesthesia induction (1 minute, 2 minutes and 15 minutes after LOC). Postoperative patients were screened for POD twice daily for five days. Spectral analysis was performed using the multitaper method. The EEG Spectrum was decomposed in periodic and aperiodic (correlates to asynchronous spectrum wide activity) components. The aperiodic component is characterized by its offset (y-intercept) and exponent (the slope of the curve). Computed EEG parameters were compared between patients who developed POD and those who did not (noPOD). Significant EEG parameters were included in a binary logistic regression analysis to predict vulnerability for POD.

Results: Out of 151 patients, 50 (33%) developed POD. At 1 minute after LOC POD patients demonstrated decreased alpha [POD: 0.3 μV^2 (0,21-0,71), noPOD: 0.55 μV^2 (0.36-0.74), p=0.019] and beta band power [POD: 0.27 μV^2 (0.12-0.38), noPOD:0.38 μV^2 (0.25-0.48): p=0.003] and lower spectral edge frequency (SEF95) [POD: 10.45 Hz (5.65-15.04), noPOD: 14.56 Hz (9.51-16.65), p=0.01].

15 minutes after LOC, POD patients displayed a decreased aperiodic offset [POD: 0.42 μV^2 (0.11-0.69), noPOD: 0.62 μV^2 (0.37-0.79), p=0.004]. The logistic regression model predicting POD vulnerability demonstrated an area under the curve (AUC) of 0.738 (0.69-0.75).

Conclusion: The findings suggest that EEG markers obtained during LOC at anesthesia induction may serve as EEG-based biomarkers to early identify patients at risk to develop POD.

Introduction

Postoperative neurocognitive disorders represent a disease complex comprising postoperative delirium (POD), and postoperative neurocognitive dysfunction (1). Up to 50% of elderly patients develop POD after surgical interventions, associated with an elevated risk to develop long-term consequences (2). Due to the hypoactive motor-aspect postoperative delirium has long been underdiagnosed and overlooked (3, 4). However, these health issues are of growing importance in the current sociodemographic context, as they also are associated with an increased mortality, prolonged hospital stay and long-term cognitive decline (5-7).

The complex pathophysiological mechanism behind the postoperative delirium stands on two central pillars: the vulnerability of elderly patients and the toxicity associated with general anesthesia and the surgical procedure. With growing age, there is a continuous decline in physiological reserve leading to frailty, a state of reduced resolution of homeostasis following stress situations (8). The inflammatory, metabolic, endocrine and overall systemic stress associated with anesthesia and surgery overstrain the available homeostasis reserves in the brain, causing the emergence of a postoperative delirium (9).

Perioperative EEG recordings have been widely implemented to guide anesthesia and recognize patterns of increased risk for POD (10, 11). This led to the possibility of models predicting reliably emergence of postoperative delirium based on clinical characteristics and intraoperative EEG signatures (12). However, a crucial importance lies in the earliest possible detection of risk patients. Anesthesiologists can adapt medication and dosage as well as enhance postoperative awareness to reduce any additional risk factors for the emergence of postoperative delirium.

The aim of our study was to describe EEG spectral signatures and their dynamics at anesthesia induction and the transition to unconsciousness pointing towards an increased risk for postoperative delirium. Our goal was to find early indicators of vulnerability for postoperative

delirium based solely on EEG-markers and thus allowing anesthesiologists to adapt their perioperative management and avert the emergence of a postoperative delirium.

Materials & Methods

This post-hoc analysis of a prospective, observational, explorative single-center study was conducted at the Charité Universitätsmedizin Berlin, Campus Virchow (ePOD study, NCT03879850). The trial was approved by the local ethics committee (Charité Universitätsmedizin Berlin, EA 1/161/17). Written approval was obtained from all participants according to the Declaration of Helsinki. Ethical and scientific quality standards were respected following the ICH-GCP guidelines.

Between March 2019 and November 2022 348 patients over 70 years old undergoing general anesthesia for a surgical intervention at Charité Universitätsmedizin Berlin, Campus Virchow Klinikum were included in the study. Patients were eligible if the surgery was planned to last for a minimum of 60 minutes and general anesthesia with either volatile gases or propofol was administered. Exclusion criteria comprised known neurological/psychiatric diseases, long-term medication with centrally active drugs, insufficient knowledge of German language to ensure reliable detection of postoperative delirium as well as intraoperative administration of ketamine or nitrous oxide.

General anesthesia was conducted following the standard operating procedure of the clinic (13). In case of preoperative anxiety, patients were premedicated with midazolam. Anesthesia was induced with fentanyl or remifentanil and propofol. Anesthetic dosages were determined individually based on patient characteristics. A non-depolarizing neuromuscular blocker was given for endotracheal intubation. Patients were either ventilated through an endotracheal tube or a laryngeal mask. The anesthesiologists had access to neuromonitoring and were free to adjust anesthetic doses based on the EEG and the derived parameters.

EEG recording

Frontal EEG was recorded from four electrodes (Fp1, Fp2, F7, F8) with a SEDline Root monitor (Masimo Corporation, Irvine USA) at a sampling frequency of 178 Hz. The earth electrode was placed at Fpz and the reference electrode 1 cm above. Impedances were kept under 5 kOhm.

A baseline EEG recording in awake state with eyes closed was recorded on the day before surgery. Additionally, the Mini-Mental-State-Examination (MMSE) was performed prior to surgery to screen for preexisting cognitive impairment. On the day of the surgery, perioperative EEG recordings were started before administration of anesthetic agents in awake state. Event markers were set at the following clinical time points: start of opiate injection, start of propofol injection, loss of consciousness (LOC), intubation, and surgical skin incision. During induction of anesthesia the study personal tested the lid closure reflex every five to ten seconds after loss of responsiveness. Loss of consciousness was defined as the suppression of lid closure reflex.

Postoperative delirium screening

After arrival in the recovery room patients were screened for postoperative delirium every 15 minutes for 1 hour with the Nursing Delirium Screening Scale (Nu-DESC) if they reached a Richmond Agitation-Sedation Scale (RASS) score above -2. In the five days following surgery patients were visited twice a day (in the morning 8-10 a.m. and in the evening 5-7 p.m.) to screen for postoperative delirium with the Nu-DESC, the Diagnostic and Statistical Manual of Mental Disorder criteria (DSM V) and the Delirium Detection Score (DDS). If patients were required to stay on the intensive care unit (ICU), the Confusion Assessment Method for ICU (CAM-ICU) was used. Patients were classified as POD if any of the scores were positive at any time point during the postoperative care, including the recovery room. Discharge before the 5th postoperative day was not considered as lost to follow up as this implied a good neurocognitive and functional recovery. To minimize inter-investigator bias screening for postoperative delirium was completed with three standardized, reliable screening tools and added daily chart

review as well as twice daily questioning of responsible nurses regarding delirious symptoms. The timeline of EEG acquisition and postoperative delirium screening is shown in figure 1.

EEG data and spectral analysis

EEG data and spectral analysis were performed in MATLAB (*MATLAB version: 9.13.0 (R2022b), Natick, Massachusetts: The MathWorks Inc.; 2022*.) with custom written scripts. EEG epochs were extracted with a duration of each 10 seconds from the perioperative recordings at the following time points: baseline (on the day prior to surgery), LOC_1 (1 minute after loss of consciousness), LOC_2 (2 minutes after loss of consciousness) and LOC_15 (15 minutes after loss of consciousness) (Figure 1).

EEG raw data preprocessing comprised bandpass filtering (0.1-40 Hz), trendline removal and single-patient raw data inspection for artifacts. All EEG segments were inspected visually regarding burst suppression patterns. Spectral analysis was performed with the multitaper method in the Chronux toolbox (version 2.12 v03, http://chronux.org/) (14) with a moving window length of 2 seconds, a window shift of 0.1 seconds, time-bandwidth product of 2 and 3 tapers. The spectrograms (Density Spectral Arrays (DSA)) and the power spectrum (PS) were computed for each EEG epoch.

EEG spectra can be decomposed into periodic and aperiodic components. The periodic activity corresponds to coordinated oscillations of cortical populations within frequency bands (□-band power 30.1-45Hz, □-band power 12.1-30Hz, □-band power 8-12Hz, □-band power 4-7.9Hz, □-band power 1.6-3.9Hz and sub-□-band power 0-1.5Hz), arising from common subcortical generators (15). The aperiodic activity translates in an underlying spectrum-wide slope and reflects the balance between excitatory and inhibitory synaptic current (16, 17). Aperiodic fitting was conducted for each time-segment using the Fitting Oscillations and One-Over-f (FOOOF) toolbox (version 1.0.0) (18) with the default parameters. To characterize the aperiodic activity, the offset (the y-intercept of the slope) and the exponent (the slope of the curve) were calculated. By deducting the aperiodic component from the power spectrum,

periodic power peaks were unveiled. We applied a similar method in a previous investigation with a detailed methodic explanation (19).

The following EEG parameters were computed: the spectral edge frequency (the frequency under which 95 percent of the power are located (SEF-95)), the mean power of the power peak in the alpha range (8-12 Hz), the alpha peak frequency (the frequency with the highest power within the alpha band) , the alpha power difference between baseline and LOC_1/2/15, the mean power of the beta range before decomposition, the mean power of the power peak in the beta range (12-30 Hz), beta peak frequency (the frequency with the highest power within the beta band) and the beta ratio. The beta ratio calculation was derived from the method of Rampil: BetaRatio = log((P30-47Hz)/(P11-20Hz)) (20). We further calculated the aperiodic offset, the aperiodic exponent and specifically the aperiodic exponent in the gamma range (30-40 Hz).

Statistical Analysis

Statistical analysis was performed in MATLAB (*MATLAB version: 9.13.0 (R2022b), Natick, Massachusetts: The MathWorks Inc.; 2022*). Because of the explorative study design, we did not correct for multiple testing and accepted p-values < 0.05 as significant. Differences in population demographics were assessed with Chi-square-test and Mann-Whitney-U-Test for categorical and continuous variables, respectively. Results are reported as frequencies or median (25^{th}-75^{th}).

The computed EEG parameters were compared between POD and noPOD groups with the Mann-Whitney-U-Test. We aimed to perform a binary logistic regression predicting the emergence of postoperative delirium based on EEG parameters. To reduce the number of parameters in our model we accepted a ratio of down to 5 samples per predictor in this explorative analysis (21), which corresponded to 10 predictors in our case. The 10 parameters that were the most significant in the univariate analyses were selected. To test for multicollinearity, we calculated the Pearson correlation and the Variance Inflation Factor (VIF). Parameters were excluded when the r was > 0.7 and the VIF was ≥ 5. After this analysis Mean

Alpha Power at 15 minutes after loss of consciousness and the Beta Ratio at 15 minutes after loss of consciousness were excluded. The remaining parameters were incorporated in a binary logistic regression predicting the emergence of postoperative delirium. We employed bootstrapped logistic regression to assess the stability and variability of the logistic regression model in MATLAB. Subsequently, the model was applied to 10,000 bootstrapped samples, and the area under the receiver operating characteristic curve was computed for each iteration. The mean receiver operating characteristic (ROC) curve was computed over the bootstrap replicates and plotted with the 95% confidence interval. A representation of the distribution of the area under the curve (AUC) values was also plotted with the mean and 95% confidence interval of the AUC.

We did not include clinical parameters, because our goal was to develop a model based solely on the EEG-parameters within the first 15 minutes of anesthesia. However, we also did not see a difference in relevant risk factors for postoperative delirium like age, ASA score and preoperative cognitive performance between POD and noPOD patients.

We interpreted the area under the curve of the receiver operating characteristic as following: outstanding: $1 \geq AUC \geq 0.9$; excellent: $0.9 > AUC \geq 0.8$; acceptable: $0.8 > AUC \geq 0.7$ (22).

To further validate our approach, we conducted sensitivity analyses. First, we also included parameters as sex and anesthesia maintenance in our model. In a second model we included precipitating risk factors as anesthesia duration or drug used for anesthesia maintenance. Finally, we computed four different models, each one including the EEG-parameters of one single time point. The results can be found in the supplementary materials (https://links.lww.com/ALN/D458).

Results

Out of 348 patients primarily included in the study, 48 patients dropped out, 46 patients had to be excluded due to sever artefacts or missing EEGs and 103 patients had to be excluded because the EEG was unexpectedly recorded at lower sampling rates (89Hz). This was related to a system update from the SEDline monitors, where different display settings affected the sampling rate (23). Patients' characteristics of excluded patients did not differ from the included patients (see supplementary material, https://links.lww.com/ALN/D458).

Out of the 151 patients included in this analysis 50 patients developed postoperative delirium (33%). The remaining 101 patients did not score positive in the POD tests at any postoperative time point (noPOD, 66%) (Figure S1, https://links.lww.com/ALN/D458). Patients' characteristics are shown in table 1. We did not see a difference in age, ASA score or preoperative MMSE score. Compared to noPOD patients, a higher proportion of POD patients received inhalational anesthesia [Inhalational anesthesia maintenance: POD 60% (n=30) vs noPOD 31.7% (n=32), p = 0.01]. Additionally, a higher proportion of men developed postoperative delirium compared to women [sex (men/women %) POD 43%/25% vs noPOD 57%/75%, p=0.018]. When further investigated, it became apparent that women received significantly more often propofol for anesthesia maintenance than men [female: n=65 (75.6%), male: n=21 (24.4%), p=<0.001], which might be explained by higher risk for postoperative nausea and vomiting (PONV) in female, leading to more total intravenous anesthesia (TIVA) and thereby reducing their risk of developing a postoperative delirium. As expected, overall anesthesia duration was prolonged in POD patients as compared to noPOD patients [Anesthesia duration (min) POD 270 (175-360) vs noPOD 219 min (139 – 303), p = 0.018].

EEG data analysis

Figure 2 shows as group-wise mean spectrograms of the baseline recording on the day before surgery, during anesthesia induction around loss of consciousness and at 15 minutes after induction. The computed EEG parameters are shown in Table 2. Figure 3A shows the PS before

decomposition for POD (red) and noPOD (blue) at the four previously defined time-segments, where 3B refers to the aperiodic and 3C to the periodic components of the EEG spectrum.

The most prominent difference between the groups laid in the periodic alpha/beta activity. At baseline we saw a reduced power in the mean beta band before decomposition in the POD group, which persisted in the following time points. We also observed a lower aperiodic exponent in the gamma range in POD patients, which persisted at loss of consciousness.

LOC_1 was characterized by a difference in SEF, mean alpha power, alpha peak, mean beta power and beta ratio. In general, the alpha power increase over LOC was significantly reduced in the POD group as compared to noPOD group.

At LOC_2, we saw a reduced beta ratio [POD: 2.64 (1.86-2.98), noPOD: 2.94 (2.43-3.47), p=0.002] and aperiodic offset in the POD group.

Towards LOC_15 POD patients showed a decrease in mean alpha power, alpha peak frequency, mean beta power, beta peak, beta ratio and the aperiodic offset.

During the first 15 minutes of anesthesia there was no statistically significant difference in the occurrence of burst suppression pattern between the POD and noPOD group.

During induction of anesthesia, we found in all patients an increase in periodic alpha/beta power and in the aperiodic exponent, corresponding to a steepening of the slope at LOC_1 (Figure B and C).

A detailed overview of the results is displayed in Table 2.

Modeling

After testing for significance and collinearity the following EEG parameters were included in a binary regression model: SEF95 at LOC 1, aperiodic offset at LOC 15, mean beta power at LOC 1-and 15, beta peak frequency at LOC 15, beta ratio at LOC 1 and 2 and the difference in alpha between LOC 15 and baseline. The calculated mean ROC curve demonstrated an acceptable mean AUC of 0.73 (0.69-0.75) (Figure 4, Figure S3,

https://links.lww.com/ALN/D458). The model characteristics are shown in Table S3 (https://links.lww.com/ALN/D458).

Discussion

Elderly patients at risk to develop postoperative delirium present specific EEG signatures in the periodic and aperiodic components at baseline as well as over the dynamic transition to unconsciousness during anesthesia induction. Including all these specific EEG parameters in a binary logistic regression model, patients at risk to develop postoperative delirium could be identified as early as within the first 15 minutes of anesthesia. This implies that already during induction of anesthesia, the EEG phenotype of a "vulnerable brain" (24) can be recognized and the following anesthetic procedure and postoperative surveillance and therapy can be adapted.

EEG signatures

In this analysis we demonstrate that with induction of anesthesia, POD patients develop a decreased alpha peak power and alpha peak frequency compared to noPOD patients of the same age. These findings are in line with previous research (11, 25, 26). During the anesthesia-induced transition to unconsciousness, elderly patients also show a reduced power in the alpha range (8-12 Hz) compared to young adults (19). We assume that a post-induction reduced alpha power might be a sign of a vulnerable brain, leading to a higher risk to develop postoperative delirium (24). Furthermore, we observed that POD patients exhibit a reduced post-induction beta arousal, associated with a lower spectral edge frequency within the first minute after LOC. Reduced preoperative beta and gamma power has been described as a marker pointing towards an elevated risk for postoperative delirium (11, 27). In our study we also saw a preoperative reduced beta power in POD patients, confirming the results of the previous studies. Given that there was no significant difference in age or cognitive function among our group of patients, beta mean power could serve as a useful early indicator for detecting cognitive decline.

We further demonstrated that the difference in the gamma power arises from a decrease in the aperiodic slope in the POD group, rather than from the coordinated periodic activity. The neural noise theory assumes that with aging due to a desynchronization of neuronal spiking the background neural noise activity increases (28). Hong and Rebec argue that because of reduced nerve conductivity, the aging brain compensates by increasing the neuronal firing rate. In the EEG this leads to a flattening of the aperiodic slope (29). In a computational modeling study, Gao et al. demonstrated that the balance between excitatory and inhibitory synaptic currents corresponds to the aperiodic slope specifically in the gamma frequency range (30-70 Hz) (17). Hence, we might assume the decreased exponent in the gamma range might be also a sign of a more vulnerable brain.

The transition to anesthesia-induced unconsciousness follows a chronological succession of EEG signatures (30). In a previous study, we showed that the aperiodic exponent over loss of consciousness age-independently increases after induction of anesthesia in geriatric as well as in young patients (19). Here we again observed an increase of the aperiodic exponent after loss of consciousness, which notably did not differ between POD and noPOD patients. This implies that an increase of the aperiodic exponent could serve as an EEG based marker of loss of consciousness independently of age or the neurocognitive condition.

At two minutes after loss of consciousness POD patients notably showed a lower aperiodic offset, transcribing as a broadband shift, which was still present at 15 minutes after loss of consciousness. Changes in the aperiodic offset are positively correlated with neuronal population spiking (31, 32) and a corresponding blood oxygenation level dependent (BOLD) response in the fMRI (33). This phenomenon has not yet been described in POD patients and the neurophysiological background of this finding needs to be further examined.

During induction of anesthesia, elderly patients tend to experience anesthesia overdose (34). The EEG marker of excessive depth of anesthesia – burst suppression - is related to the emergence of postoperative delirium in elderly (35). However, in our study group POD patients received lower dosage of anesthetics and we found no increased occurrence of burst suppression pattern after anesthesia induction in our POD group. This finding underlies the relevance of preexisting brain vulnerability as risk factor for the emergence of postoperative delirium, independently of other risk factors that can occur during anesthesia.

Identification of vulnerable patients

Our statistical model can identify vulnerable patients regarding the development of postoperative delirium as early as during anesthesia induction. While various precipitating risk factors associated with postoperative delirium manifest later during the surgical course, such as anesthesia depth and burst-suppression duration, the choice of the anesthetic agent given, the overall duration of the surgery, or intraoperative blood loss (35-38), patients developing postoperative delirium could be identified based on EEG derived parameters within only 15 minutes of anesthesia. These findings highlight the relevance of predisposing risk factors in the development of postoperative delirium, underscore the importance of neuromonitoring and the necessity to develop an EEG-based risk assessment tool.

In our study cohort anesthesia maintenance with volatile gases was a risk factor for the emergence of postoperative delirium. This is in line with a previous retrospective study data analysis done by our group (37), and was also shown in a meta-analysis (38). Hence, prospective studies should examine whether patients presenting the described EEG signatures after loss of consciousness would profit from a total intravenous anesthesia with propofol for anesthesia maintenance.

To improve prevention of postoperative delirium it would be ideal to develop an algorithm that automatically recognizes EEG patterns associated with postoperative delirium. If implemented in EEG neuromonitors, it could alert anesthesiologists of the risk, giving them the possibility

to reduce further risk factors, possibly adjust anesthesia guidance and intensify postoperative surveillance. However, this model would need to be validated prospectively with an independent patient cohort and then might be implemented in commonly used neuromonitors, if technically feasible. The lack of validation and possible technical limitations in the clinical routine should be called out as limitations of our model. It is important to note that we performed the prediction of postoperative delirium in a hypothesis-generating fashion in this post-hoc analysis of our data (39). Our goal was to explore whether vulnerable patients could be identified after induction of anesthesia, at a timepoint when emergence of postoperative delirium possibly can still be averted.

Limitations

One limitation of the study is the uneven distribution of sex in POD and noPOD patients, despite sex not being a known risk factor of postoperative delirium. As this was an observational study, the treatment of study patients was not influenced, and anesthesiologist chose the medication and dosage according to their clinical evaluation. Because of the higher PONV risk in female, they received more often propofol as an anesthetic agent. In our analysis volatile anesthesia maintenance was a risk factor for developing postoperative delirium, hence we attributed the difference in the sex distribution rather to the administration of the anesthetics.

Unfortunately, after a software update the sampling frequency of the recorded data stored in the SEDline monitor was affected by the display setting (23). In our clinic, neuromonitoring is part of the routine protocol in general anesthesia for elderly patients. As anesthesiologists have learned to rely on the perioperative EEG and the derived indices, they adapted the settings to their usual practices. This led to modified raw traces. Furthermore, the built-in low pass filter at 45 Hz was shifted to around 28 Hz in the recordings with a sampling frequency of 89 Hz instead of 178 Hz (Figure S2, https://links.lww.com/ALN/D458). After recognizing the issue and resetting the monitor settings to default, the sampling rate reverted to 178 Hz. Since we also wanted to investigate the beta and gamma frequency band and those frequencies were not

assessable in the EEGs with the lower sampling rate, we decided to exclude 103 EEGs with a sampling rate of 89 Hz.

Because of the technical issues we faced, half of the patients initially included had to be excluded. Even though we did not see broad differences in patients' characteristics between included and excluded patients, except in the use of drug agent for anesthesia maintenance. Included patients received significantly more often a total intravenous anesthesia. This could lead to selections bias.

Additionally, no adjustments were made for multiple comparisons due to the hypothesis-generating nature of this analysis.

Conclusions

This study provides evidence that vulnerable patients regarding postoperative delirium may be recognized based on predisposing EEG biomarkers assessed preoperatively and during the transition to unconsciousness. If confirmed, our findings could be implemented in EEG neuromonitors to enable early detection and adapted perioperative management.

Details of authors' contributions

SK, ENB and CS designed the clinical trial. SK, MP and SL coordinated the study. SK, MP, SL and VR discussed the results and conducted the data analysis. SK, MP and SL wrote the first draft of the manuscript. All authors contributed to the analysis and approved the final manuscript.

Acknowledgements

The authors would like to thank all participants and collaborators involved in this trial.

Further we would like to thank Julia Jansche, Marc Dorenbeck, Christin Irrgang und Elisa Schneller for the good cooperation in the patient recruitment and data processing.

Supplemental Digital Content

Supplemental material: Biomarkers of postoperative delirium vulnerability, https://links.lww.com/ALN/D458

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Figure Legends

Figure 1: Timeline of EEG segments (yellow) and clinical markers of anesthesia (orange). Baseline EEG was recorded on the day before surgery. LOC occurred on average 2.5 minutes after the application of anesthesia.

Figure 2: Group averaged spectrograms for POD and noPOD group.

Left column: Baseline: awake, eyes closed.

Middle column: 2 minutes before until 2 minutes after LOC (Time 0)

Right column: 15 minutes after LOC.

LOC was defined as the suppression of the lid closure reflex. EEG analysis was performed on 10 second intervals at baseline, 1 minute after LOC (LOC 1), 2 minutes after LOC (LOC 2) and 15 minutes after LOC (LOC 15).

Figure 3: Decomposition of the power spectrum (PS) in periodic and aperiodic components for POD (red) and noPOD (blue) group at four timepoints: baseline, 1 minute, 2 minutes and 15 minutes after LOC.

Top row (A): raw PS; Middle row (B): aperiodic component of the PS; Lower row (C): periodic component of the PS. Shaded areas correspond to the interquartile range [25^{th}-75^{th}], vertical dashed lines mark frequency bands.

Figure 4: Mean receiver operating characteristics (ROC) curve of the fitted binary logistic model with an area under the curve (AUC) of 0.73 for 10,000 bootstrap replicates. The shaded blue area corresponds to the confidence interval.

TABELS: Biomarkers of postoperative delirium vulnerability

	POD (n=50)	noPOD (n=101)	All (n=151)	p-Value
Age, years	77 [72-80]	77 [73-81]	77 [72-81]	0.763
Sex				**0.018**
Male	29 (58%)	38 (37.6%)	67 (44.4%)	
Female	21 (42%)	63 (62.4%)	84 (55.6%)	
ASA status				0.197
1/2/3/4	0/22/25/3	3/46/51/1	3/68/76/4	
(%)	(0/44/50/6)	(3/45.5/50.5/1)	(2/45/50.4/2.6)	
BMI (kg/m^2)	25.31 (24.03-28.13)	24.92 (22.41-27.94)	24.94 (22.62-28.13)	0.301
MMSE	(n= 40) 27.5 (24-29)	(n=78) 28 (27-29)	(n=118) 28 (26.75-29)	0.189
Duration anesthesia (min)	270 (175-360)	219 (139-303)	233 (147-328)	**0.018**
Premedication with midazolam	3 (6%)	3 (3%)	6 (4%)	0.37
Induction anesthesia				
Propofol	49 (98)	99 (98)	148 (98)	0.199
Dose (mg)	150 (100-195)	145 (100-150)	150 (100-170)	
Thiopental	1	1	2	
Maintenance anesthesia				**0.01**
TIVA	19 (38)	67 (66.3)	86 (57)	
Volatile anesthetics	30 (60)	32 (31.7)	62 (41.2)	
Dosage				
Propofol (mg/kg/h)	5.5 (5-6)	6 (5.5-6)	6 (5.45-6)	0.1
Sevoflurane (et vol %)	1.55(1,4-1,8)	1.7 (1.5-2)	1.7 (1.5-2)	0.106
Desflurane (et vol %)	4.65 (4,15-5)	4.85 (4.6-5.05)	4.85 (4.35-5)	0.486
EEGs with burst suppressions n (%)	15 (30%)	24 (23.8%)	39 (25.8)	0.413
Time (minutes)				
Propofol to LOC	2.63 (1.97-3.33)	2.57 (2.03-3.3)	2.63 (2.03-3.3)	0.991
LOC to Intubation	2.37 (0.97-3.67)	2.67 (1.1-3.6)	2.47 (1.02-3.62)	0.855

Table 1: Baseline patients' characteristics. Categorical data was calculated using Chi-Quadrat-test and results, for continuous data Mann-Whitney-U-Test was used. Results are reported as frequencies or median [25th-75th percentile]. P-values <0.05 are presented bold. ASA: American society of Anesthesiologist, BMI: body mass index, et: end-tidal, LOC: loss of consciousness, MMSE: Mini-mental state examination, noPOD: no postoperative delirium, POD: postoperative delirium, TIVA: total intravenous anesthesia.

	Timepoint	POD	noPOD	p-value
SEF95 (Hz)	Baseline	22.85 (18.37-29.07)	25.76 (19.22-30.83)	0.187
	LOC_1	**10.45 (5.65-15.04)**	**14.56 (9.51-16.65)**	**0.010**
	LOC_2	11.62 (7.66-17.9)	14.93 (9.43-17.85)	0.330
	LOC_15	15.24 (12.96-18)	16.04 (14.17-17.81)	0.241
Mean alpha power after decomposition (μV^2)	Baseline	0.24 (0.12-0.4)	0.22 (0.07-0.34)	0.292
	LOC_1	**0.3 (0.21-0.71)**	**0.55 (0.36-0.74)**	**0.019**
	LOC_2	0.46 (0.28-0.76)	0.55 (0.39-0.85)	0.066
	LOC_15	**0.54 (0.29-0.92)**	**0.74 (0.5-0.92)**	**0.002**
Alpha peak frequency (Hz)	Baseline	8.7 (8-9.83)	8.7 (8-9.74)	0.724
	LOC_1	**9.92 (8.96-11.13)**	**10.44 (9.74-11.48)**	**0.038**
	LOC_2	10.09 (9.04-11.48)	10.44 (9.39-11.48)	0.295
	LOC_15	**10.09 (8.35-11.13)**	**10.44 (9.74-11.48)**	**0.037**
Alpha power difference (LOC_15-Baseline) (μV^2)		**0.29 (0.07-0.51)**	**0.47 (0.23-0.76)**	**0.002**
Mean beta power before decomposition (μV^2)	Baseline	**0.06 (0.04-0.1)**	**0.08 (0.05-0.13)**	**0.014**
	LOC_1	**0.05 (0.03-0.08)**	**0.09 (0.05-0.15)**	**<0.001**
	LOC_2	**0.05 (0.02-0.1)**	**0.9 (0.06-0.15)**	**0.001**
	LOC_15	**0.03 (0.02-0.07)**	**0.6 (0.4-0.1)**	**0.001**
Mean beta power after decomposition (μV^2)	Baseline	0.12 (0.06-0.16)	0.13 (0.09-0.21)	0.100
	LOC_1	**0.27 (0.12-0.38)**	**0.38 (0.25-0.48)**	**0.003**
	LOC_2	**0.27 (0.17-0.43)**	**0.38 (0.22-0.5)**	**0.017**
	LOC_15	**0.31 (0.18-0.44)**	**0.41 (0.3-0.53)**	**0.002**
Beta peak frequency after decomposition (Hz)	Baseline	20.87 (17.22-27.75)	20.18 (15.83-25.57)	0.397
	LOC_1	16.7 (13.14-22.62)	16.01 (12.53-20.18)	0.250
	LOC_2	16.01 (12.53-20.53)	14.27 (12.53-18.62)	0.359
	LOC_15	**16.18 (12.79-18.88)**	**13.22 (12.18-16.18)**	**0.001**
Beta ratio	Baseline	1.1 (0.52-1.54)	0.93(0.27-1.5)	0.463
	LOC_1	**2.4 (1.79-2.97)**	**2.81 (2.33-3.22)**	**0.006**
	LOC_2	**2.64 (1.86-2.98)**	**2.94 (2.43-3.47)**	**0.002**
	LOC_15	**2.44 (1.89-2.99)**	**2.98 (2.65-3.39)**	**<0.001**
Aperiodic offset (μV^2)	Baseline	0.16 (-0.9-0.39)	0.17 (-0.03-0.43)	0.771
	LOC_1	0.85 (0.45-1.35)	0.91 (0.61-1.19)	0.326
	LOC_2	**0.71 (0.37-1.15)**	**0.89 (0.61-1.32)**	**0.028**
	LOC_15	**0.42 (0.11-0.69)**	**0.62 (0.37-0.79)**	**0.004**
Aperiodic exponent (μV^2/Hz)	Baseline	1.15 (0.97-1.32)	1.1 (0.89-1.31)	0.290
	LOC_1	1.84 (1.73-2.08)	1.83 (1.66-2)	0.531
	LOC_2	1.82 (1.64-1.98)	1.78 (1.64-2.12)	0.515
	LOC_15	1.67 (1.51-1.8)	1.74 (1.59-1..84)	0.193

Aperiodic exponent	Baseline	**1.64 (0.61-2.96)**	**2.32 (1.38- 3.38)**	**0.044**
gamma range	LOC_1	**2.17 (0.66-4.21)**	**3.03 (2.09-4.79)**	**0.025**
(μV2/Hz)	LOC_2	3.45 (1.94-4.71)	3.39 (2.33-4.55)	0.802
	LOC_15	3.05 (1.62-5.21)	3.53 (2.32-5.06)	0.220

Table 2: Perioperative EEG parameters comparing results between POD and noPOD group.

Parameters were compared using Mann-Whitney-U-Test for each time point, results are reported as median (25^{th}-75^{th} percentile). P-values < 0.05 are represented bold. The beta ratio was calculated as log((P30-47Hz)/(P11-20Hz)). noPOD: no postoperative delirium, POD: postoperative delirium, SEF95: spectral edge frequency under which 95% of the power lies.

Figure 1

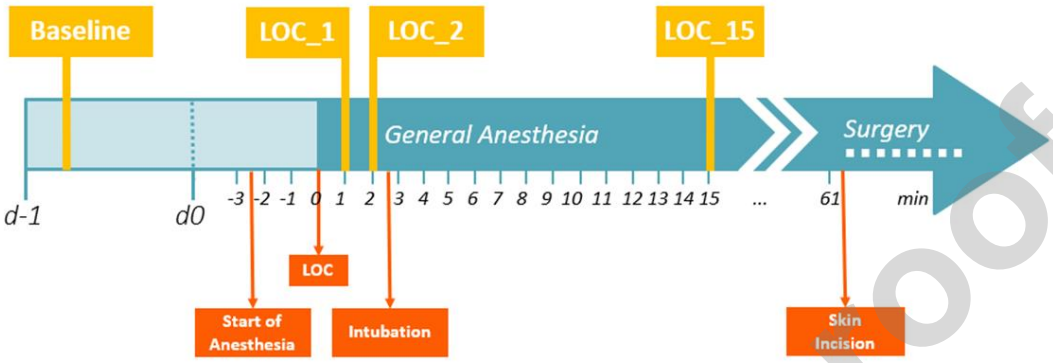

Figure 2

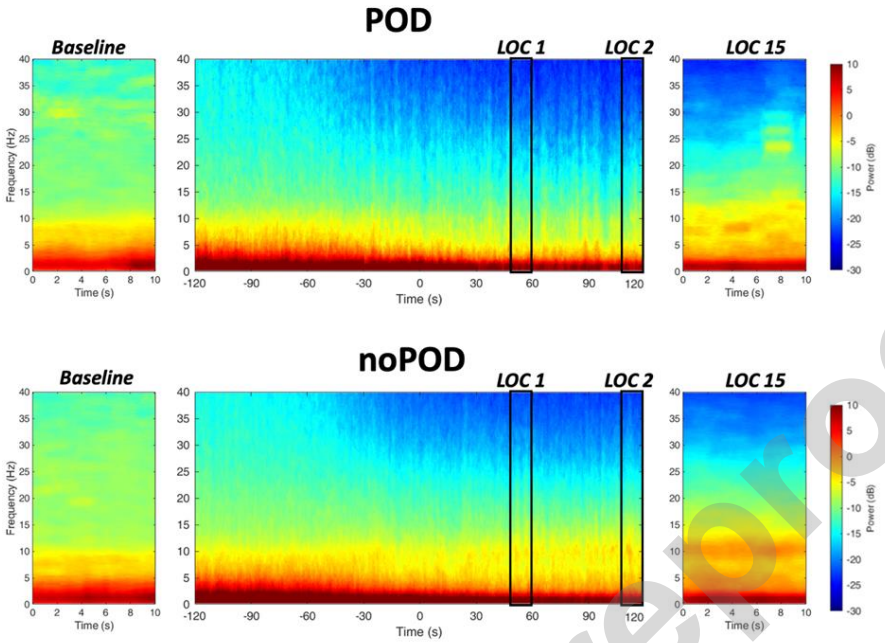

Figure 3

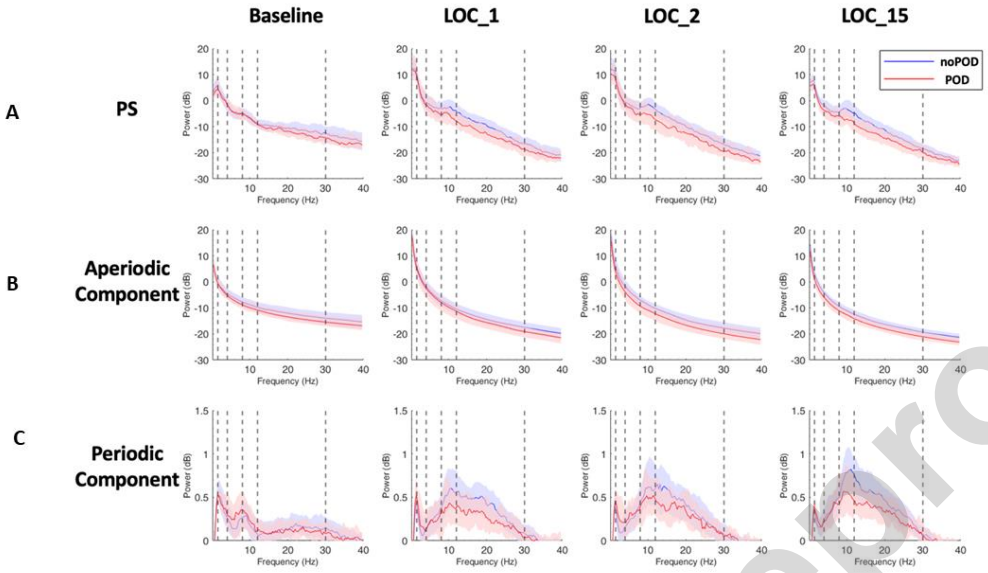

Figure 4