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Cognitive Impairment Is Associated with Absolute Intraoperative Frontal α-Band Power but Not with Baseline α-Band Power: A Pilot Study

Susanne Koch[a,b], **Insa Feinkohl**[c], **Sourish Chakravarty**[d], **Victoria Windmann**[a], **Gregor Lichtner**[a], **Tobias Pischon**[b,c,e], **Emery N. Brown**[d,f,g,h,i,j], **Claudia Spies**[a], **BioCog Study Group**

[a]Department of Anaesthesiology and Intensive Care Medicine, Charité – Universitätsmedizin Berlin, Campus Virchow-Klinikum and Campus Charité Mitte, Berlin, Germany;

[b]Berlin Institute of Health (BIH), Berlin, Germany;

[c]Molecular Epidemiology Research Group, Max-Delbrueck Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany;

[d]Picower Institute for Learning and Memory, MIT, Cambridge, MA, USA;

[e]MDC/BIH Biobank, Max-Delbrueck Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany;

[f]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA;

[g]Institute for Medical Engineering and Science, MIT, Cambridge, MA, USA;

[h]Institute for Data, Systems and Society, MIT, Cambridge, MA, USA;

[i]Harvard-MIT Health Sciences and Technology Program, Massachusetts Institute of Technology, Cambridge, MA, USA;

[j]Department of Brain and Cognitive Sciences, MIT, Cambridge, MA, USA

Abstract

Background: Cognitive abilities decline with aging, leading to a higher risk for the development of postoperative delirium or postoperative neurocognitive disorders after general anesthesia. Since frontal α-band power is known to be highly correlated with cognitive function in general, we

Dr. Susanne Koch, Department of Anaesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, DE–13353 Berlin (Germany), susanne.koch@charite.de.

Author Contributions

S.K., C.S. designed the study. S.K. and V.W. collected the EEG data and the cognitive data. S.K., S.C., V.W., G.L., and E.N.B. analyzed the EEG data. I.F. and T.P. analyzed the cognitive data. S.K. wrote the manuscript, and all authors reviewed the final manuscript.

Statement of Ethics

Ethics approval was obtained from the institutional review board (EA2/092/14). Patients gave their written informed consent on study inclusion, the day before surgery.

Disclosure Statement

The authors declare no conflict of interest.

hypothesized that preoperative cognitive impairment is associated with lower baseline and intraoperative frontal α-band power in older adults.

Methods: Patients aged ≥65 years undergoing elective surgery were included in this prospective observational study. Cognitive function was assessed on the day before surgery using six age-sensitive cognitive tests. Scores on those tests were entered into a principal component analysis to calculate a composite "*g* score" of global cognitive ability. Patient groups were dichotomized into a lower cognitive group (LC) reaching the lower 1/3 of "*g* scores" and a normal cognitive group (NC) consisting of the upper 2/3 of "*g* scores." Continuous pre- and intraoperative frontal electroencephalograms (EEGs) were recorded. EEG spectra were analyzed at baseline, before start of anesthesia medication, and during a stable intraoperative period. Significant differences in band power between the NC and LC groups were computed by using a frequency domain (δ 0.5–3 Hz, θ 4–7 Hz, α 8–12 Hz, β 13–30 Hz)-based bootstrapping algorithm.

Results: Of 38 included patients (mean age 72 years), 24 patients were in the NC group, and 14 patients had lower cognitive abilities (LC). Intraoperative α-band power was significantly reduced in the LC group compared to the NC group (NC −1.6 [−4.48/1.17] dB vs. LC −6.0 [−9.02/−2.64] dB), and intraoperative α-band power was positively correlated with "*g* score" (Spearman correlation: $r = 0.381$; $p = 0.018$). Baseline EEG power did not show any associations with "*g*."

Conclusions: Preoperative cognitive impairment in older adults is associated with intraoperative absolute frontal α-band power, but not baseline α-band power.

Keywords

Aging and cognition; Aging brain; Clinical trials; Cognitive decline; Electroencephalography

Introduction

Cognitive abilities decline with aging, leading to a higher risk to develop postoperative delirium (POD), when general anesthesia is needed [1–3]. POD is the most frequent brain dysfunction occurring after surgery, and it is related to increased mortality [4] and the occurrence of postoperative neurocognitive disorders [5–7]. Therefore, it is important to reduce the incidence of POD in elderly patients [8, 9].

Intraoperative unconsciousness induced by propofol or ether-derived anesthetics is characterized by an elevated, frontal, coherent α-band activity in intraoperative, electroencephalogram (EEG) recordings [10, 11]. However, elderly patients show a reduction of intraoperative, frontal α-band power accompanied by an increased risk to develop periods of burst suppression [10]. Burst suppression (isoelectric epochs intermittently appearing with high-amplitude oscillations) is related to phases of high level of anesthesia with pronounced suppression of brain metabolism [12]. By avoiding these phases of high-level anesthesia and burst suppression in the EEG, the incidence of POD in elderly patients can be reduced [13–15].

In general, lower α-band power is related to reduced cognitive function [16, 17]. Patients with Alzheimer's disease and mild cognitive impairment show a decreased α-band power in

awake, eye closed situation [18]. Moreover, lower intraoperative α-band power in older patients has been shown to correlate with lower preoperative cognitive function [19].

Cognitive assessments in the preoperative, anesthesiological evaluation center would be helpful to identify older patients at risk for the development of POD. However, cognitive examinations are time consuming and difficult to include in routine clinical procedures. Thus, identifying patients with poor preoperative cognitive function by characteristic EEG signatures recorded at the forehead within a short test (max. 1 min) could be helpful to risk-stratify patients at higher risk of developing POD and postoperative neurocognitive disorders.

We hypothesized that cognitively impaired elderly patients show reduced preoperative baseline as well as intraoperative frontal α-band power.

Methods

Study Design

This prospective, observational cohort study was performed as a subproject of the BioCog Study at the University hospital Charité – Universitätsmedizin Berlin Campus Charité Mitte and Campus VirchowKlinikum, Germany (NCT02265263; www.biocog.eu). Ethics approval was obtained from the institutional review board (EA2/092/14). While inclusion of patients for the BioCog study took place from October 2014 until April 2017, patients for this subproject were examined between February 2015 and April 2017.

Patients were eligible if they were aged 65 years or older, able to give written informed consent, with a planned surgery of at least 60 min undergoing a general anesthesia. Exclusion criteria comprised preoperative Mini-Mental State Examination < 24 points, neurological preconditions, such as history of seizures or stroke, or a proposed neurosurgical procedure. The surgical procedures included interventions in abdominal, gynecological, oral-otolaryngology, eye, cardiothoracic, and musculoskeletal surgery.

Medication and dosage of anesthesia, analgesia, and muscle relaxation were not part of the study protocol and chosen according to clinical needs by the anesthesiologist in charge.

Cognitive Assessment

Patients received cognitive assessments mainly on the day before surgery in sessions that lasted approximately 60 min. The battery consisted of 6 age-sensitive neuropsychological tests of which 4 (Paired Associates Learning; Verbal Recognition Memory; Spatial Span; Simple Reaction Time) were part of the CANTAB computerized battery and tapped the cognitive domains visual memory, verbal memory, working memory, and processing speed. Full details of the cognitive tests and testing procedure can be found elsewhere [20]. Two paper-pencil tests, Trail-Making Test-B and Grooved Pegboard, measuring executive function and fine motor skills, respectively, supplemented the battery. From performance on the 6 tests, the *g* factor was calculated as a summary index of global cognitive ability using principal components analysis [21]. "*G*" can be derived on the basis that people who

perform well on one cognitive test tend to perform well on other tests, too, and has repeatedly been demonstrated [22].

Cognitive impairment was defined relative to the total sample as scoring in the lowest tertile of "*g*."

EEG Data Collection and Analysis

A continuous preoperative (baseline) and intraoperative frontal EEG was recorded with the SEDline Root Monitor (Masimo Corporation, Irvine, CA, USA) starting before induction of anesthesia and lasting throughout the entire anesthesia. Following skin preparation with alcohol, electrodes were placed on the patients' forehead according to the SEDline electrode array at Fp1, Fp2, F7, and F8, with earth electrode at Fpz and reference electrode approximately 1 cm above Fpz. Electrode impedance was kept below 5 kΩ for each electrode. The EEG data were obtained with a sampling rate of 250 Hz.

For EEG, preprocessing bandpass filters (0.5–40 Hz) were applied to the raw EEG. Subsequently, the EEGs were inspected visually and one 10-s artefact-free time windows were selected manually from the period before induction of anaesthesia (baseline) and from a period about 30 min after anesthesia induction (intraoperative), excluding periods containing burst suppression.

Spectral analysis of the EEG data was performed with a custom-written Matlab codes (The MathWorks Inc., Natick, MA, USA) that estimated multitaper spectra using the Chronux toolbox [23] and estimated confidence intervals (CIs) (on statistics derived from multitaper spectra) using frequency domain bootstrap analyses [10, 24]. We calculated a pooled electrode that equally weighted the signals recorded from Fp1, Fp2, F7, and F8 to obtain estimates of absolute frontal power spectra, at β-band power 13–30 Hz, α-band power 8–12 Hz, θ-band power 4–7 Hz, and δ-band power 0.5–3 Hz. Within the α-band, we calculated the α-peak frequency (Hz), which is the frequency with the highest power within the α-band, and additionally we calculated the related α-peak power (dB), which is the power of the α-peak frequency. Power spectra quantifying the energy in the EEG at each frequency band were calculated by using a multitaper method with 2-s time windows with 1.9 s overlap, time-bandwidth product TW = 3, number of tapers K = 5, and spectral resolution of 2 W = 3 Hz.

The resulting data were transformed to a decibel scale [Power (dB) = 10log 10 (Power(μV))]. Grouplevel spectrograms displaying the power at different frequencies over time were computed by taking the median across patient groups.

Statistical Analysis

Numerical calculations were performed with SPSS, Version 24 (Copyright SPSS, Inc., Chicago, IL 60606, USA). Patients were divided into two groups according to their cognitive abilities; the "low cognition group" (LC) were compared with patients with normal cognitive abilities (NC). Significant differences in patient characteristics for the LC versus the NC group were calculated using the Mann-Whitney U test or the χ^2 test. Correlations between clinical parameters (age, gender, ASA score, anesthetic agent used [sevoflurane, desflurane,

propofol], sevoflurane [et Vol%], or type of analgesia [fentanyl, remifentanil]) and EEG band power were analyzed by Spearman correlation. Correlations between single cognitive test readouts (Paired Associates Learning; Verbal Recognition Memory; Spatial Span; Simple Reaction Time, Trail-Making Test B and Grooved Pegboard data) and EEG band power were analyzed by Spearman-Rho correlations. To determine the impact of age and EEG activity on the overall cognitive ability, we performed a univariate logistic regression.

For spectral analysis of the EEG data, we computed the 95% CI of the median difference at each frequency band (β-band power 13–30 Hz, α-power 8–12 Hz, θ-band power 4–7 Hz, and δ-band power 0.5–3 Hz) to assess the difference in power by using a frequency domain-based bootstrapping algorithm [10, 24].

Data are expressed as mean with standard deviation, median with 95% CI, or as frequencies (%). Values were considered significant if $p < 0.05$.

Results

Sample Characteristics

Of 38 included patients (mean age 71.8 years), 24 patients were in the NC group, and 14 patients were in the LC group.

Patients' characteristics are shown in Table 1. There were no statistically significant differences between the NC and LC groups in terms of age, surgery type, anesthesia procedure or further clinical parameters, but interestingly LC patients received a lower sevoflurane et Vol% dosage during the chosen intraoperative EEG period compared to the NC patients group.

Impact of Clinical Parameters

Intraoperative α-band power and α-peak power were negatively correlated with age, where α-band power and α-peak power decreased with increasing age ($r = -0.398$, $p = 0.013$ and 0.332, $p = 0.041$, respectively). We found no correlation with gender, ASA score, years of education, anesthetic agent used (sevoflurane, desflurane, propofol), sevoflurane (et Vol%) dosage, or type of analgesia (fentanyl, remifentanil). We did not find a correlation between baseline α-band power and any of the above-mentioned clinical parameters, either. Age was negatively correlated with the overall cognitive ability "*g*" score ($r = -334$, $p = 0.040$).

EEG Associations with Cognitive Impairment

Absolute, frontal β-, α-, θ- and δ-band power and α-peak frequency (Hz), and α-peak power (dB) at baseline and at intraoperative state for the NC and LC groups are shown in Table 2.

Baseline EEG showed no significant difference in β-, α-, θ-, and δ-band power, α-peak frequency (Hz), and α-peak power (dB) between the NC and LC group. There was no significant correlation between preoperative baseline α-band power and preoperative overall cognitive function indicated by "*g*" (Fig. 1).

In contrast, intraoperative frontal α-band power and α-peak power (dB) were significantly reduced in the LC group compared to the NC group (Fig. 2). Intraoperative α-band power and α-peak power (dB) were positively correlated with "*g*" ($r = 0.381$, $p = 0.018$; $r = 0.366$, $p = 0.024$, respectively).

In a detailed analysis related to the single cognitive tests, we found a positive correlation between intraoperative α-band power and the Paired Associates Learning of the CANTAB computerized battery ($r = 0.337$, $p = 0.038$; where a lower visual memory score is related to reduced α-band power) and Grooved pegboard test ($r = -0.337$, $p = 0.038$; where slower test performance is related to reduced α-band power). We did not find a correlation between any other cognitive tests of the CANTAB computerized battery, the Trail-Making Test B, and intraoperative frontal α-band power.

In contrast, we did not find any correlations between baseline EEG β-, α-, θ-, and δ-band power, and a single cognitive test readout.

We adjusted the impact of age on our primary outcome. In a univariate logistic regression for confounders related to overall cognitive impairment (age [years]; intraoperative α-band power), intraoperative α-band power showed an independent significant association ($p = 0.031$, OR 0.906, CI 95% 0.828–0.991), but not age ($p = 0.972$, OR 1.003, CI 95% 0.845–1.190).

Discussion

We demonstrate that cognitive function, preoperatively assessed in older patients, positively correlates with intraoperative, frontal α-band power and α-peak power. Patients with reduced cognitive abilities present with lower intraoperative α-band power. In contrast, in preoperative, baseline EEG, frontal α-band power showed no correlation with cognitive abilities. Additionally, we found no correlation between baseline and intraoperative frontal β-, θ,- and δ-band power and the overall cognitive ability of older patients.

Intraoperative increased frontal α-band and δ-band power and decreased β-band power are the typical EEG signature of unconsciousness induced by propofol or ether-derived anesthetics [11, 25] triggered by activation of the $GABA_A$ receptor and other ion channels, as the glycine receptor, glutamate receptor, and two-pore potassium channel [26–31]. In a mathematical model, it has been shown, that the intraoperative frontal α-band power is directly related to a $GABA_A$ activation inducing a thalamocortical feedback mechanism [28, 32].

Intraoperative frontal α-band power decreases with age [10, 33], which is in line with our findings. We could demonstrate this age-related α-band dynamic, even though we had only included patients 65 years and older. Reduced α-band power is not only described intraoperatively in elderly patients but also in resting state baseline EEGs in older patients compared to young patients [34]. However, this correlation was not seen in our patient groups. This difference indicates a higher sensitivity of physiological age-related changes in cerebral activity seen after $GABA_A$ activation induced by general anesthesia compared to baseline cerebral activity.

Cognitive decline is a hallmark of aging [35], also being correlated to a reduction in frontal α-band power in resting state, baseline EEG [36]. In recent years, frontal α-band power has even been suspected to be a prognostic factor, distinguishing patients with mild cognitive deficits (MCI) who will develop a dementia within the next years from MCI patients who will not suffer a further cognitive decline [37].

Accordingly, we proposed that the decline in frontal intraoperative α-band power is not only related to aging, as seen in the studies of Purdon and Schultz, but also to a decline in cognitive abilities. In a study from Giattino et al. [19], it has been shown that preoperative cognitive function in older adults correlates with a reduction of intraoperative frontal α-band power. In contrast, at the occipital or parietal cortical pole, no correlation with a cognitive decline was found, nor any correlation with β-, θ-, and δ-band power band power. Our data are in line with these findings, exhibiting a decline in intraoperative frontal α-band in cognitively impaired, older patients. Additionally, we found that intraoperative EEG analysis is more sensitive than baseline EEG data analysis to distinguish cognitive impaired patients from healthy aging patients. These results let us conjecture that neuronal inhibition is crucial for cognitive function in patients, since the intraoperative frontal α-band power is triggered by a pharmacological $GABA_A$ activation, translating to neuronal inhibition [27].

Since preoperative cognitive decline is a risk factor for the development of POD and postoperative neurocognitive disorders, our data may be of help to early identify patients with an increased risk for POD and postoperative neurocognitive disorders by reduced intraoperative EEG frontal α-band power. This may help to adapt the anesthesiological procedures and to tightly monitor these patients, to have the possibility to intervene early when first delirious symptoms occur.

Limitations

In this observational study, intraoperative drug administration and anesthesia management were not part of the study protocol, which may have biased our results. The anesthesiologists in charge were aware of the study performed in their patients, which would have increased their effort to avoid high level of anesthesia in those patients, and this might have influenced our results. Mainly the concentration of the anesthetic agent could have a major impact on our data [38], moreover since the sevoflurane concentrations (et Vol%) were lower in the LC group compared to the NC group (Table 1). However, we did not find a correlation between sevoflurane concentration (et Vol%) and intraoperative α-band power, α-peak frequency, or α-peak power in our study group. Additionally, lower sevoflurane concentration (et Vol%) should have led even to higher α-peak frequency in the LC group as shown in a study of Hight et al. [38], but the contrary was the case. Taken together, we think that the reduction of intraoperative α-band power and α-peak power in our LC group was not tampered by the anesthetic concentration the patients received, and might have been even more clearly shown, had we stratified our groups based on anesthetic concentration they received intraoperatively.

Furthermore, since this was a subproject within the BioCog study, focusing on patients aged ≥65 years, our observations cannot be applied to all ages and patient groups. But since older cognitively impaired patients are primarily at risk to develop POD and postoperative

neurocognitive disorders, and α-band power declines with age [10, 34] and cognitive impairment, we think our data focus on the patient group of interest, and it is even more helpful to show a correlation between α-band power and cognitive impairment in this subgroup of older patients. Still, our data are limited with respect to the small sample size.

Conclusion

Our data reveal reduced, intraoperative, frontal α-band power (intraoperative anteriorization) in cognitively impaired, older patients. In the future, large, controlled trials are needed to prove if reduced intraoperative, frontal α-band power is also related to the development of POD or postoperative neurocognitive disorder. Two studies are now underway focusing on these questions (Australian and New Zealand Clinical Trial Registry, ID: 12617001354370 [39], and Clinical Trial NCT03879850). Then, intraoperative, frontal α-band power may be used as an EEG-based marker to early identify patients at risk to develop POD, enabling the anesthesiologist to adapt the following anesthesia procedure and medication.

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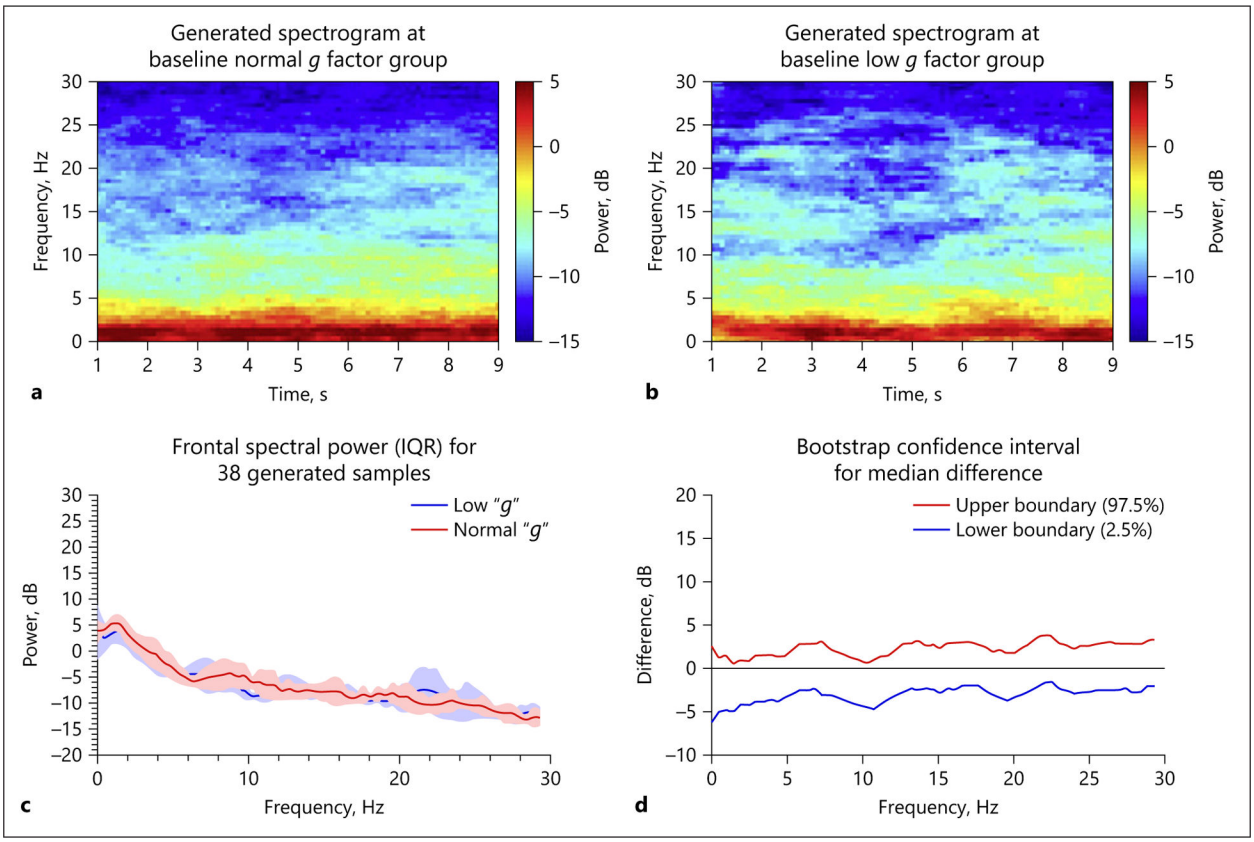

Fig. 1.

Preoperative baseline frontal group spectrograms over a single EEG window of 10 s comparing the normal*g* group (*n* = 24) (a) with the low*g* group (n = 14) (**b**). 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** No correlation between preoperative, baseline EEG spectrogram parameters, and normal vs. low cognitive abilities is shown. **d** Also using a frequency domain-based bootstrapping algorithm resampling the Fourier coefficients did not show any differences.

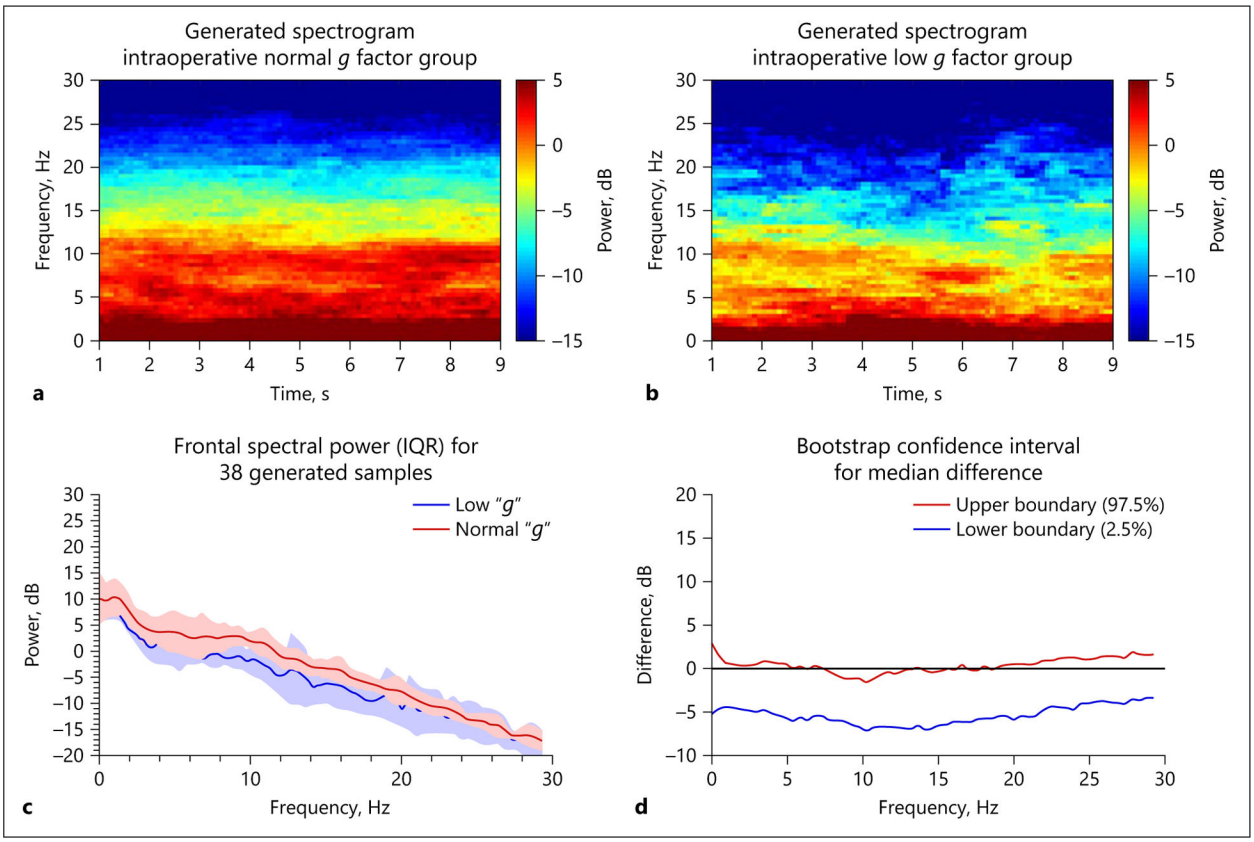

Fig. 2.

Intraoperative frontal group spectrograms over a single EEG window of 10 s comparing the normal *g* group (*n* = 24) (**a**) with the low *g* group (*n* = 14) (**b**). A significant intraoperative reduced α-band power (8–12 Hz) is shown for the low *g* 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** A reduction within the α-band (8–12 Hz) in the low *g* group compared to the normal *g* group is shown. **d** Using a frequency domain-based bootstrapping algorithm resampling the Fourier coefficients showed a significant difference between the low *g* group compared to the normal *g* group.

Table 1.

Baseline characteristics of patients

	All patients (*n* = 38)	NC group (*n* = 24)	LC group (*n* = 14)	*p* value
Age, years	71.8±4.6	71.3±3.9	72.8±5.6	0.463
Males/females	19/19	12/12	7/7	0.631
BMI	26.8±4.2	27.6±4.0	25.6±4.4	0.191
ASA status (1/2/3)	1/27/10	1/18/5	0/9/5	0.479
Education, years	12+4 (n = 27)	13±4 (*n* = 16)	11±4(*n* = 11)	0.512
Cognitive function (*g* score)	−0.079±0.97	0.496±0.60	−1.066±0.59	<0.0001 **
MMSE preoperative	28.8±1.1	29.1±1.0	28.3±1.2	0.038 *
Maintenance anesthetic agent (sevoflurane/desflurane/propofol)	24/6/8	16/5/3	8/1/5	0.179
Sevoflurane et Vol%	1.6±0.3	1.7±0.2	1.4±0.3	0.038 *
Maintenance analgesia type (fentanyl/remifentanil/both)	16/13/9	9/7/8	7/6/1	0.185

Continuous data were calculated by the Mann-Whitney U test, categorical data were analyzed by the χ^2 test.

* $p < 0.05$;

** $p < 0.0001$.

Table 2.

Baseline and intraoperative pooled band power

	NC group (*n* = 24)	LC group (*n* = 14)	*p* value
Baseline			
Delta band power 0.5–3 Hz, dB	−3.25 (−5.06/−0.19)	−2.33 (−4.7/0.4)	0.777
Theta band power 4–7 Hz, dB	−9.36 (−10.95/−7.53)	−8.36 (−9.88/−5.26)	0.988
Alpha band power 8–12 Hz, dB	−11.08 (−13.26/−8.14)	−10.91 (−13.29/−7.62)	0.988
Beta band power 13–30 Hz, dB	−13.73 (−15.49/−11.25)	−14.26 (−16.42/−9.99)	0.777
Alpha band Peak frequency, Hz	9.3 (8.8/9.8)	9.4 (8.6/10.1)	1.0
Alpha Peak frequency power, dB	−22.09 (−24.94/−19.25)	−20.78 (−25.91/−15.66)	0.964
Intraoperative			
Delta band power 0.5–3 Hz, dB	1.51 (−1.71/4.19)	−0.07 (−2.9/3.02)	0.54
Theta band power 4–7 Hz, dB	−1.57 (−5.54/1.32)	−4.73 (−7.42/−0.22)	0.482
Alpha band power 8–12 Hz, dB	−1.6 (−4.48/1.17)	−6.0 (−9.02/−2.64)	0.012*
Beta band power 13–30 Hz, dB	−14.52 (−16.12/−12.77)	−15.66 (−19.09/−13.18)	0.687
Alpha band peak frequency, Hz	9.4 (9.0/9.8)	9.3 (8.7/9.8)	0.560
Alpha peak frequency power, dB	1.4 (−2.2/5.0)	−7.5 (−14.1/−0.95)	0.016*

Comparison of EEG parameters between the NC group (“normal *g*”) and the LC group (“lower *g*”). The table presents frontal absolute, pooled band power at baseline and intraoperative time point and alpha band peak frequency (Hz) and alpha peak frequency power (dB). Mann-Whitney U test.

*$p < 0.05$.