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Pollak, Marie; Leroy, Sophie; Röhr, Vera; Brown, Emery Neal; Spies, Claudia; Koch, Susanne

Published in:
Anesthesiology

DOI:
10.1097/ALN.0000000000004929

Publication date:
2024

Document version:
Final published version

Document license:
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Citation for pulished version (APA):

Pollak, M., Leroy, S., Röhr, V., Brown, E. N., Spies, C., & Koch, S. (2024). Electroencephalogram Biomarkers from Anesthesia Induction to Identify Vulnerable Patients at Risk for Postoperative Delirium. *Anesthesiology*, 140(5), 979-989. <https://doi.org/10.1097/ALN.0000000000004929>

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ANESTHESIOLOGY

Electroencephalogram Biomarkers from Anesthesia Induction to Identify Vulnerable Patients at Risk for Postoperative Delirium

Marie Pollak, M.D., Sophie Leroy, M.D.,
Vera Röhr, Emery Neal Brown, M.D. Univ. Prof. Dr.,
Claudia Spies, M.D. Univ. Prof. Dr.,
Susanne Koch, M.D. Assoc. Prof. Dr.

ANESTHESIOLOGY 2024; 140:979–90



EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative delirium arises from the acute interactions of anesthesia and surgery with a pre-existing vulnerable brain
- Characteristic electroencephalogram patterns during maintenance and emergence from general anesthesia are associated with the risk of postoperative delirium
- It is unknown whether electroencephalogram patterns seen before anesthesia correlate with a vulnerable brain associated with postoperative delirium

What This Article Tells Us That Is New

- Electroencephalogram responses, seen before and during induction of anesthesia, might be useful biomarkers of a vulnerable brain phenotype
- At induction of anesthesia, electroencephalogram signatures indicative of a vulnerable brain show reduced alpha and beta waveband peak power and lower spectral edge frequency

ABSTRACT

Background: Postoperative delirium 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 postoperative delirium remains a challenge. This study aims to identify predictors of postoperative delirium by analyzing frontal electroencephalogram at propofol-induced loss of consciousness.

Methods: This prospective, observational single-center study included patients older than 70 yr undergoing general anesthesia for a planned surgery. Frontal electroencephalogram was recorded on the day before surgery (baseline) and during anesthesia induction (1, 2, and 15 min after loss of consciousness). Postoperative patients were screened for postoperative delirium twice daily for 5 days. Spectral analysis was performed using the multitaper method. The electroencephalogram spectrum was decomposed in periodic and aperiodic (correlates to asynchronous spectrum wide activity) components. The aperiodic component is characterized by its offset (γ intercept) and exponent (the slope of the curve). Computed electroencephalogram parameters were compared between patients who developed postoperative delirium and those who did not. Significant electroencephalogram parameters were included in a binary logistic regression analysis to predict vulnerability for postoperative delirium.

Results: Of 151 patients, 50 (33%) developed postoperative delirium. At 1 min after loss of consciousness, postoperative delirium patients demonstrated decreased alpha (postoperative delirium: $0.3 \mu V^2$ [0.21 to 0.71], no postoperative delirium: $0.55 \mu V^2$ [0.36 to 0.74]; $P = 0.019$) and beta band power [postoperative delirium: $0.27 \mu V^2$ [0.12 to 0.38], no postoperative delirium: $0.38 \mu V^2$ [0.25 to 0.48]; $P = 0.003$] and lower spectral edge frequency (postoperative delirium: 10.45 Hz [5.65 to 15.04], no postoperative delirium: 14.56 Hz [9.51 to 16.65]; $P = 0.01$). At 15 min after loss of consciousness, postoperative delirium patients displayed a decreased aperiodic offset (postoperative delirium: $0.42 \mu V^2$ [0.11 to 0.69], no postoperative delirium: $0.62 \mu V^2$ [0.37 to 0.79]; $P = 0.004$). The logistic regression model predicting postoperative delirium vulnerability demonstrated an area under the curve of 0.73 (0.69 to 0.75).

Conclusions: The findings suggest that electroencephalogram markers obtained during loss of consciousness at anesthesia induction may serve as electroencephalogram-based biomarkers to identify at an early time patients at risk of developing postoperative delirium.

(ANESTHESIOLOGY 2024; 140:979–90)

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). M.P. and S.L. contributed equally to this article.

Submitted for publication July 21, 2023. Accepted for publication January 19, 2024. Published online first on January 31, 2024.

Marie Pollak, M.D.: Department of Anesthesiology and Operative Intensive Care Medicine, Charité University Medicine Berlin, Berlin, Germany.

Sophie Leroy, M.D.: Department of Anesthesiology and Operative Intensive Care Medicine, Charité University Medicine Berlin, Berlin, Germany.

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The article processing charge was funded by Charité Research Support.

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, which is associated with an elevated risk of developing long-term consequences.² Due to the hypoactive motor aspect, POD has long been underdiagnosed and overlooked.^{3,4} However, these health issues are of growing importance in the current sociodemographic context, because they also are associated with an increased mortality, prolonged hospital stay, and long-term cognitive decline.⁵⁻⁷

The complex pathophysiological mechanism behind the POD stands on two central pillars: the vulnerability of elderly patients and the toxicity associated with general anesthesia and surgical procedures. With growing age, there is a continuous decline in physiologic reserve leading to frailty, a state of reduced resolution of homeostasis after 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 POD.⁹

Perioperative electroencephalogram (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 reliably predicting emergence of POD 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 POD.

The aim of our study was to describe EEG spectral signatures and their dynamics at anesthesia induction and the transition to unconsciousness pointing toward an increased risk for POD. Our goal was to find early indicators of vulnerability for POD based solely on EEG markers, thus allowing anesthesiologists to adapt their perioperative management and avert the emergence of POD.

Materials and 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice.

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

General anesthesia was conducted following the standard operating procedure of the clinic.¹³ In cases of preoperative anxiety, patients were premedicated with midazolam. Anesthesia was induced with fentanyl or remifentanyl and propofol. Anesthetic dosages were determined individually based on patient characteristics. A nondepolarizing neuromuscular blocker was given for endotracheal intubation. Patients were ventilated through either 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, and F8) with a SEDline Root monitor (Masimo Corporation, USA) at a sampling frequency of 178 Hz. The earth electrode was placed at Fpz with the reference electrode 1 cm above. Impedances were kept under 5 kOhm.

A baseline EEG recording in the awake state with eyes closed was recorded on the day before surgery. Additionally, the Mini Mental State Examination was performed before surgery to screen for pre-existing cognitive impairment. On the day of the surgery, perioperative EEG recordings were started before administration of anesthetic agents in the 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 personnel tested the lid closure reflex every 5 to 10 s after loss of responsiveness. LOC was defined as the suppression of lid closure reflex.

Postoperative Delirium Screening

After arrival in the recovery room, patients were screened for POD every 15 min for 1 h with the Nursing Delirium Screening Scale if they reached a Richmond Agitation–Sedation Scale score above –2. In the 5 days after surgery,

Vera Röhr: Neurotechnology Group, Technical University Berlin, Berlin, Germany.

Emery Neal Brown, M.D. Univ. Prof. Dr.: Harvard–MIT Health Sciences and Technology Program, Massachusetts Institute of Technology, Cambridge, Massachusetts; and Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Claudia Spies, M.D. Univ. Prof. Dr.: Department of Anesthesiology and Operative Intensive Care Medicine, Charité University Medicine Berlin, Berlin, Germany.

Susanne Koch, M.D. Assoc. Prof. Dr.: Department of Anesthesiology and Operative Intensive Care Medicine, Charité University Medicine Berlin, Berlin, Germany; and Department of Anesthesia, University of Southern Denmark, Odense, Denmark.

patients were visited twice a day (in the morning between 8:00 and 10:00 AM and in the evening between 5:00 and 7:00 PM) to screen for POD with the Nursing Delirium Screening Scale, the Diagnostic and Statistical Manual of Mental Disorder criteria, and the Delirium Detection Score. If patients were required to stay on the intensive care unit (ICU), the Confusion Assessment Method for the ICU was used. Patients were classified as having POD if any of the scores were positive at any time point during the postoperative care, including the recovery room. Discharge before the fifth postoperative day was not considered as lost to follow-up because this implied a good neurocognitive and functional recovery. To minimize interinvestigator bias, screening for POD 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 POD screening is shown in figure 1.

EEG Data and Spectral Analysis

EEG data and spectral analysis were performed in MATLAB (version 9.13.0, MathWorks Inc., USA) with custom written scripts. EEG epochs were extracted with a duration of 10 s each from the perioperative recordings at the following time points: baseline (on the day before surgery), LOC_1 (1 min after LOC), LOC_2 (2 min after LOC), and LOC_15 (15 min after LOC; fig. 1).

EEG raw data preprocessing comprised bandpass filtering (0.1 to 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, <https://chronux.org/>)¹⁴ with a moving window length of 2 s, a window shift of 0.1 s, time–bandwidth product of two and three tapers. The spectrograms (density spectral arrays) and the power spectrum 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 (gamma–band power, 30.1 to 45 Hz; beta–band power, 12.1 to 30 Hz; alpha–band power, 8 to 12 Hz; theta–band power, 4 to 7.9 Hz; delta–band power, 1.6 to 3.9 Hz; and sub–delta–band power, 0 to 1.5 Hz), 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 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% of the power is located), the mean power of the power peak in the alpha range (8 to 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 to 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: beta ratio = $\log[(P_{30 \text{ to } 47 \text{ Hz}})/(P_{11 \text{ to } 20 \text{ Hz}})]$.²⁰ We further calculated the aperiodic offset, the aperiodic exponent, and specifically the aperiodic exponent in the gamma range (30 to 40 Hz).

Statistical Analysis

Statistical analysis was performed in MATLAB. 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. The results are reported as frequencies or medians (25th to 75th percentiles).

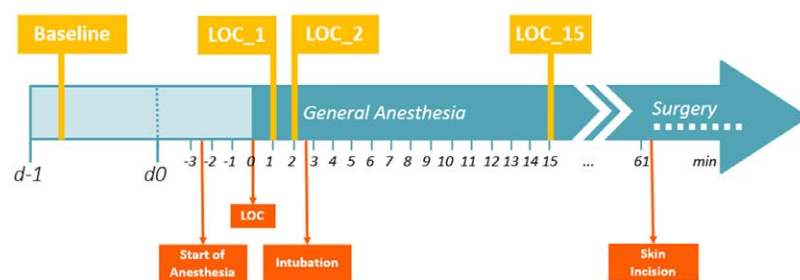


Fig. 1. Timeline of electroencephalogram (EEG) segments (yellow) and clinical markers of anesthesia (orange). Baseline EEG was recorded on the day before surgery. Loss of consciousness (LOC) occurred on average 2.5 min after the application of anesthesia.

The computed EEG parameters were compared between the groups with and without POD with the Mann–Whitney *U* test. We aimed to perform a binary logistic regression predicting the emergence of POD based on EEG parameters. To reduce the number of parameters in our model, we accepted a ratio of down to five 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. Parameters were excluded when the *r* was greater than 0.7, and the variance inflation factor was 5 or higher. After this analysis, the mean alpha power at 15 min after LOC and the beta ratio at 15 min after LOC were excluded. The remaining parameters were incorporated in a binary logistic regression predicting the emergence of POD. 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 (AUC) was computed for each iteration. The mean receiver operating characteristic curve was computed over the bootstrap replicates and plotted with the 95% CI. A representation of the distribution of the AUC values was also plotted with the mean and 95% CI 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 min of anesthesia. However, we also did not see a difference in relevant risk factors for POD like age, American Society of Anesthesiologists Physical Status, and preoperative cognitive performance between POD and patients without POD. We interpreted the area under the curve of the receiver operating characteristic as follows: for outstanding, the AUC was between 0.9 and 1; for excellent the AUC was between, 0.8 and 0.9; and for acceptable, the AUC was between 0.7 and 0.8.²²

To further validate our approach, we conducted sensitivity analyses. First, we also included parameters such as sex and anesthesia maintenance in our model. In a second model, we included precipitating risk factors such 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

Of 348 patients primarily included in the study, 48 patients dropped out, 46 patients had to be excluded due to severe artefacts or missing EEGs, and 103 patients had to be excluded because the EEG was unexpectedly recorded at lower sampling rates (89 Hz). This was related to a system update from the SEDline monitors, in which different display settings affected the sampling rate.²³ The patient

characteristics of the excluded patients did not differ from the included patients (see supplementary material, <https://links.lww.com/ALN/D458>).

Of the 151 patients included in this analysis, 50 patients developed POD (33%). The remaining 101 patients did not score positive in the POD tests at any postoperative time point (no POD, 66%; fig. S1, <https://links.lww.com/ALN/D458>). The patient characteristics are shown in table 1. We did not see a difference in age, American Society of Anesthesiologists Physical Status, or preoperative Mini Mental State Examination score. Compared to patients without POD, a higher proportion of POD patients received inhalational anesthesia (inhalational anesthesia maintenance: POD, 60% [n = 30] vs. no POD, 31.7% [n = 32]; *P* = 0.01). Additionally, a higher proportion of men developed POD compared to women (sex [men/women %] POD, 43%/25% vs. no POD, 57%/75%; *P* = 0.018). When further investigated, it became apparent that women received propofol for anesthesia maintenance significantly more often than men (women: n = 65 (75.6%), men: n = 21 (24.4%); *P* ≤ 0.001), which might be explained by higher risk for postoperative nausea and vomiting in women, leading to more total intravenous anesthesia and thereby reducing their risk of developing POD. As expected, overall anesthesia duration was prolonged in POD patients as compared to patients without POD (anesthesia duration: POD, 270 min [175 to 360 min] vs. no POD, 219 min [139 to 303 min]; *P* = 0.018).

EEG Data Analysis

Figure 2 shows group-wise mean spectrograms of the baseline recording on the day before surgery, during anesthesia induction around LOC, and at 15 min after induction. The computed EEG parameters are shown in table 2. Figure 3A shows the power spectrum before decomposition for POD (red) and no POD (blue) at the four previously defined time segments, whereas figure 3B shows the aperiodic and figure 3C shows the periodic components of the EEG spectrum.

The most prominent difference between the groups was 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 LOC.

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 the group without POD. At LOC_2, we saw a reduced beta ratio (POD, 2.64 [1.86 to 2.98]; no POD, 2.94 [2.43 to 3.47]; *P* = 0.002) and aperiodic offset in the POD group. Toward 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 min of anesthesia, there was no statistically significant difference in the occurrence of burst suppression pattern between the

Table 1. Baseline Patient Characteristics

	POD (n = 50)	no POD (n = 101)	All (n = 151)	P Value
Age, yr	77 (72 to 80)	77 (73 to 81)	77 (72 to 81)	0.763
Sex, n (%)				0.018
Male	29 (58%)	38 (37.6%)	67 (44.4%)	
Female	21 (42%)	63 (62.4%)	84 (55.6%)	
ASA Physical Status				0.197
I/II/III/IV	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	
Body mass index, kg/m ²	25.31 (24.03 to 28.13)	24.92 (22.41 to 27.94)	24.94 (22.62 to 28.13)	0.301
Mini Mental State Examination score	(n = 40) 27.5 (24 to 29)	(n = 78) 28 (27 to 29)	(n = 118) 28 (26.75 to 29)	0.189
Duration of anesthesia, min	270 (175 to 360)	219 (139 to 303)	233 (147 to 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 to 195)	145 (100 to 150)	150 (100 to 170)	
Thiopental	1	1	2	
Maintenance anesthesia				0.01
Total intravenous anesthesia	19 (38)	67 (66.3)	86 (57)	
Volatile anesthetics	30 (60)	32 (31.7)	62 (41.2)	
Dosage				
Propofol, mg · kg ⁻¹ · h ⁻¹	5.5 (5 to 6)	6 (5.5 to 6)	6 (5.45 to 6)	0.1
Sevoflurane, end-tidal volume %	1.55 (1.4 to 1.8)	1.7 (1.5 to 2)	1.7 (1.5 to 2)	0.106
Desflurane, end-tidal volume %	4.65 (4.15 to 5)	4.85 (4.6 to 5.05)	4.85 (4.35 to 5)	0.486
EEGs with burst suppressions, n (%)	15 (30%)	24 (23.8%)	39 (25.8)	0.413
Time, min				
Propofol to LOC	2.63 (1.97 to 3.33)	2.57 (2.03 to 3.3)	2.63 (2.03 to 3.3)	0.991
LOC to intubation	2.37 (0.97 to 3.67)	2.67 (1.1 to 3.6)	2.47 (1.02 to 3.62)	0.855

The categorical data were calculated using Chi-Quadrat-test and results for continuous data Mann-Whitney U test was used. The results are reported as frequencies or medians [25th to 75th percentile]. P values less than 0.05 are presented in bold type.

ASA, American Society of Anesthesiologists; EEG, electroencephalogram; LOC, loss of consciousness; POD, postoperative delirium.

groups with and without POD. 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 LOC₁ (fig. 3, 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: spectral edge frequency under which 95% of the power lies at 1 min after LOC, aperiodic offset at 15 min after LOC, mean beta power at 1 and 15 min after LOC, beta peak frequency at 5 min after LOC, beta ratio at 1 and 2 min after LOC, and the difference in alpha between 15 min after LOC and baseline. The calculated mean receiver operating characteristic curve demonstrated an acceptable mean AUC of 0.73 (0.69 to 0.75; fig. 4; fig. 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 of developing POD 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 of developing POD could be identified as early as within the first 15 min of anesthesia. This implies that already during induction of anesthesia, the EEG phenotype of a “vulnerable brain”²⁴ can be recognized and the ensuing 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 patients without POD 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 to 12 Hz) compared to young adults.¹⁹ We hypothesized that a postinduction reduced alpha power might be a sign of a vulnerable brain, leading to a higher risk to develop POD.²⁴ Furthermore, we observed that POD patients exhibit a reduced postinduction 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 toward an elevated

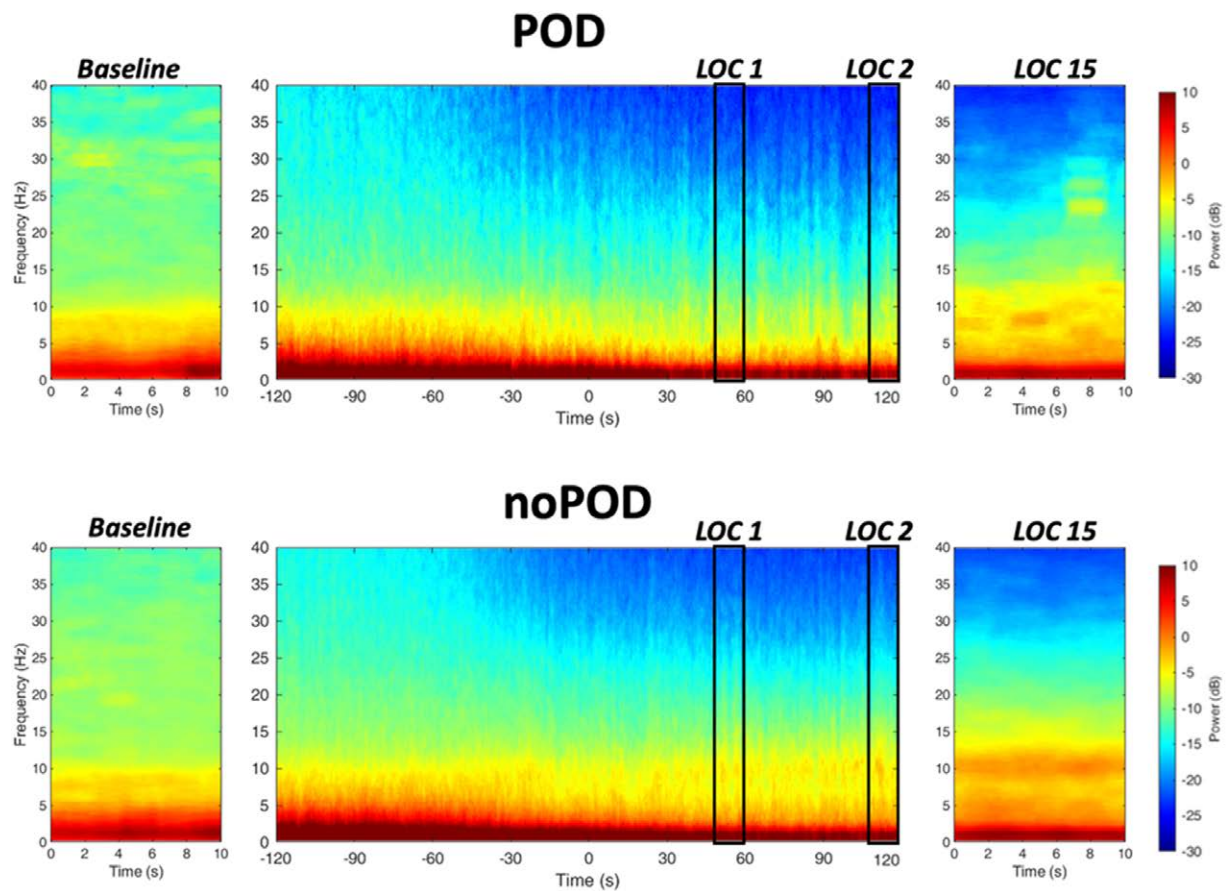


Fig. 2. Group averaged spectrograms for postoperative delirium (POD) group and the group without POD. (Left) Baseline: awake, eyes closed. (Middle) Levels from 2 min before until 2 min after loss of consciousness (LOC; time 0). (Right) Levels at 15 min after LOC. LOC was defined as the suppression of the lid closure reflex. EEG analysis was performed at 10-s intervals at baseline, 1 min after LOC (LOC 1), 2 min after LOC (LOC 2), and 15 min after LOC (LOC 15).

risk for POD.^{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 Rebec²⁹ 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.*¹⁷ demonstrated that the balance between excitatory and inhibitory synaptic currents corresponds to the aperiodic slope specifically in the gamma frequency range (30

to 70 Hz). 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 LOC 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 LOC, which notably did not differ between patients with and without POD. This implies that an increase of the aperiodic exponent could serve as an EEG-based marker of LOC independently of age or the neurocognitive condition.

At 2 min after LOC, POD patients showed a notably lower aperiodic offset, transcribing as a broadband shift, which was still present at 15 min after LOC. Changes in the aperiodic offset are positively correlated with neuronal population spiking^{31,32} and a corresponding blood oxygenation level-dependent response in the functional

Table 2. Perioperative EEG Parameters Comparing Results between Groups with and without POD

	Time Point	POD	No POD	P Value
Spectral edge frequency under which 95% of the power lies, Hz	Baseline	22.85 (18.37 to 29.07)	25.76 (19.22 to 30.83)	0.187
	LOC_1	10.45 (5.65 to 15.04)	14.56 (9.51 to 16.65)	0.010
	LOC_2	11.62 (7.66 to 17.9)	14.93 (9.43 to 17.85)	0.330
	LOC_15	15.24 (12.96 to 18)	16.04 (14.17 to 17.81)	0.241
Mean alpha power after decomposition, μV^2	Baseline	0.24 (0.12 to 0.4)	0.22 (0.07 to 0.34)	0.292
	LOC_1	0.3 (0.21 to 0.71)	0.55 (0.36 to 0.74)	0.019
	LOC_2	0.46 (0.28 to 0.76)	0.55 (0.39 to 0.85)	0.066
	LOC_15	0.54 (0.29 to 0.92)	0.74 (0.5 to 0.92)	0.002
Alpha peak frequency, Hz	Baseline	8.7 (8 to 9.83)	8.7 (8 to 9.74)	0.724
	LOC_1	9.92 (8.96 to 11.13)	10.44 (9.74 to 11.48)	0.038
	LOC_2	10.09 (9.04 to 11.48)	10.44 (9.39 to 11.48)	0.295
	LOC_15	10.09 (8.35 to 11.13)	10.44 (9.74 to 11.48)	0.037
Alpha power difference (LOC_15 to Baseline), μV^2		0.29 (0.07 to 0.51)	0.47 (0.23 to 0.76)	0.002
Mean beta power before decomposition, μV^2	Baseline	0.06 (0.04 to 0.1)	0.08 (0.05 to 0.13)	0.014
	LOC_1	0.05 (0.03 to 0.08)	0.09 (0.05 to 0.15)	< 0.001
	LOC_2	0.05 (0.02 to 0.1)	0.9 (0.06 to 0.15)	0.001
	LOC_15	0.03 (0.02 to 0.07)	0.6 (0.4 to 0.1)	0.001
Mean beta power after decomposition, μV^2	Baseline	0.12 (0.06 to 0.16)	0.13 (0.09 to 0.21)	0.100
	LOC_1	0.27 (0.12 to 0.38)	0.38 (0.25 to 0.48)	0.003
	LOC_2	0.27 (0.17 to 0.43)	0.38 (0.22 to 0.5)	0.017
	LOC_15	0.31 (0.18 to 0.44)	0.41 (0.3 to 0.53)	0.002
Beta peak frequency after decomposition, Hz	Baseline	20.87 (17.22 to 27.75)	20.18 (15.83 to 25.57)	0.397
	LOC_1	16.7 (13.14 to 22.62)	16.01 (12.53 to 20.18)	0.250
	LOC_2	16.01 (12.53 to 20.53)	14.27 (12.53 to 18.62)	0.359
	LOC_15	16.18 (12.79 to 18.88)	13.22 (12.18 to 16.18)	0.001
Beta ratio	Baseline	1.1 (0.52 to 1.54)	0.93(0.27 to 1.5)	0.463
	LOC_1	2.4 (1.79 to 2.97)	2.81 (2.33 to 3.22)	0.006
	LOC_2	2.64 (1.86 to 2.98)	2.94 (2.43 to 3.47)	0.002
	LOC_15	2.44 (1.89 to 2.99)	2.98 (2.65 to 3.39)	< 0.001
Aperiodic offset, μV^2	Baseline	0.16 (−0.9 to 0.39)	0.17 (−0.03 to 0.43)	0.771
	LOC_1	0.85 (0.45 to 1.35)	0.91 (0.61 to 1.19)	0.326
	LOC_2	0.71 (0.37 to 1.15)	0.89 (0.61 to 1.32)	0.028
	LOC_15	0.42 (0.11 to 0.69)	0.62 (0.37 to 0.79)	0.004
Aperiodic exponent, $\mu V^2/Hz$	Baseline	1.15 (0.97 to 1.32)	1.1 (0.89 to 1.31)	0.290
	LOC_1	1.84 (1.73 to 2.08)	1.83 (1.66 to 2)	0.531
	LOC_2	1.82 (1.64 to 1.98)	1.78 (1.64 to 2.12)	0.515
	LOC_15	1.67 (1.51 to 1.8)	1.74 (1.59 to 1.84)	0.193
Aperiodic exponent gamma range, $\mu V^2/Hz$	Baseline	1.64 (0.61 to 2.96)	2.32 (1.38 to 3.38)	0.044
	LOC_1	2.17 (0.66 to 4.21)	3.03 (2.09 to 4.79)	0.025
	LOC_2	3.45 (1.94 to 4.71)	3.39 (2.33 to 4.55)	0.802
	LOC_15	3.05 (1.62 to 5.21)	3.53 (2.32 to 5.06)	0.220

The parameters were compared using a Mann–Whitney U test for each time point. The results are reported as medians (25th to 75th percentile). *P* values less than 0.05 are represented in bold type. The beta ratio was calculated as $\log[(P30-47 \text{ Hz})/(P11-20 \text{ Hz})]$.

EEG, electroencephalogram; LOC, loss of consciousness; POD, postoperative delirium.

magnetic resonance imaging.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 POD in the 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 pre-existing brain vulnerability as a risk factor for the emergence of

POD, 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 POD as early as during anesthesia induction. Although various precipitating risk factors associated with POD 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 POD could be identified based on EEG-derived parameters within

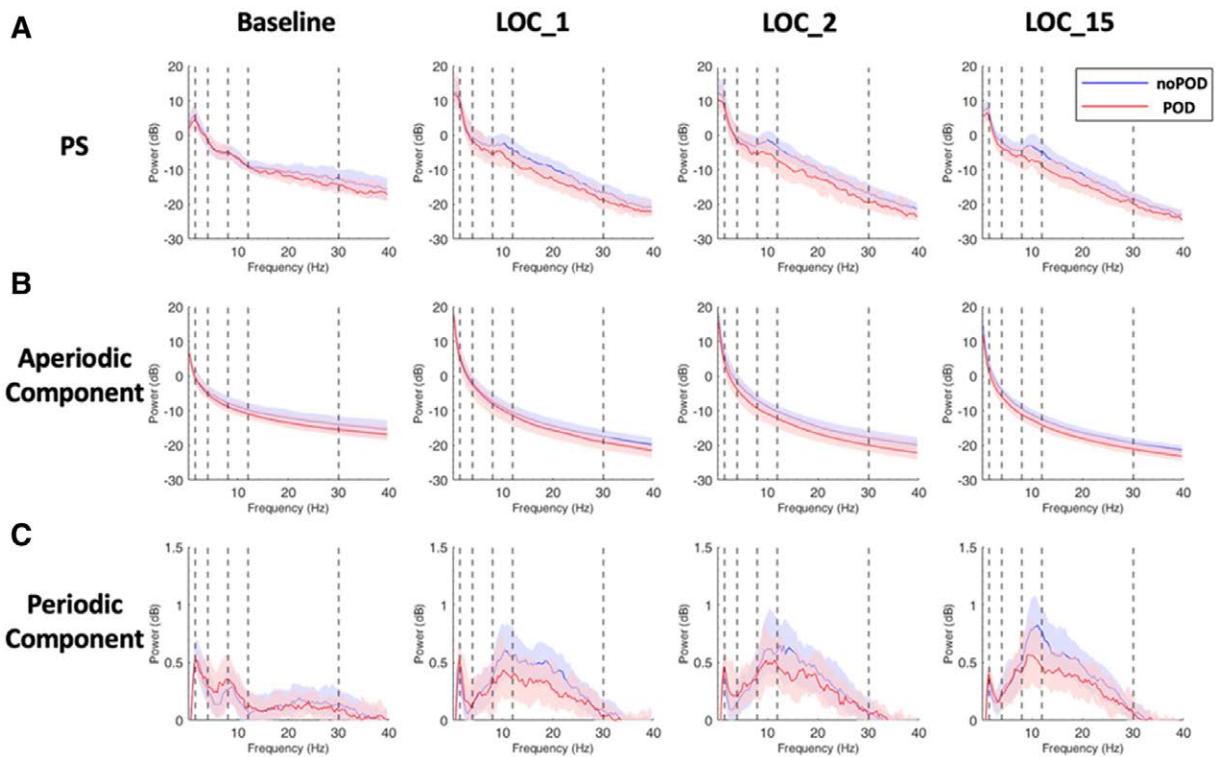


Fig. 3. Decomposition of the power spectrum (PS) in periodic and aperiodic components for postoperative delirium (POD; *red*) and no POD (*blue*) groups at four time points: baseline and 1, 2, and 15 min after loss of consciousness (LOC). (A) Raw PS. (B) Aperiodic component of the PS. (C) Periodic component of the PS. *Shaded areas* correspond to the interquartile range [25th to 75th percentile], and the *vertical dashed lines* mark frequency bands.

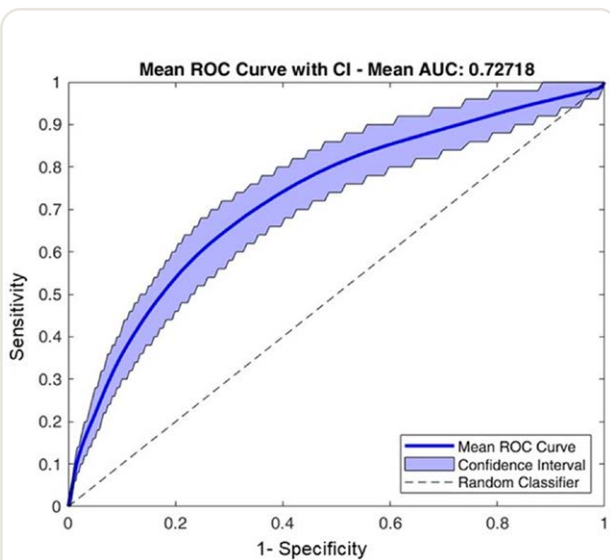


Fig. 4. Mean receiver operating characteristic (ROC) curve of the fitted binary logistic model with an area under the curve (AUC) of 0.73 for 10,000 bootstrap replicates. The *blue-shaded area* corresponds to the CI.

only 15 min of anesthesia. These findings highlight the relevance of predisposing risk factors in the development of POD and underscore the importance of neuromonitoring and the necessity of developing an EEG-based risk assessment tool.

In our study cohort, anesthesia maintenance with volatile gases was a risk factor for the emergence of POD. This is in line with a previous retrospective study data analysis done by our group³⁷ and was also shown in a meta-analysis.³⁸ Hence, prospective studies should examine whether patients presenting the described EEG signatures after LOC would profit from a total intravenous anesthesia with propofol for anesthesia maintenance.

To improve prevention of POD, it would be ideal to develop an algorithm that automatically recognizes EEG patterns associated with POD. If implemented in EEG neuromonitors, it could alert anesthesiologists of the risk, giving them the possibility of reducing further risk factors, possibly adjusting anesthesia guidance, and intensifying 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 POD 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 time point when emergence of POD possibly can still be averted.

Limitations

One limitation of the study is the uneven distribution of sex in patients with and without POD, despite sex not being a known risk factor of POD. 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 risk for postoperative nausea and vomiting in women, female patients received more often propofol as an anesthetic agent. In our analysis, volatile anesthesia maintenance was a risk factor for developing POD; 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, neuro-monitoring is part of the routine protocol in general anesthesia for elderly patients. Because 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 (fig. 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. Because 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 choice of drug agent for anesthesia maintenance, the included patients received significantly more often a total intravenous anesthesia. This could lead to selection bias. Additionally, no adjustments were made for multiple comparisons due to the hypothesis-generating nature of this analysis.

Conclusions

This study provides evidence that patients vulnerable to POD 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.

Acknowledgments

The authors thank all participants and collaborators involved in this trial. In addition, the authors thank Julia Jansche, Marc Dorenbeck, Christin Irrgang, und Elisa Schneller for the good cooperation in the patient recruitment and data processing.

Research Support

Supported by German Research Society (Bonn, Germany) project No. KO 4249/3-1 and by Charité–Universitätsmedizin Berlin (Germany).

Competing Interests

Dr. Univ. Prof. Brown holds patents on anesthetic state monitoring and control; holds a founding interest in Personalized Anesthesia State Control for All (PASCALL), a start-up developing physiologic monitoring systems; and receives royalties from intellectual property through Massachusetts General Hospital (Boston, Massachusetts) licensed to Masimo. The interests of Dr. Brown were reviewed and are managed by Massachusetts General Hospital and Mass General Brigham (Boston, Massachusetts) in accordance with their conflict-of-interest policies. Dr. Univ. Prof. Brown received grants to support this work by the Jeffrey Picower Barbara (JPB) Foundation (New York, New York), the Picower Institute for Learning and Memory (Cambridge, Massachusetts), the Anesthesia Initiative Fund at Massachusetts Institute of Technology (Boston, Massachusetts) and Massachusetts General Hospital, and the National Institutes of Health Awards P01 GM118269 and R01 NS123120 (Bethesda, Maryland). Dr. Univ. Prof. Spies is an inventor on patents and reports grants during the study from the European Commission (Brussels, Belgium), the German Research Society, the German Aerospace Center (Köln, Germany), the Einstein Foundation Berlin (Germany), the European Society of Anesthesiology (Brussels, Belgium), the Federal Joint Committee (Berlin, Germany), and Inner University (Berlin, Germany), and Philips Electronics Nederland (Amsterdam, The Netherlands). Dr. Spies has also received personal fees from Georg Thieme Verlag (New York, New York), Dr. F. Köhler Chemie GmbH (Bensheim, Germany), Sintetica GmbH (Mendrisio, Schweiz), the European Commission, Stifterverband für die Deutsche Wissenschaft e.V. (Essen, Germany), Medtronic (Dublin, Ireland), Max-Planck-Gesellschaft zur Förderung der Wissenschaft e.V. (Berlin, Germany), Federal Ministry for Economic Affairs and Climate Action (BMWi; Berlin, Germany), Federal Ministry of Education and Research (BMBF; Berlin, Germany). Dr. Spies reports leadership or fiduciary role in the Association of Scientific Medical Societies in Germany (Berlin, Germany), German Research Foundation (Bonn, Germany), German National Academy of Sciences – Leopoldina (Halle, Germany), Berlin Medical

Society (Berlin, Germany), European Society of Intensive Care Medicine (Brussels, Belgium), European Society of Anaesthesiology and Intensive Care, German Society of Anaesthesiology and Intensive Care Medicine (Nürnberg, Germany), German Interdisciplinary Association for Intensive Care and Emergency Medicine (Berlin, Germany), German Sepsis Foundation (Berlin, Germany), and participation on a monitoring board for Prothor (Dresden, Germany) in 2023 and Takeda Pharmaceutical Company Ltd. (Berlin, Germany) in 2024. Dr. Koch is also an inventor on patents supported by Deutsche Forschungsgemeinschaft project No. KO 4249/3-1. Dr. Koch is also an inventor on patents sold to Medtronic (Dublin, Ireland) and received a speakers' fee from Medtronic and personal fees from Georg Thieme Verlag. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Koch: Charité – Universitätsmedizin Berlin, Campus Charité Mitte and Virchow-Klinikum, Augustenburger Platz 1, D-13353 Berlin, Germany. susanne.koch@charite.de

Supplemental Digital Content

Biomarkers of postoperative delirium vulnerability, <https://links.lww.com/ALN/D458>

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