Perioperative Electroencephalogram Spectral Dynamics Related to Postoperative Delirium in Older Patients

ORIGINAL CLINICAL RESEARCH REPORT

Perioperative Electroencephalogram Spectral Dynamics Related to Postoperative Delirium in Older Patients

Susanne Koch, MD, PhD,*† Victoria Windmann, MD,* Sourish Chakravarty, PhD,‡ Jochen Kruppa, PhD,†§ Fatima Yürek, MD, PhD,* Emery N. Brown, MD, PhD,‡‖ Georg Winterer, MD, PhD,* and Claudia Spies, MD, PhD,* on behalf of the BioCog Study Group

BACKGROUND: Intraoperative electroencephalography (EEG) signatures related to the development of postoperative delirium (POD) in older patients are frequently studied. However, a broad analysis of the EEG dynamics including preoperative, postinduction, intraoperative and postoperative scenarios and its correlation to POD development is still lacking. We explored the relationship between perioperative EEG spectra-derived parameters and POD development, aiming to ascertain the diagnostic utility of these parameters to detect patients developing POD.

METHODS: Patients aged ≥65 years undergoing elective surgeries that were expected to last more than 60 minutes were included in this prospective, observational single center study (Biomarker Development for Postoperative Cognitive Impairment [BioCog] study). Frontal EEGs were recorded, starting before induction of anesthesia and lasting until recovery of consciousness. EEG data were analyzed based on raw EEG files and downloaded excel data files. We performed multitaper spectral analyses of relevant EEG epochs and further used multitaper spectral estimate to calculate a corresponding spectral parameter. POD assessments were performed twice daily up to the seventh postoperative day. Our primary aim was to analyze the relation between the perioperative spectral edge frequency (SEF) and the development of POD.

RESULTS: Of the 237 included patients, 41 (17%) patients developed POD. The preoperative EEG in POD patients was associated with lower values in both SEF (POD 13.1 ± 4.6 Hz versus no postoperative delirium [NoPOD] 17.4 ± 6.9 Hz; $P = .002$) and corresponding γ-band power (POD −24.33 ± 2.8 dB versus NoPOD −17.9 ± 4.81 dB), as well as reduced postinduction absolute α-band power (POD −7.37 ± 4.52 dB versus NoPOD −5 ± 5.03 dB). The ratio of SEF from the preoperative to postinduction state (SEF ratio) was ~1 in POD patients, whereas NoPOD patients showed a SEF ratio >1, thus indicating a slowing of EEG with loss of unconscious. Preoperative SEF, preoperative γ-band power, and SEF ratio were independently associated with POD ($P = .025$; odds ratio [OR] = 0.892, 95% confidence interval [CI], 0.808–0.986; $P = .029$; OR = 0.568, 95% CI, 0.342–0.944; and $P = .009$; OR = 0.108, 95% CI, 0.021–0.568, respectively).

CONCLUSIONS: Lower preoperative SEF, absence of slowing in EEG while transitioning from preoperative state to unconscious state, and lower EEG power in relevant frequency bands in both these states are related to POD development. These findings may suggest an underlying pathophysiology and might be used as EEG-based marker for early identification of patients at risk to develop POD. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

- **Question:** Are characteristic perioperative electroencephalography (EEG) patterns related to the development of postoperative delirium (POD) in older patients?
- **Findings:** Lower preoperative spectral edge frequency (SEF) based on reduced γ-band power and absence of change in SEF with loss of consciousness (LOC) and lower intraoperative α-band power are related to the development of POD.
- **Meaning:** The EEG of POD patients reveal distinct signatures in their preoperative EEG spectrum and in the manner in which these spectral characteristic change with LOC, which suggests that these EEG signatures may serve as candidate POD markers in future studies, and may also provide insights into the pathophysiology underlying POD.

From the *Department of Anesthesiology and Intensive Care Medicine, Campus Virchow-Klinikum and Campus Charité Mitte, Charité-Universitätsmedizin Berlin, Berlin, Germany; †Technical Transfer Department, Berlin Institute of Health (BIH), Berlin, Germany, ‡Harvard-MIT, Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts; §Department of Biometry and Clinical Epidemiology, Charité-Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany; and ‖Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Accepted for publication June 4, 2021.

Funding: The research leading to these results has received funding from the European Union Seventh Framework program [FP7/2007-2013] under grant agreement no. 602461. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest: See Disclosures at the end of the article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

Clinical trails NCT02265263, www.biocog.eu.

Reprints will not be available from the authors.

Address correspondence to Susanne Koch, MD, PhD, Department of Anesthesiology and Intensive Care Medicine, Charité Universitätsmedizin Berlin, Campus Virchow-Klinikum and Campus Mitte, Augustenburger Platz 1, D-13353 Berlin, Germany. Address e-mail to susanne.koch@charite.de.

DOI: 10.1213/ANE.0000000000005668

GLOSSARY

ASA = American Society of Anesthesiologists; **AUC** = area under the curve; **BioCog** = Biomarker Development for Postoperative Cognitive Impairment; **BMI** = body mass index; **CAM** = Confusion Assessment Method; **CAM-ICU** = Confusion Assessment Method for Intensive Care Unit; **CI** = confidence interval; **DSM** = Diagnostic and Statistical Manual of Mental Disorders; **EEG** = electroencephalography; **GABAA** = γ-aminobutyric acid receptor type A; **IQR** = interquartile range; **LOC** = loss of consciousness; **MMSE** = Mini-Mental State Examination; **NoPOD** = no postoperative delirium; **NPV** = negative predictive value; **NuDesc** = Nursing Delirium Screening Scale; **OR** = odds ratio; **POD** = postoperative delirium; **PPV** = positive predictive value; **PSI** = patients state index; **ROC** = receiver operating curve; **SD** = standard deviation; **SEF** = spectral edge frequency

Postoperative delirium (POD) is a frequent complication in older patients, and is often associated with a poor overall outcome and long-term cognitive dysfunction.[1–4] Intraoperative total electroencephalography (EEG) power decreases significantly with age, which is accompanied by an increased risk of experiencing burst suppression during general anesthesia.[5,6] In the multifactorial etiology of POD, it has been shown that prolonged burst suppression periods are associated with the incidence of POD.[7,8] However, it is still unknown whether specific preoperative, preexisting EEG signatures are related to an increased risk to develop POD.

Preoperative EEG in awake patients shows an age-dependent slowing characterized by a decreased spectral edge frequency (SEF).[9] SEF values in the awake state are known to be higher compared to sleep or general anesthesia.

Intraoperative EEG signatures after loss of consciousness are represented by a slowing of the EEG spectral activity and an increase in frontal α-band power, which is reversed at recovery of consciousness.[10] This characteristic intraoperative α-band power decreases with age,[6] and is reduced in older patients with either preexisting reduced cognitive abilities[11] or at risk to develop POD.[12,13]

The aim of our study was to identify perioperative EEG-based signatures associated with the development of POD. We hypothesized that POD patients show slowing in their perioperative EEG spectral activity. We further aimed to ascertain the utility of perioperative EEG signatures in detecting patients at risk of developing POD.

METHODS

The Biomarker Development for Postoperative Cognitive Impairment (BioCog) study included 747 patients at the Charité-Universitätsmedizin Berlin (Campus Virchow Klinikum and Campus Mitte) between October 2014 and April 2017. The BioCog study (www.biocog.eu, NCT02265263) is a large prospective, observational, multicenter study aimed at developing valid biomarkers to predict POD and long-term postoperative neurocognitive dysfunction.[14] Within the BioCog study, our EEG substudy was performed during a 24-month period (from November 2014 to December 2016), including 237 patients who received a perioperative frontal EEG recording. The institutional review board of the Charité approved the study, and written informed consent of all patients was obtained according to the Declaration of Helsinki (Charité EA2/061/06). Patients older than 65 years, undergoing planned surgery and with an expected surgery duration of more than 60 minutes, were included in our study. Patients were excluded if they satisfied one of the following exclusion criteria: preexisting cognitive deficits characterized by Mini-Mental State Examination (MMSE) below 24, being homeless or unreachable for follow-up, participating in another prospective interventional clinical study during hospital stay, neuropsychiatric morbidity, anacusis or hypoacusis, intake of centrally acting medication or any other condition which could interfere with neurocognitive testing. Additional exclusion criteria for the perioperative EEG substudy were neurosurgery and cardiac surgery (to avoid unknown influences on the perioperative EEG based on neuronal dysfunction or cerebral hypoperfusion) and ear-nose-throat-surgery, oral-maxillofacial-surgery and eye-surgery (when EEG electrodes were located in the field of surgery to avoid artefacts based on surgery activity). Premedication and anesthesia were conducted according to our standard operation procedures.

Assessment of POD

POD screening was performed twice daily by trained medical personnel until the seventh postoperative day or until discharge from the hospital. POD was diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 criteria, Nursing Delirium Screening Scale (NuDesc) ≥2, positive Confusion Assessment Method (CAM) and/or positive Confusion Assessment Method for Intensive Care Unit (CAM-ICU) scoring, or a positive chart review indicating delirious symptoms (eg, confused, agitated, drowsy, delirious, receiving antipsychotic medication). Based on a single positive screening, patients were characterized as POD patients, whereas all other patients were assigned to the no postoperative delirium (NoPOD) group.

EEG Recording/Analysis

Bifrontal EEG was recorded from the time point before induction of anesthesia until extubation of the patient following surgery (SEDline Root). Five minutes before induction of anesthesia, bilateral, frontal EEG electrodes were applied to the patients' forehead and EEGs were recorded using the SEDline brain function monitor (Masimo Corporation). The patients were asked to close their eyes. Filter settings included a notch filter at 50 Hz, with a bandwidth of 0.5 to 92 Hz. The sampling rate was 250 Hz. EEG electrodes were positioned at Fp1, Fp2, F7, and F8 with the earth electrode at Fpz and reference electrode 1 cm above Fpz. The skin was prepared with alcohol to reduce impedance. Electrode impedance was <8 kOhm in each channel, and differences between each channel were below 5 kOhm.

We extracted the csv-files from SEDline Monitor to analyze SEF, patients state index (PSI), and burst suppression duration (min). We calculated the SEF as the frequency below which 95% of the power in the EEG is located (inside the frequency range of 0.5 to 92 Hz).[15,16] The "PSI" is based on an EEG data processing algorithm indicating the clinical state of a patient during general anesthesia, ranging from 0 (isoelectric line) to 100 (awake), and an optimal anesthesia level of 25 to 50.[17,18] For the analysis of SEF and PSI, data for each patient at 4 time epochs within the EEG recording were selected (

Supplemental Digital Content, Figure S1, http://links.lww.com/AA/D606):

1. Preoperative EEG: a continuous, artifact-free 30-second EEG epoch 2 minutes after the beginning of the EEG recording and 2 minutes before induction of anesthesia in the awake patient;
2. Postinduction EEG: a continuous, artifact free 2 minutes EEG epoch approximately 15 minutes after induction of anesthesia;
3. Intraoperative EEG: a continuous, artifact free 2 minutes EEG epoch intraoperatively, about 60 minutes after start of anesthesia during a stable situation;
4. Postoperative EEG: a continuous, artifact free 30-second EEG epoch 2 minutes after extubation.

We analyzed a total of 119 preoperative EEG epochs, 224 postinduction EEG epochs, 237 intraoperative EEG epochs, and 123 postoperative EEG epochs after removing epochs with artifacts or missing recordings.

To analyze the changes in the EEG spectral characteristics from preoperative state to postinduction state, we calculated the ratio of the preoperative over the postinduction value for both SEF and PSI. A ratio greater than 1 indicates slowing of EEG spectral activity from the preoperative to postinduction state (the physiological situation) and ratio equal to 1 indicates an absence of the aforementioned of slowing phenomenon.

Burst suppression activity in the EEG is characterized by alternating epochs of near-isoelectric activity and α-band activity and is indicative of a very deep level of anesthesia. Burst suppression duration was calculated for the complete anesthesia procedure from intubation until extubation of the patient.

Additionally, we could extract raw EEG data from the SEDline monitor in a subgroup of our patients (n = 75). Raw EEGs were bandpass filtered at 0.5 to 45 Hz. Ten-second artifact-free time windows were selected manually by visual inspection of the EEG, from the epoch before induction of general anesthesia (preoperative), an epoch between 15 and 30 minutes after anesthesia induction (postinduction), an epoch around 60 minutes after anesthesia induction (intraoperative) and an epoch 5 minutes after extubation of the patient (postoperative). EEG epochs showing burst suppression activity were excluded from this analysis. Multitaper spectral analyses were performed using custom Matlab (The MathWorks, Inc) code based on the Chronux toolbox.[19–22] For each subject and epoch analyzed, a single voltage time-series (averaged across 4 frontal electrodes: Fp1, Fp2, F7, and F8) was used to calculate the overall frontal power spectra. From the power spectra, we calculated the power in the following frequency bands: γ-band (30.1–45 Hz), β-band (12.1–30 Hz), α-band (8–12 Hz), Θ-band (4–7.9 Hz), δ-band (1.6–3.9 Hz), and sub-δ-band (0–1.5 Hz). Time-varying spectra (multitaper spectrograms) where estimated in the decibel (dB) scale using 2-second sliding time-windows with 1.9-second overlap, time-half-bandwidth product of 3 and 5 tapers. We compared the POD and NoPOD groups based on their spectrograms. Finally, we extracted the α-peak frequency, defined here as the frequency corresponding to the highest power within the range of 8 to 12 Hz.

Statistical Analysis

Patients were divided into 2 groups according to the results of the POD screening as POD group versus NoPOD group. The primary end point of this observational study was to analyze the perioperative SEF dynamic related to the development of POD. Additionally, we used the spectra and the associated frequency band-wise power values to compare between the POD and NoPOD groups.

Results were expressed as arithmetic mean ± standard deviation (SD) for EEG data, median, and (25/75) percentiles for nonnormally distributed data, or frequencies (%) for qualitative data. Statistical analyses were conducted with both nonparametric tests (Mann-Whitney *U* test for 2 independent samples) and parametric tests (Student *t* test for data with

normal distribution). Receiver operating curve (ROC) analysis were conducted to determine sensitivity, specificity, and cutoff values based on the Youden's index for preoperative SEF, SEF ratio, and MMSE score and clinically defined POD labels.[23] Positive predictive value (PPV) and negative predictive value (NPV) were calculated based on the proportion of a true-positive or true-negative result. Statistical analysis was performed using SPSS, Version 24, Copyright SPSS, Inc and SAS, Version 9.1, Copyright SAS Institute, Inc. Values were considered significant if $P < .05$.

To compare the EEG spectra between 2 groups, we computed the 95% confidence interval (CI) on the median difference of power in each frequency band using a frequency domain bootstrap algorithm.[24]

We performed a multivariable logistic regression to adjust for the impact of possible confounders, age (years), MMSE score, and premedication with midazolam (yes/no) on the primary outcome.

The sample size of this single center EEG substudy was based on the available cohort of the BioCog study. Based on the need to record artifact-free intraoperative EEGs, additional exclusion criteria were applied. Ultimately, 237 patients were included.

RESULTS

Study Population

Within the 237 patients group, a total of 41 patients (17%) developed POD (POD group), whereas 196 (83%) patients did not (NoPOD group). POD patients were significantly older, had a more severe preoperative American Society of Anesthesiologists (ASA) physical status, lower MMSE scores, and longer duration of anesthesia (Table 1).

EEG Spectral Parameters and POD

POD patients had a significantly reduced preoperative SEF compared to NoPOD patients. Postinduction, intraoperative, and postoperative SEF parameters showed no differences between POD and NoPOD patients (Table 2).

The SEF ratio (preoperative/postinduction SEF) was above 1 for NoPOD patients, indicating a physiological decrease in frequency of EEG activity from the preoperative awake to postinduction unconscious state. In contrast, the SEF ratio was ~1 for POD patients (POD 0.98 ± 0.36, 95% CI, 0.793–1.162 versus NoPOD 1.3 ± 0.49, 95% CI, 1.203–1.404; $P = .003$; Table 2).

ROC curve analysis indicating the development of POD showed a cutoff value for preoperative SEF of 17.75 Hz with a sensitivity of 0.944, a specificity of 0.426, and area under the curve (AUC) of 0.718; 95% CI, 0.596–0.839, $P = .004$ (Figure 1). When using the preoperative SEF cutoff value of 17.75 Hz for indicating the risk of developing POD, a PPV of 0.23 and a NPV of 0.977 were calculated (Supplemental Digital Content, Table S2, http://links.lww.com/AA/D606).

The cutoff value for SEF ratio was 0.99, with a sensitivity of 0.647, a specificity of 0.716, and AUC of 0.698, 95% CI, 0.57–0.827, $P = .01$ (Figure 1). When using the SEF ratio cutoff value of 0.99 for indicating the risk of developing POD, a PPV of 0.289 and a NPV of 0.919 were calculated (Supplemental Digital Content, Table S3, http://links.lww.com/AA/D606).

The cutoff value for MMSE was 27.5 to predict POD risk with a sensitivity of 0.366, a specificity of 0.831, and an AUC of 0.595.

Duration of burst suppression periods (min) did not differ significantly between POD and NoPOD

Table 1. Baseline Characteristics of Patients

	All patients (n = 237)	NoPOD group (n = 196)	POD group (n = 41)	*P* value
Age[a] (y)	72.8 ± 5.3	72.3 ± 5.3	74.8 ± 5.4	.005
Sex male/female (%)	126/111 (53%/47%)	107/89 (55%/45%)	19/22 (46%/54%)	.391
BMI	27.3 ± 5.1	27.3 ± 5.0	27.6 ± 5.6	.871
ASA physical status I/II/III/IV (%)[a]	5/144/84/3 (2%/61%/36%/1%)	4/131/59/2 (2%/67%/30%/1%)	1/14/25/1 (2.4%/34.1%/61%/2.4%)	.001
MMSE preoperative[a]	28.6 ± 1.4	28.7 ± 1.3	28.1 ± 1.8	.008
Midazolam premedication: yes/no (%)	38/199 (16%/84%)	33/163 (17%/83%)	5/36 (12%/88%)	.64
Anesthesia induction agent: propofol/thiopental (%)	229/8 (96%/4%)	190/6 (97%/3%)	39/2 (95%/5%)	.861
Anesthesia maintenance agent: sevoflurane/propofol/desflurane/isoflurane (%)	113/69/52/3 (48%/29%/22%/1%)	97/56/41/2 (49%/29%/21%/1%)	16/13/11/1 (39%/32%/27%/2%)	.602
Propofol, mg/kg/h	5.8 ± 1.4 (n = 69)	5.6 ± 1.4 (n = 56)	6.4 ± 1.3 (n = 13)	.117
Sevoflurane et vol %	1.6 ± 0.3 (n = 113)	1.6 ± 0.3 (n = 97)	1.6 ± 0.2 (n = 16)	.794
Desflurane et vol %	4.8 ± 0.9 (n = 52)	4.7 ± 0.9 (n = 41)	4.8 ± 0.86 (n = 11)	.91
Anesthesia duration (min)[a]	217 ± 149	192 ± 139	330 ± 180	<.001
Ketamine perfusor: yes/no (%)	8/229 (3.4/96.6)	5/191 (2.6/97.4)	3/38 (7.3/92.7)	.464

Continuous data were calculated by Mann-Whitney *U* test, and if applicable by students *t* test (MMSE, anesthesia duration), categorical data were analyzed by Fisher exact test.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; MMSE, Mini-Mental State Examination; NoPOD, no postoperative delirium; POD, postoperative delirium.

[a]<.01.

Table 2. Perioperative EEG Parameter

	All patients (n = 237)	NoPOD (n = 196)	POD (n = 41)	*P* value
Preoperative SEF (Hz)[a]	16.8 ± 6.8 (n = 119)	17.4 ± 6.9 (n = 101)	13.1 ± 4.6 (n = 18)	.002
Postinduction SEF (Hz)	12.7 ± 4.3 (n = 224)	12.7 ± 3.9 (n = 186)	12.4 ± 5.5 (n = 38)	.739
Intraoperative SEF (Hz)	12.8 ± 3.6 (n = 237)	12.8 ± 3.2 (n = 196)	12.4 ± 5.2 (n = 41)	.564
Postoperative SEF (Hz)	23.5 ± 10.1 (n = 123)	23.5 ± 10.2 (n = 106)	23.1 ± 9.6 (n = 17)	.868
Preoperative PSI	91.7 ± 4.4 (n = 119)	91.9 ± 4.2 (n = 101)	90.8 ± 5.4 (n = 18)	.407
Postinduction PSI	34.1 ± 8.6 (n = 224)	33.9 ± 8.8 (n = 186)	35.4 ± 7.9 (n = 38)	.306
Intraoperative PSI	33.6 ± 9.4 (n = 237)	33.4 ± 9.0 (n = 196)	34.3 ± 11.3 (n = 41)	.655
Postoperative PSI	85.4 ± 6.5 (n = 123)	85.1 ± 6.7 (n = 106)	87.1 ± 5.3 (n = 17)	.184
SEF ratio[a] (preoperative SEF/intraoperative SEF)	1.26 ± 0.49 (n = 112)	1.3 ± 0.49 (n = 95)	0.98 ± 0.36 (n = 17)	.003
Ratio PSI (preoperative PSI/intraoperative PSI)	3 ± 1.04 (n = 112)	3 ± 0.96 (95)	2.99 ± 1.51 (17)	.973
Burst suppression duration (min)	19 (20/47) (n = 224)	17 (16/39) (n = 186)	32 (7/200) (n = 38)	.227

Perioperative EEG parameter comparing results between NoPOD and POD patients. Data are presented as mean and SD (mean ± SD) or median and 95% CI (median [95% lower limit–upper limit]). Data were calculated by Student *t* test and Mann-Whitney *U* test for Burst Suppression duration.

Abbreviations: CI, confidence interval; EEG, electroencephalography; NoPOD, no postoperative delirium; POD, postoperative delirium; SD, standard deviation; SEF, spectral edge frequency; PSI, patient state index.

[a]<.01.

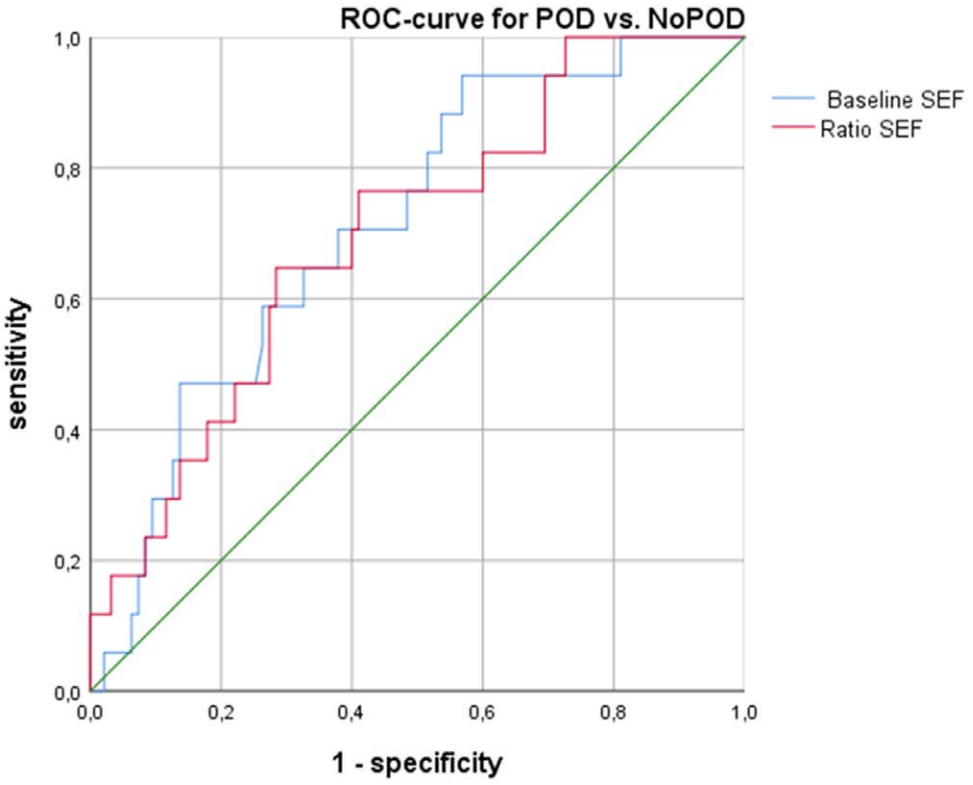

Figure 1. ROC curve for POD/NoPOD calculated for preoperative SEF (blue line) and ratio SEF (red line). Preoperative SEF ≤17.75 has a sensitivity of 0.944, a specificity of 0.426, and an AUC of 0.718, 95% CI, 0.596–0.839, *P* = .004. Ratio SEF ≤0.99 has a sensitivity of 0.647, a specificity of 0.72, and an AUC of 0.698, 95% CI, 0.57–0.827, *P* = .01. AUC indicates area under the curve; CI, confidence interval; NoPOD, no postoperative delirium; POD, postoperative delirium; ROC, receiver operating curve; SEF, spectral edge frequency.

patients (POD 32 minutes [95% CI, 7–200] versus NoPOD 17 minutes [95% CI, 16–39], *P* = .227).

PSI parameter showed no differences between POD and NoPOD patients (Table 2).

Raw EEG subgroup analysis showed significantly lower preoperative absolute γ-band power in POD patients (POD −24.33 ± 2.8 dB versus NoPOD −17.9 ± 4.81 dB) (Supplemental Digital Content, Table S4, http://links.lww.com/AA/D606, Figure 2), as well as a reduced absolute α-band power at the postinduction state (POD −7.37 ± 4.52 dB versus NoPOD −5 ± 5.03 dB; Supplemental Digital Content, Table S4, http://links.lww.com/AA/D606, Figure 3), and reduced γ-band power at postoperative epoch (POD −17.76 ± 3.15 dB versus NoPOD −15.15 ± 3.32 dB; Supplemental Digital Content, Table S4, http://links.

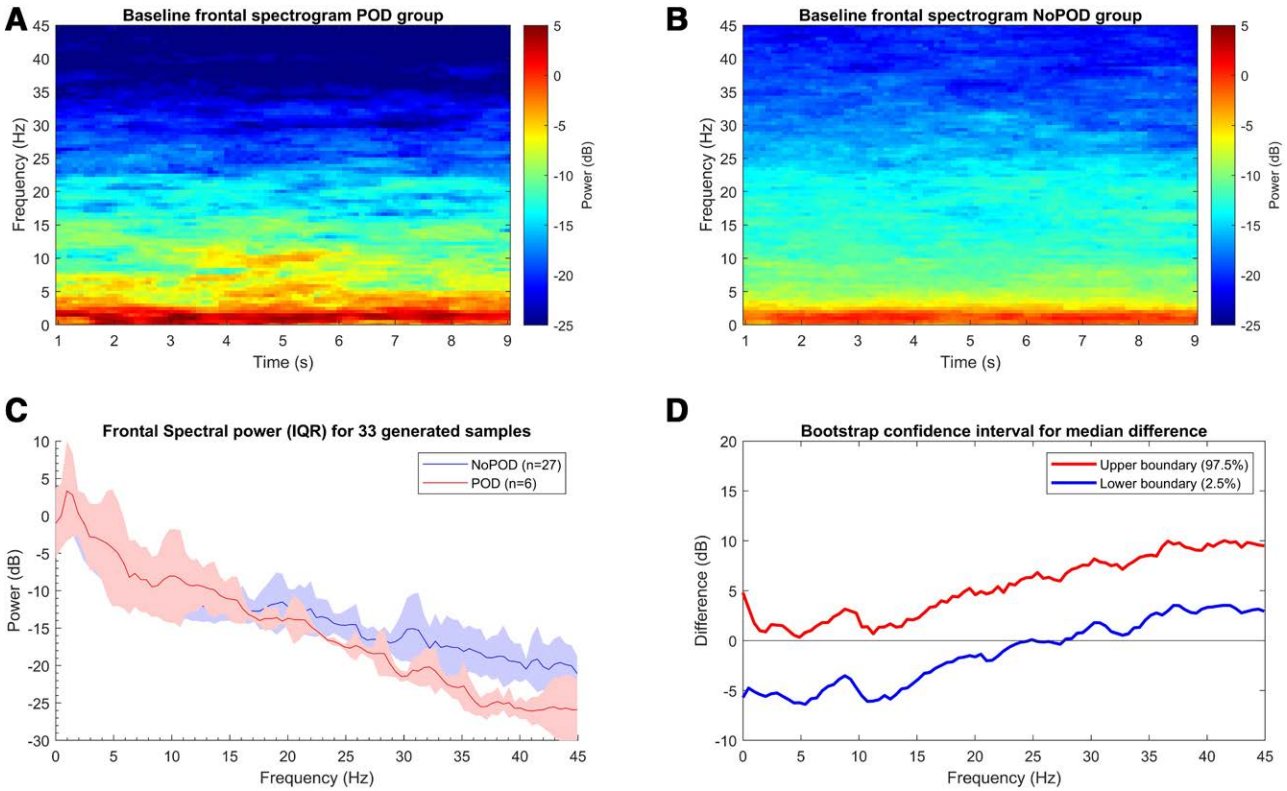

Figure 2. Preoperative frontal group spectrograms over a single EEG window of 10 s comparing POD (n = 6) (A) with NoPOD group (n = 27) (B). Showing a significant reduced γ-band power (30.1–45 Hz) for the POD group. We used a custom-written Matlab code (MathWorks Inc), computing the 95% CI of the median difference at each frequency to assess statistical significance for the difference in power within different frequency bands. In the spectrograms, time (s) is arranged along the x-axis and frequencies (Hz) are arranged along the y-axis. C, POD group compared to the NoPOD group, (D) using a frequency domain-based bootstrapping algorithm resampling the Fourier coefficients showed no significant difference between the POD group, compared to the NoPOD group. CI indicates confidence interval; EEG, electroencephalography; IQR, interquartile range; NoPOD, no postoperative delirium; POD, postoperative delirium.

lww.com/AA/D606, Figure 4). We did not find significant differences at the intraoperative state between POD and NoPOD groups (Supplemental Digital Content, Table S4, Figure S2, http://links.lww.com/AA/D606). The α-peak frequency between POD and NoPOD patients did not differ across the preoperative, postinduction, intraoperative, and postoperative states (preoperative: POD 10.01 ± 1.1 Hz versus NoPOD 9.0 ± 0.99 Hz; postinduction: POD 8.96 ± 1.21 Hz versus NoPOD 9.52 ± 0.98 Hz; intraoperative: POD 8.84 ± 1.2 Hz versus NoPOD 9.91 ± 1.72 Hz; postoperative: POD 9.83 ± 1.41 Hz versus NoPOD 10.21 ± 1.22 Hz).

Overall, we did not find a correlation between EEG parameters and the medication given at the 4 different time points (Supplemental Digital Content, Table S5, http://links.lww.com/AA/D606).

By using our multivariable logistic regression model that included the confounders MMSE score, age, and premedication with midazolam, we found an independent association with POD for preoperative SEF (Hz) (P = .025; odds ratio [OR] = 0.892, 95% CI, 0.808–0.986), preoperative γ-band power (dB) (P = .029; OR = 0.568, 95% CI, 0.342–0.944), and SEF ratio (P = .009; OR = 0.108, 95% CI, 0.021–0.568).

DISCUSSION

Preoperative SEF and γ-band power were significantly reduced in POD patients. A calculated cutoff value for preoperative SEF at 17.75 Hz was associated with a higher risk of developing POD. Our analyses also revealed that the signature pattern, of slowing down of EEG spectral activity as a patient transitioned from preoperative state to unconscious state, is present in the NoPOD patients but absent in the POD patients. Preoperative SEF and SEF ratio are independently associated with POD, indicating the ability to identify patients with a higher risk to develop POD during an early stage of anesthesia.

Baseline EEG rhythms decline with aging, as older patients show reduced EEG spectral activity in the EEG during awake situation compared to younger patients.[9] Moreover, mild cognitive decline in older patients is again related to slower EEG frequencies.[25] In particular, the γ-band power is more closely related to cognitive abilities and is decreased in patients presenting frontotemporal dementia.[26] In our study group, POD patients showed lower SEF values and reduced γ-band power in the preoperative awake state. POD patients were (on average) only 2 years older than

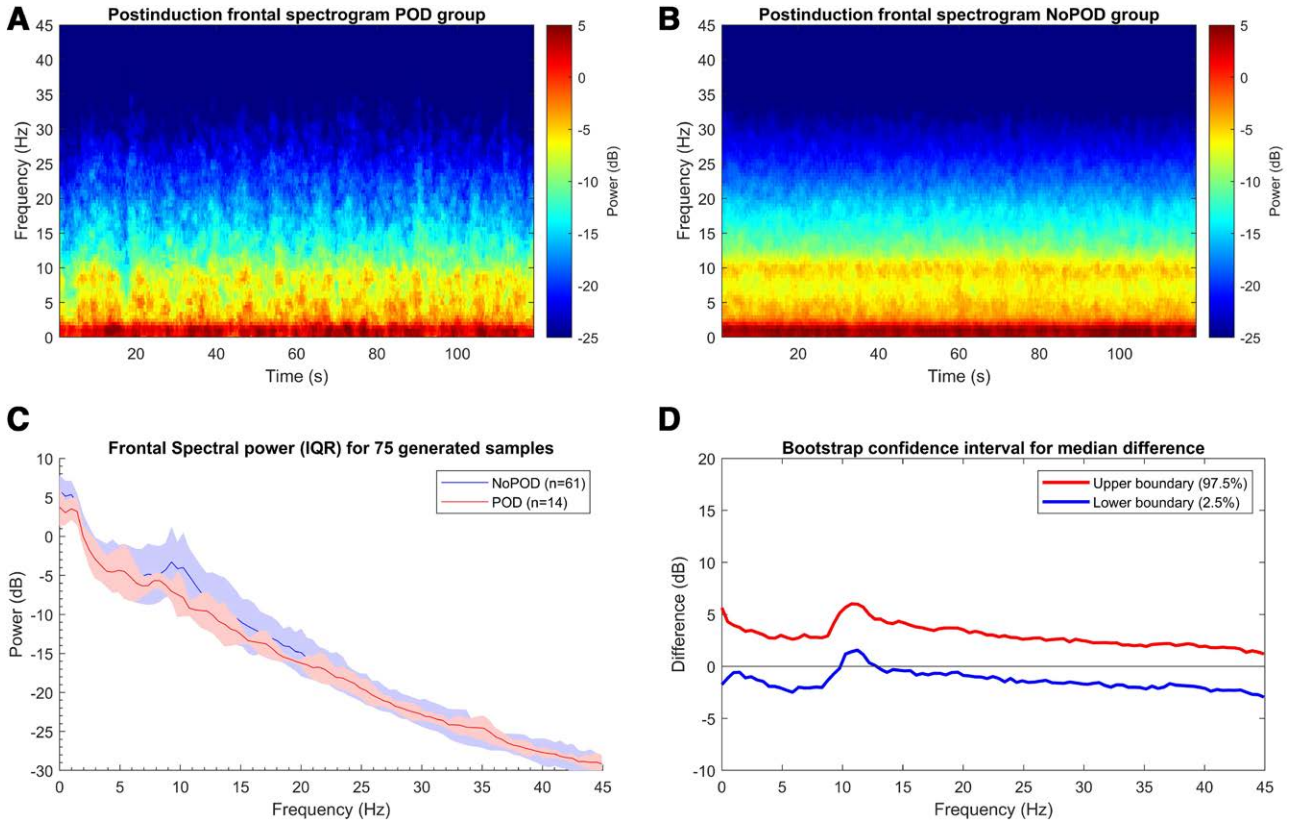

Figure 3. Postinduction frontal group spectrograms over a single EEG window of 10 s comparing POD (n = 14) (A) with NoPOD group (n = 61) (B). Showing a significant reduced α-band power (8–12 Hz) for the POD group. We used a custom-written Matlab code (MathWorks Inc), computing the 95% CI of the median difference at each frequency to assess statistical significance for the difference in power within different frequency bands. In the spectrograms, time (s) is arranged along the x-axis and frequencies (Hz) are arranged along the y-axis, (C) showing a reduction within the α-band (8–12 Hz) within the POD group compared to the NoPOD group, (D) using a frequency domain-based bootstrapping algorithm resampling the Fourier coefficients showed a significant difference between the POD group, compared to the NoPOD group. CI indicates confidence interval; EEG, electroencephalography; IQR, interquartile range; NoPOD, no postoperative delirium; POD, postoperative delirium.

NoPOD patients, indicating that the differences in spectral signatures that we observed in our 2 groups were not due to age differences. Also, POD patients showed reduced preoperative MMSE scores compared to the NoPOD patients, whereas a decline in cognitive function is a predisposing factor related to an increased risk to develop POD.[4,27] Therefore, it seems reasonable to propose that the preexisting lower cognitive ability in our POD patients might be causative for the reduced preoperative SEF values and the lower γ-band power.

We conclude that a lower preoperative SEF is a function of both age and reduced cognitive abilities in patients, both of which are well-documented risk factors for POD. The calculated cutoff value for preoperative SEF was 17.75 Hz, with lower values indicating patients at risk of developing POD with both high sensitivity (0.944) and a high NPV (0.977). This means that a preoperative SEF recording can indicate patients who are at risk to develop POD. Additionally, the NPV was 0.977 suggests that patients with preoperative SEF values above 17.75 Hz are more unlikely to develop POD. In contrast, the MMSE score reached only a sensitivity of 0.366 to early identify patients at risk to develop POD. Since we could also show that preoperative SEF is an independent predictor for POD, in contrast to the MMSE score, preoperative SEF could be a more sensitive preoperative marker to descry patients at risk of developing POD compared to cognitive assessments.

Perioperative EEG Dynamics and POD

Loss of consciousness in healthy adults is marked by a slowing of EEG frequencies,[10] an EEG dynamic that is reversed when patients regain consciousness. This physiological EEG dynamic over loss of consciousness was seen in our NoPOD group, but were missing in POD patients, which may be indicative of pathophysiological mechanisms of POD development. Interestingly, both NoPOD and POD patients showed an increase in EEG frequencies at regain of consciousness, as expected. However, POD patients present lower β-band power compared to NoPOD patients. General anesthetic agents have multiple targets, and a major mechanism is the activation of the γ-aminobutyric acid receptor type A ($GABA_A$).[28] $GABA_A$ stimulation, which induces a cortical inhibition, has a biphasic effect on EEG oscillations. At light sedation,

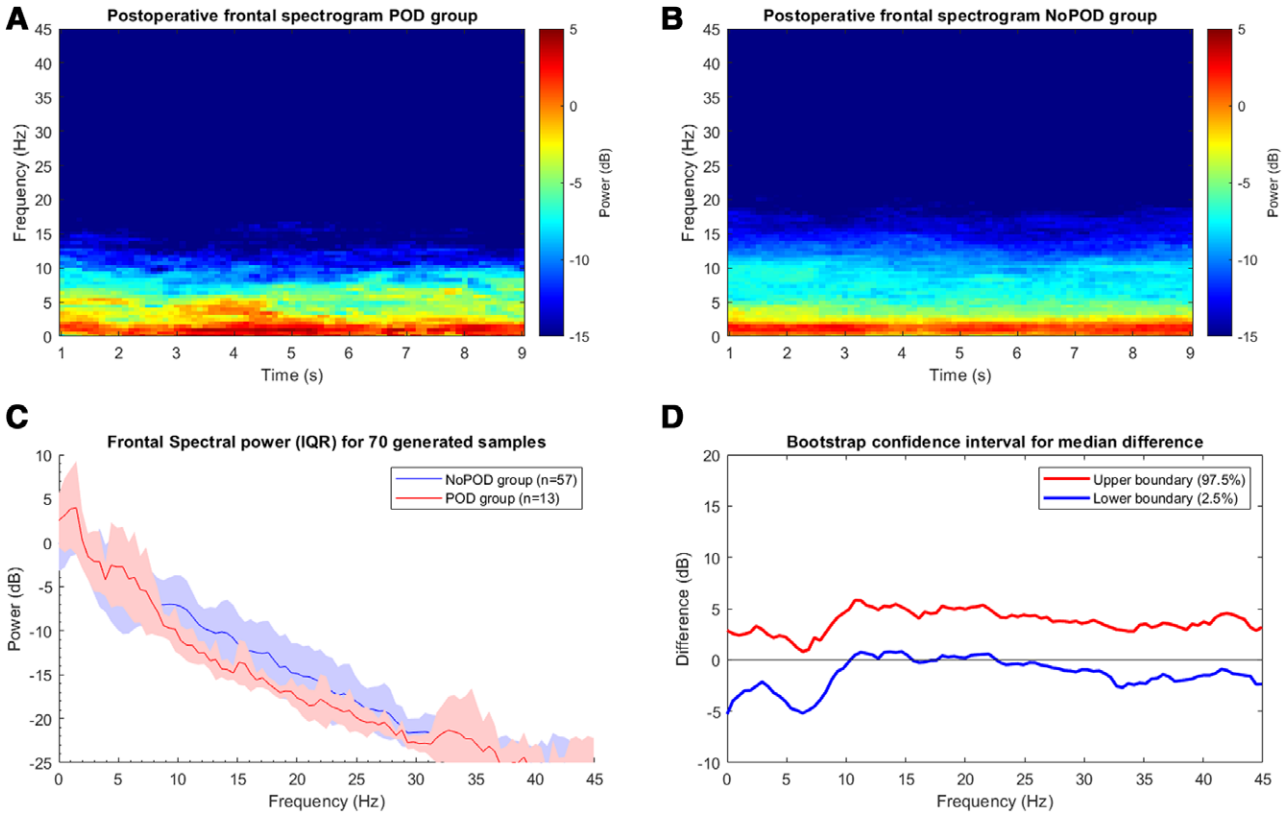

Figure 4. Postoperative frontal group spectrograms over a single EEG window of 10 s comparing POD (n = 13) (A) with NoPOD group (n = 57) (B). Showing a significant reduced β-band power in the lower β-range (13–25 Hz) for the POD group. We used a custom-written Matlab code (MathWorks Inc), computing the 95% CI of the median difference at each frequency to assess statistical significance for the difference in power within different frequency bands. In the spectrograms, time (s) is arranged along the x-axis and frequencies (Hz) are arranged along the y-axis, (C) showing a reduction within the β-band (13–25 Hz) within the POD group compared to the NoPOD group, (D) using a frequency domain-based bootstrapping algorithm resampling the Fourier coefficients showed a significant difference between the POD group, compared to the NoPOD group. CI indicates confidence interval; EEG, electroencephalography; IQR, xxx; NoPOD, no postoperative delirium; POD, postoperative delirium.

increased spectral frequencies with higher level of β-oscillations are seen,[29] whereas during unconsciousness, decreased spectral frequencies are presented with coherent, frontal slow wave and α-band activity.[10] Mathematical modeling of this physiological, biphasic EEG oscillation phenomena showed that different $GABA_A$-ergic networks in the cortex, thalamus, and brainstem are involved in this dynamic.[30] After loss of consciousness, a coupling between thalamus and frontal cortex serves to induce an oscillatory activity in the slow wave and α-band, causing a high spatial coherence in frontal EEG activity.[31] On the other hand, the β- and γ-band oscillations observed, after a patient regains consciousness, is extubated and is maintained under light sedation are related to $GABA_A$-ergic interneuron activation.[31] Importantly, activation of frontal $GABA_A$-ergic interneurons contributes to memory formation and cognitive abilities and are also related to elevated γ-band power.[32] These $GABA_A$-ergic–induced EEG dynamic parallels our findings in the NoPOD group, whereas a different dynamic was observed in our POD patient group. Baseline γ-band power at the preoperative state was reduced in POD patients, which is most likely related to cognitive deficits, as seen by lower MMSE scores in POD patients compared to the NoPOD patients. In contrast, postoperative EEG recordings differ between POD and NoPOD patients in the β-band activity. This finding may be interpreted as persistent slight activation of frontal GABA-ergic interneurons by anesthetic agents, which is lower in POD patients compared to NoPOD patients. On the other hand, based on the reduced intraoperative coherent, frontal α-band power in our POD patients, it seems that activation of thalamic GABA-ergic neurons to trigger the thalamo-cortical feedback mechanism is hindered in POD patients. Overall GABA-ergic neuronal activity is lower in POD patients at baseline, intraoperative, and postoperative situation compared to NoPOD patients.

Intraoperative EEG Characteristics Related to POD

Under general anesthesia, intraoperative total EEG power, α-band power, and spectral frequencies decrease with age.[5,6] EEG power reduction in older patients is accompanied by an increased risk to develop burst suppression periods during general

anesthesia.[6] In turn, increased duration of burst suppression periods during general anesthesia significantly correlates with the development of POD.[7,8,13,33,34] These findings are in line with our data, as duration of burst suppression activity during general anesthesia tended to be prolonged in POD patients. On the other hand, we found a reduced α-band power during the intraoperative EEG in POD patients, which supports the results of Shao et al[35] showing a higher propensity for burst suppression periods in the presence of lower α-band power, as an indicator of a more vulnerable brain.[35]

Limitations

Since our study is a prospective observational study, the administration of premedication and the dosage of intraoperative anesthetic agents were not controlled by study protocol. Based on our small sample size with 41 POD patients, adjustment for potential confounders is limited. Due to frequent artifacts in EEG recordings, the comparative EEG time points analyzed were heterogeneous. We used different methods to identify delirious symptoms to ensure POD does not go unrecognized during the hospital stay. However, different methods inherently imply different levels of sensitivity and specificity.

CONCLUSIONS

Preoperative spectral EEG signatures and reduced EEG dynamics at loss of consciousness are associated with the development of POD in older patients, where changes in EEG signatures are most likely related to reduced GABA-ergic neuronal activation in POD patients. These findings can be described as predisposing EEG factors for POD, which might be used as a potential EEG-based marker for early identification of patients at risk to develop POD.

ACKNOWLEDGMENTS

We are grateful for the patience and courage of our patients and their consenting relatives. We thank Rudolf Mörgeli for final editing of our manuscript. We thank Christin Irrgang for helping with preprocessing of the raw EEG data files.

DISCLOSURES

Name: Susanne Koch, MD, PhD.
Contribution: This author helped conceive and design the study, perform the experiments, analyze the data, write and revise the manuscript.
Conflicts of Interest: S. Koch is an inventor on patents and has received speaker's honoraria from Medtronic.
Name: Victoria Windmann, MD.
Contribution: This author helped perform the experiments, analyze the data, and write and revise the manuscript.
Conflicts of Interest: None.
Name: Sourish Chakravarty, PhD.
Contribution: This author helped analyze the data and revise the manuscript.
Conflicts of Interest: None.
Name: Jochen Kruppa, PhD.
Contribution: This author helped analyze the data and revise the manuscript.
Conflicts of Interest: None.
Name: Fatima Yürek, MD, PhD.
Contribution: This author helped conceive the study, perform the experiments, and revise the manuscript.
Conflicts of Interest: None.
Name: Emery N. Brown, MD, PhD.
Contribution: This author helped interpret the data and revise the manuscript.
Conflicts of Interest: E. N. Brown is an inventor on patents pending on brain monitoring technologies assigned to Massachusetts General Hospital; inventor on a patent assigned to Massachusetts General Hospital and licensed nonexclusively to Masimo Corporation; and is a cofounder of PASCALL Systems, Inc, a startup company developing closed-loop physiological control systems.
Name: Georg Winterer, MD, PhD.
Contribution: This author helped conceive and design the study, revise the manuscript, and supervise the overall study.
Conflicts of Interest: None.
Name: Claudia Spies, MD, PhD.
Contribution: This author helped conceive and design the study, revise the manuscript, and supervise the overall study.
Conflicts of Interest: C. Spies is an inventor on patents, she reports research grants from the European Commission, 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 internal 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., and Pfizer 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 Charité, AGUETTANT Deutschland GmbH, AbbVie Deutschland GmbH & Co. KG, Amomed Pharma GmbH, InTouch 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.
This manuscript was handled by: Robert Whittington, MD.

REFERENCES

1. Müller A, Lachmann G, Wolf A, Mörgeli R, Weiss B, Spies C. Peri- and postoperative cognitive and consecutive functional problems of elderly patients. *Curr Opin Crit Care.* 2016;22:406–411.
2. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA.* 2010;304:443–451.
3. Newman S, Stygall J, Hirani S, Shaefi S, Maze M. Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. *Anesthesiology.* 2007;106:572–590.
4. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA.* 1996;275:852–857.

5. Schultz A, Grouven U, Zander I, Beger FA, Siedenberg M, Schultz B. Age-related effects in the EEG during propofol anaesthesia. *Acta Anaesthesiol Scand.* 2004;48:27–34.
6. Purdon PL, Pavone KJ, Akeju O, et al. The ageing brain: age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. *Br J Anaesth.* 2015;115(suppl 1):i46–i57.
7. Soehle M, Dittmann A, Ellerkmann RK, Baumgarten G, Putensen C, Guenther U. Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. *BMC Anesthesiol.* 2015;15:61.
8. Fritz BA, Kalarickal PL, Maybrier HR, et al. Intraoperative electroencephalogram suppression predicts postoperative delirium. *Anesth Analg.* 2016;122:234–242.
9. Scally B, Burke MR, Bunce D, Delvenne JF. Resting-state EEG power and connectivity are associated with alpha peak frequency slowing in healthy aging. *Neurobiol Aging.* 2018;71:149–155.
10. Purdon PL, Pierce ET, Mukamel EA, et al. Electroencephalogram signatures of loss and recovery of consciousness from propofol. *Proc Natl Acad Sci U S A.* 2013;110:E1142–E1151.
11. Koch S, Feinkohl I, Chakravarty S, et al; BioCog Study Group. Cognitive impairment is associated with absolute intraoperative frontal α-band power but not with baseline α-band power: a pilot study. *Dement Geriatr Cogn Disord.* 2019;48:83–92.
12. Gutierrez R, Egaña JI, Saez I, et al. Intraoperative low alpha power in the electroencephalogram is associated with postoperative subsyndromal delirium. *Front Syst Neurosci.* 2019;13:56.
13. Pedemonte JC, Plummer GS, Chamadia S, et al. Electroencephalogram burst-suppression during cardiopulmonary bypass in elderly patients mediates postoperative delirium. *Anesthesiology.* 2020;133:280–292.
14. Winterer G, Androsova G, Bender O, et al; BioCog consortium. Personalized risk prediction of postoperative cognitive impairment - rationale for the EU-funded BioCog project. *Eur Psychiatry.* 2018;50:34–39.
15. Schwender D, Daunderer M, Mulzer S, Klasing S, Finsterer U, Peter K. Spectral edge frequency of the electroencephalogram to monitor "depth" of anaesthesia with isoflurane or propofol. *Br J Anaesth.* 1996;77:179–184.
16. Rampil IJ, Sasse FJ, Smith NT, Hoff BH, Flemming DC, FFARCS. Spectral edge frequency - a new correlate of anesthetic depth. *Anesthesiology.* 1980;53(3 suppl):S12.
17. Drover DR, Lemmens HJ, Pierce ET, et al. Patient state index: titration of delivery and recovery from propofol, alfentanil, and nitrous oxide anesthesia. *Anesthesiology.* 2002;97:82–89.
18. Schneider G, Gelb AW, Schmeller B, Tschakert R, Kochs E. Detection of awareness in surgical patients with EEG-based indices–bispectral index and patient state index. *Br J Anaesth.* 2003;91:329–335.
19. Cornelissen L, Kim SE, Purdon PL, Brown EN, Berde CB. Age-dependent electroencephalogram (EEG) patterns during sevoflurane general anesthesia in infants. *Elife.* 2015;4:e06513.
20. Bokil H, Andrews P, Kulkarni JE, Mehta S, Mitra PP. Chronux: a platform for analyzing neural signals. *J Neurosci Methods.* 2010;192:146–151.
21. Babadi B, Brown EN. A review of multitaper spectral analysis. *IEEE Trans Biomed Eng.* 2014;61:1555–1564.
22. Thomson DJ. Spectrum estimation and harmonic analysis. *Proceed IEEE.* 1982;70:1055–1096.
23. Mascha EJ. Identifying the best cut-point for a biomarker, or not. *Anesth Analg.* 2018;127:820–822.
24. Kim SE, Ba D, Brown EN. A Multitaper frequency-domain bootstrap method. *IEEE Signal Process Lett.* 2018;25:1805–1809.
25. Musaeus CS, Nielsen MS, Østerbye NN, Høgh P. Decreased parietal beta power as a sign of disease progression in patients with mild cognitive impairment. *J Alzheimers Dis.* 2018;65:475–487.
26. Hughes LE, Rittman T, Robbins TW, Rowe JB. Reorganization of cortical oscillatory dynamics underlying disinhibition in frontotemporal dementia. *Brain.* 2018;141:2486–2499.
27. Culley DJ, Flaherty D, Fahey MC, et al. Poor performance on a preoperative cognitive screening test predicts postoperative complications in older orthopedic surgical patients. *Anesthesiology.* 2017;127:765–774.
28. Alkire MT, Hudetz AG, Tononi G. Consciousness and anesthesia. *Science.* 2008;322:876–880.
29. Xi C, Sun S, Pan C, Ji F, Cui X, Li T. Different effects of propofol and dexmedetomidine sedation on electroencephalogram patterns: wakefulness, moderate sedation, deep sedation and recovery. *PLoS One.* 2018;13:e0199120.
30. Ching S, Brown EN. Modeling the dynamical effects of anesthesia on brain circuits. *Curr Opin Neurobiol.* 2014;25:116–122.
31. Ching S, Cimenser A, Purdon PL, Brown EN, Kopell NJ. Thalamocortical model for a propofol-induced alpha-rhythm associated with loss of consciousness. *Proc Natl Acad Sci U S A.* 2010;107:22665–22670.
32. Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat Rev Neurosci.* 2007;8:45–56.
33. Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol.* 2013;25:33–42.
34. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br J Anaesth.* 2013;110(suppl 1):i98–i105.
35. Shao YR, Kahali P, Houle TT, et al. Low frontal alpha power is associated with the propensity for burst suppression: an electroencephalogram phenotype for a "vulnerable brain". *Anesth Analg.* 2020;131:1529–1539.