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Comorbidity-dependent changes in alpha and broadband electroencephalogram power during general anaesthesia for cardiac surgery

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Abstract

Background: Age and comorbidities are reported to induce neurobiological transformations in the brain. Whilst the influence of ageing on anaesthesia-induced electroencephalogram (EEG) changes has been investigated, the effect of comorbidities has not yet been explored. We hypothesised that certain diseases significantly affect frontal EEG alpha and broadband power in cardiac surgical patients.

Methods: We analysed the frontal EEGs of 589 patients undergoing isoflurane general anaesthesia from a prospective observational study. We used multi- and uni-variable regression to analyse the relationships between comorbidities and age as independent with peak and oscillatory alpha, and broadband power as dependent variables. A score of comorbidities and minimum alveolar concentration (MAC) was built to interrogate the combined effect of age and score on alpha and broadband power.

Results: At the univariable level, many comorbidities were associated with lower EEG alpha or broadband power. Multivariable regression indicated the independent association of numerous comorbidities and MAC with peak alpha (R^2=0.19) and broadband power (R^2=0.31). The association with peak alpha power is markedly reduced when the underlying broadband effect is subtracted (R^2=0.09). Broadband measures themselves are more strongly correlated with comorbidities and MAC (R^2=0.31) than age (R^2=0.15).

Conclusions: Comorbidities and age are independently associated with decreasing frontal EEG alpha and broadband power during general anaesthesia. For alpha power, the association is highly dependent on the underlying broadband effect. These findings might have significant clinical consequences for automated computation for depth of anaesthesia in comorbid patients, because misclassification might pose the risk of under- or over-dosing of anaesthetics.

Clinical trial registration: NCT02976584.

Keywords: age; alpha power; comorbidity; depth of anaesthesia; electroencephalogram; general anaesthesia; intraoperative EEG; monitoring

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Editor's key points

- EEG monitoring during surgery can be a helpful adjunct in assessing anaesthetic depth and in guiding anaesthetic titration during surgery.
- The authors investigated the alpha and broadband power of the frontal EEG for 589 patients undergoing cardiac surgery with isoflurane anaesthesia in relation to comorbidities.
- They found a weak correlation between the concentration of isoflurane and frontal EEG alpha and broadband power; they attributed this weak relationship to a higher variability of alpha power in people with comorbidities.
- For patients with comorbidities, the variability noted for frontal power may alter the utility of EEG monitoring for assessing anaesthetic depth during surgery.

Depth of anaesthesia (DoA) monitors use surface EEG-derived parameters to calculate an index number—between 0 and 100—depicting the level of hypnosis. Most of these parameters come from fast Fourier transformed epochs of EEG, which provide detailed information of the amount (power) in predefined segments of EEG frequencies.[1] Most anaesthesiologists are aware of the potential for misclassification by DoA monitor algorithms when using certain drugs (e.g. ketamine or nitrous oxide)[2] as a result of blocking or activating different pathways in the brain (or both) and inducing different surface EEG frequencies.[3] However, other influences on the intraoperative EEG, and the potential consequences for the calculation of the level of hypnosis through DoA monitors, have not been investigated.

Age has a significant negative effect on frontal alpha power and coherence during anaesthesia.[4] This is significant as the cortical alpha oscillations shift from an occipital to a frontal location during anaesthetic-induced unconsciousness—a process named anteriorisation.[5] However, there are patients with anteriorised alpha oscillations during general anaesthesia that show a volitional response despite being seemingly unconscious.[6,7] In the awake state, similar findings have been described occipitally, with older patients showing increased power in the theta-wave range and a decrease in total and alpha power.[8] However, some findings could not be reproduced in the awake state, and the differences may be explained by the underlying disease instead of the patient's age.[9] Interestingly, a lower frontal alpha power during anaesthesia could be linked to a lower preoperative cognitive function[10] and decreased cognitive performance linked to specific comorbidities (e.g. cardiovascular, renal, or metabolic).[11] Recent studies on brain function emphasise the importance of removing the underlying EEG broadband (1/*f*) activity when analysing brain oscillations, as this can distort the predictive value of the EEG measure.[12]

As such, some comorbidities can share common pathophysiological pathways. For example, low-grade chronic inflammation is associated with atherosclerosis,[13] and this inflammation also induces endothelial cell dysfunction,[14] increases stroke risk,[15] worsens kidney function, and promotes insulin resistance.[16] Furthermore, inflammation and atherosclerosis are involved in neurodegeneration through shared genetic factors,[17] whilst also contributing to cerebrovascular damage by lipid peroxidation or oxidative stress.[18]

Thus, we tested the hypothesis that a patient's comorbidity load significantly affects the power of anaesthesia-induced EEG frontal alpha oscillations and broadband activity, and how age contributes to this relationship.

Methods

The ethics committee of Bern/Switzerland approved this prospective observational study (KEK#210/15). The Strengthening the Reporting of Observational Studies in Epidemiology checklist for observational studies was used to guide the methods of this study and to structure this paper.[19]

Patient selection

A total of 1072 patients undergoing general anaesthesia for adult cardiac surgery on cardiopulmonary bypass (CPB) were enrolled between July 2016 and January 2018 as a single-centre study in a tertiary hospital (ClinicalTrials.gov identifier: NCT02976584). Inclusion criteria for this exploratory non-prespecified analysis were isoflurane as general anaesthetic, available artifact and burst-suppression-free EEG sections of the pre-CPB period, midazolam < 0.05 mg kg^{-1} to complement induction with etomidate or propofol, and the use of sufentanil as analgesic. Exclusion criteria were the use of ketamine, dexmedetomidine, or nitrous oxide in the pre-CPB period.

Data acquisition and EEG processing

We used pre-CPB frontal surface EEG signals of the scalp on each patient's forehead using a Narcotrend® DoA monitor (MonitorTechnik, Bad Bramstedt, Germany) according to the manufacturer's instructions with a minimum distance of 8 cm between the electrodes (a bipolar recording located at FP1–TP9 in the 10–20 system). Sampling frequency was 125 Hz and electrode impedance levels were kept below 5 kΩ during the recording. The EEG and ECG were extracted from Philips IntelliVue MP90 anaesthesia monitors (Philips Medical Systems, Eindhoven, Netherlands); the volatile anaesthetic concentration was extracted from the respirator (Primus®; Draeger, Lübeck, Germany) using the RugloopII software (Demed Medical, Temse, Belgium). End-tidal isoflurane concentrations were recorded every 3 s and interpolated to every second.

In MATLAB® (R2016a; MathWorks, Inc., Natick, MA, USA), artifacts in the EEG arising from the heart electrical signal (ECG) were minimised by subtracting out an artificial reference signal from the EEG, as suggested by Strobach and colleagues.[20] As a first step, the R peak of the QRS complex was detected using the findpeaks.m script of the Signal Processing Toolbox, with a minimum peak prominence of 0.4 mV. Secondly, over non-overlapping periods of 40 s, 0.8 s sections of the EEG centred on the R peak of the ECG were averaged to give a mean interference signal in the EEG. This average was then tapered using a Blackman window before being reconstituted at the time points of the R peak in the ECG, creating an artificial reference signal, which was subsequently subtracted from the EEG. We considered the EEG as artifactual when either EEG amplitudes or EEG slopes exceeded a certain threshold. For calculating this threshold, the raw surface EEG data and EEG slopes were converted to z-scores (z), where all actual values (x) are rescaled according to the signal standard deviation (SD)

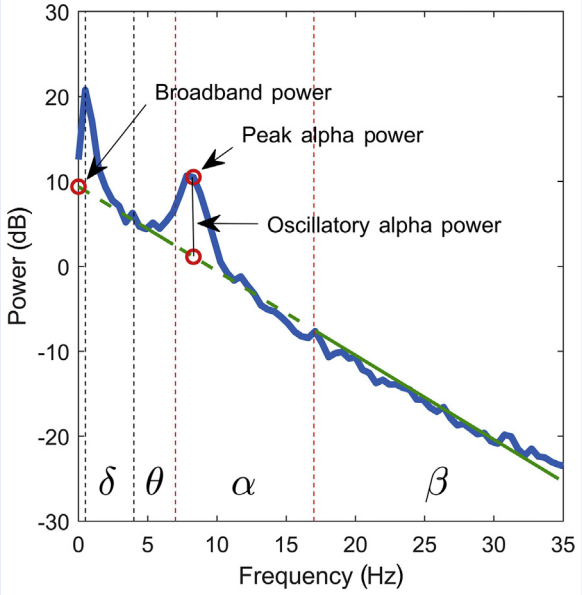

Fig 1. Power spectrum displaying the investigated EEG measures peak alpha, oscillatory alpha, and broadband power, and the implemented frequency limits for the alpha band.

and its mean (m): $z=(x-m)/\text{SD}$. All time periods where amplitudes or slopes were higher or lower than 6 z-scores (or 6 SDs away from the signal mean) were rejected.[21] The minimum artifact window size was set to 8 s. We considered as burst suppression any EEG section where amplitudes were less than 10 μV for at least 1 s. The artifact and burst-suppression detection codes were checked visually.

To minimise the effect of differing volatile anaesthetic concentrations between patients, we only included EEG data from time periods where.

(i) End-tidal isoflurane concentrations had been stable (within a range of 0.2 % isoflurane) for at least 10 min.[22]
(ii) After this equilibration period, there was at least 120 s of contiguous artifact-free EEG within this range.

If patients did not have any artifact or burst-suppression-free EEG sections available after stable isoflurane periods, they were excluded from further analysis.

Following Purdon and colleagues,[4] 2 s non-overlapping sections of EEG were transformed into the frequency domain using fast Fourier transformation (spectrogram.m with 129 discrete Fourier transform points). Spectra from artifact and burst-suppression-free EEG periods from before the patient went on CPB that fulfilled the aforementioned criteria were averaged to form a final mean power spectrum.

We chose to measure alpha power with two approaches, as the (i) peak spectral power and the (ii) oscillatory power without the underlying broadband effect. This was carried out within an extended alpha range of 7–17 Hz, as the alpha oscillation can shift within this range depending on the age of the patient and the administered concentration of general anaesthetic. We also performed an additional analysis on a further extended alpha range of 6–17 Hz in the Supplementary data section. Broadband EEG activity was measured as the y-intercept value (dB) of a linear regression on the spectrum with the oscillatory bands (0.5–4 Hz and 7–17 Hz) removed as per Sleigh and colleagues.[23] These EEG measurements are visualised in a power spectrum (Fig. 1).

Independent variable selection

The following patient characteristics and comorbidities were obtained using a structured preoperative questionnaire by the responsible attending cardiac anaesthetist and by chart reviewing and recording by a study nurse and coded for analysis as follows: age (in yr as continuous variable), gender (0=male; 1=female), anaemia (no/yes, according to WHO haemoglobin thresholds: male <130 g L^{-1} and female <120 g L^{-1}), nasopharyngeal temperature (in degrees Celsius as continuous variable), end-tidal isoflurane concentration converted into minimum alveolar concentration (MAC; not age adjusted), sodium (in mEq L^{-1} as a continuous variable), pulse pressure (systolic minus diastolic blood pressure in mm Hg on day of admission),[24] extra-cardiac arteriopathy (EA) (0=no EA; 1=EA without carotid stenosis [CS]; 2=EA with CS), aneurysmatic thoracic aorta (no/yes), cerebrovascular insult (CVI) (none=0; transient ischaemic attack/stroke without hemiplegia=1; stroke with hemiplegia=2), left ventricular ejection fraction (LVEF) (0=LVEF ≥40%; 1=LVEF <40%), coronary artery disease (CAD) (no/yes), acute endocarditis (no/yes), pulmonary arterial hypertension (no/yes; yes=mean pulmonary artery pressures >30 mm Hg), chronic pulmonary disease (no/yes; yes=long-term use of bronchodilators or steroids for lung disease), glomerular filtration rate (GFR; ml min^{-1} as continuous variable),[25] diabetes mellitus (0=none; 1=non-insulin dependent; 2=insulin dependent), and liver disease (0=none and mild; 1=moderate or severe; evaluated by magnitude of aminotransferase alteration ['mild' <5 times the upper reference limit; 'moderate' 5–10 times the upper reference limit; 'severe' >10 times the upper reference limit][26]).

Statistical methods

Descriptive statistics included means and SDs for all continuous independent variables (IVs), and counts for categorical data. To visualise the individual unadjusted effect of IVs on peak alpha power, scatter plots and box plots were generated. Then, simple linear regression was used to quantify their individual effects on peak and oscillatory alpha power, and on broadband power (R Stats Package). P-values less than 0.05 were considered significant.

As age is reported to have a significant influence on frontal alpha power and older patients might have suffered from comorbidities for a longer period of time, collinearity has to be assumed. Thus, to further interrogate the condensed effect of comorbidities without age on our frontal EEG measures, we performed least absolute shrinkage and selection operator (LASSO) regression to select the most influential IV on peak and oscillatory alpha power, and on broadband power. LASSO regression is a technique to reduce model complexity and prevent overfitting. More specifically, we used k-fold cross-validation (k=10) to optimise the regularisation parameter lambda, which was then implemented to shrink the coefficients for the final models. Thereby, the coefficients of least importance are minimised to zero and removed during the model-finding process.[27,28] The calculations were performed using the glmnet package in R (version 3.5.2).

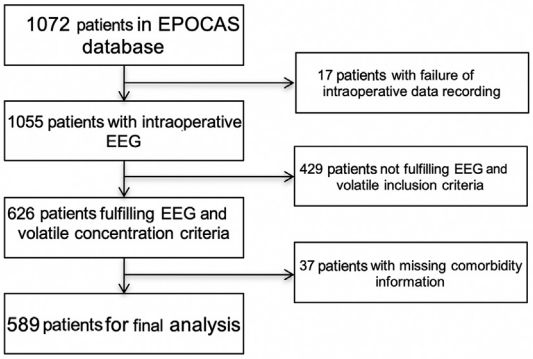

Fig 2. Flow chart of data selection. EPOCAS, epileptic potential during cardiac surgery.

To investigate the combined effect of comorbidity load, MAC, and age on frontal EEG peak, alpha and broadband power scores were created: the predicted values for peak alpha and broadband power from the LASSO regression models were used as basis for the scores, but were inverted and normalised to start at zero. Thus, higher scores correlate with a higher comorbidity load and lower MACs. We compared the scores and age against peak alpha and broadband power using a second-degree polynomial regression in a final step. A contour plot was chosen to visualise the effect of age and score on EEG peak alpha power.

The coefficient of determination (R^2) was used to estimate the goodness of fit for the regression models of (i) age alone, (ii) LASSO of IV (without age), and (iii) the score of comorbidities and MAC in combination with age. The models were compared using an *F*-test. Data analysed were based on availability and not by pre-specified power calculation.

In a Supplementary data analysis, we evaluated the detailed contribution of MAC, temperature, and comorbidities to the prediction of peak alpha and broadband power by performing explanatory model analysis for the LASSO regression.[29]

Results

Of the initial 1072 patients, 483 patients were excluded from further analysis. In 429 patients, the end-tidal anaesthetic concentration was not stable long enough to calculate an accurate effect site concentration, or there was artifact or burst suppression present in all 2 min EEG sections after these stable isoflurane periods, thus leaving a total of 589 patients to enter the final analysis (Fig 2).

Descriptive statistics

Table 1 shows mean and SDs for continuous data, and the count per level for categorical data. A typical preponderance of male cardiac surgery cases could be found. At the univariable level, about half of the 18 IVs show a significant association with the dependent variables peak alpha, oscillatory alpha, or broadband power (55.6%, 44.4%, and 50%, respectively). Age, MAC, GFR, and diabetes presented consistent associations with all three EEG measures. The relationship of the IVs with peak alpha power are presented as scatter and box plots in Supplementary Figure S2.

Multivariate analysis

LASSO regression chose the same 9 out of the 17 IVs for all three models (peak and oscillatory alpha and broadband power). These variables were anaemia, temperature, MAC, pulse pressure, EA, CVI, pulmonary hypertension, GFR, and diabetes. The variables aneurysmatic thoracic aorta, reduced LVEF, CAD, and endocarditis were not consistent between models (Table 2). All three models explain a significant amount of variance ($P<0.001$). Comorbidities and MAC are more strongly associated with the underlying broadband power ($R^2=0.31$) than with peak alpha ($R^2=0.19$) or oscillatory power ($R^2=0.09$). Age alone explains 19% of variance for peak, 10% for oscillatory, and 15% for broadband power (Table 3). When looking at the combined effect of age and the score of comorbidities and MAC on peak alpha and broadband power by polynomial regression, they could explain 29% of variance for peak alpha and 37% for broadband power ($P<0.001$).

When comparing the models, no significant difference between age and LASSO regression models could be found for peak alpha power. In contrast, the age plus score of comorbidities and MAC model performed significantly better than the age-only model ($P<0.001$). Concerning oscillatory alpha power models, age-only nor LASSO of IV could perform significantly better. Regarding the models for broadband power, the combined effect of age and score performed significantly better than age alone ($P<0.001$). Additionally, the LASSO-generated regression model of comorbidities and MAC outperformed the age-only regression model ($P<0.001$).

A contour plot displays the combined effect of age and score of comorbidity and MAC on peak alpha power (Fig. 3), which illustrates the relationship of low comorbidity load and older patients ending up with similar peak alpha power as younger patients with numerous comorbidities. The score of comorbidities and MAC for peak alpha power ranged from 0.3 to 25.7 (median: 12.7; inter-quartile range: 10.8–15.1) and for broadband power from 0.4 to 26.1 (median: 16.4; inter-quartile range: 14.0–19.1).

The explanatory model analysis for the LASSO regression confirms the significant contribution of comorbidities and MAC to the prediction of peak alpha and broadband power, but with substantial differences in the prediction for comorbid *vs* healthier patients (Supplementary Fig. S3). Whilst the attribution of MAC to the prediction is limited in comorbid patients, it basically drives the prediction of peak alpha and broadband power in healthy individuals. The attribution of temperature change is negligible under physiological temperatures.

Discussion

This exploratory data analysis from a prospective observational study reports a significant negative effect of

Table 1 Descriptive statistics and univariate analysis of patient characteristics, comorbidities, and neurophysiological factors *vs* intraoperative peak alpha, oscillatory alpha, and broadband power. CAD, coronary artery disease; CI, confidence interval; CVI, cerebrovascular insult; GFR, glomerular filtration rate; IDDM, insulin-dependent diabetes mellitus; LVEF, left ventricular ejection fraction; MAC, minimum alveolar concentration; NIDDM, non-insulin-dependent diabetes mellitus; SD, standard deviation; TIA, transient ischaemic attack.

Independent variable	Level	Count or mean of independent variable (SD)	Peak alpha power		Oscillatory alpha power		Broadband power	
			Mean (dB) (SD)	Univariable coefficient (CI; P-value)	Mean (dB) (SD)	Univariable coefficient (CI; P-value)	Mean (dB) (SD)	Univariable coefficient (CI; P-value)
Age (yr)	—	63.6 (11.5)	7.1 (4.4)	-0.17 (-0.20 to -0.14; <0.001)	6.8 (3.0)	-0.08 (-0.10 to -0.06; <0.001)	8.1 (3.9)	−0.13 (−0.16 to −0.11; <0.001)
Gender (male/female)	0	447	7.1 (4.3)	—	6.9 (2.9)	—	8.1 (3.9)	—
	1	142	6.9 (4.8)	-0.21 (-1.04 to 0.63; 0.627)	6.6 (3.0)	-0.32 (-0.88 to 0.24; 0.260)	8.0 (3.9)	−0.10 (−0.84 to 0.65; 0.798)
Anaemia (no/yes)	0	439	7.4 (4.5)	—	6.9 (3.0)	—	8.4 (4.0)	—
	1	150	6.0 (4.1)	-1.43 (-2.25 to -0.62; 0.001)	6.5 (2.9)	-0.46 (-1.01 to 0.09; 0.098)	7.1 (3.7)	−1.27 (−1.99 to −0.54; 0.001)
Temperature (°C)	—	35.8 (0.61)	7.1 (4.4)	-0.34 (-0.92 to 0.25; 0.262)	6.8 (3.0)	0.39 (0.00–0.78; 0.049)	8.1 (3.9)	−0.68 (−1.20 to −0.16; 0.010)
MAC	—	0.64 (0.16)	7.1 (4.4)	8.52 (6.38–10.67; <0.001)	6.8 (3.0)	-1.94 (-3.44 to -0.45; 0.011)	8.1 (3.9)	11.68 (9.92–13.45; <0.001)
Sodium (mEq L^{-1})	—	140.1 (2.9)	7.1 (4.4)	0.03 (-0.09 to 0.15; 0.591)	6.8 (3.0)	0.02 (-0.06 to 0.10; 0.563)	8.1 (3.9)	0.01 (−0.10 to 0.12; 0.845)
Pulse pressure (mm Hg)	—	55.4 (16.4)	7.1 (4.4)	-0.02 (-0.05 to -0.00; 0.027)	6.8 (3.0)	-0.01 (-0.02 to 0.01; 0.235)	8.1 (3.9)	−0.03 (−0.04 to −0.01; 0.009)
Extra-cardiac arteriopathy (none/peripheral/carotid)	0	501	7.3 (4.5)	—	6.9 (3.0)	—	8.2 (4.0)	—
	1	50	6.3 (4.5)	-0.94 (-2.23 to 0.34; 0.149)	6.6 (2.6)	-0.33 (-1.19 to 0.53; 0.453)	7.4 (4.1)	−0.77 (−1.91 to 0.37; 0.185)
	2	38	5.6 (3.6)	-1.70 (-3.15 to -0.24; 0.022)	5.8 (3.2)	-1.09 (-2.07 to -0.12; 0.028)	7.0 (3.2)	−1.22 (−2.52 to 0.07; 0.065)
Aneurysmatic thoracic aorta (no/yes)	0	484	7.1 (4.4)	—	6.8 (2.9)	—	8.1 (3.9)	—
	1	105	7.0 (4.7)	−0.09 (−1.03 to 0.84; 0.847)	6.9 (3.0)	0.16 (−0.46 to 0.79; 0.613)	7.9 (4.2)	−0.18 (−1.01 to 0.65; 0.666)
CVI (none/TIA or stroke without/with hemiplegia)	0	533	7.2 (4.4)	—	6.9 (2.9)	—	8.1 (4.0)	—
	1	45	6.7 (4.9)	−0.52 (−1.86 to 0.82; 0.445)	6.7 (3.5)	−0.20 (−1.10 to 0.69; 0.652)	7.6 (3.8)	−0.55 (−1.75 to 0.65; 0.369)
	2	11	3.0 (3.5)	−4.23 (−6.85 to −1.60; 0.002)	3.7 (2.5)	−3.21 (−4.96 to −1.46; <0.001)	6.5 (2.7)	−1.69 (−4.04 to 0.66; 0.159)
Reduced LVEF (no/yes)	0	415	7.4 (4.3)	—	6.9 (2.9)	—	8.3 (3.9)	—
	1	174	6.2 (4.5)	−1.20 (−1.98 to −0.42; 0.003)	6.5 (3.1)	−0.42 (−0.95 to 0.10; 0.113)	7.5 (3.9)	−0.86 (−1.55 to −0.16; 0.016)
CAD (no/yes)	0	215	7.3 (4.7)	—	7.2 (2.8)	—	8.1 (4.2)	—
	1	374	6.9 (4.3)	−0.43 (−1.17 to 0.32; 0.259)	6.6 (3.0)	−0.59 (−1.09 to −0.10; 0.019)	8.0 (3.8)	−0.11 (−0.77 to 0.55; 0.738)
Acute endocarditis (no/yes)	0	570	7.1 (4.4)	—	6.8 (2.9)	—	8.1 (3.9)	—
	1	19	6.5 (5.1)	−0.62 (−2.65 to 1.40; 0.546)	5.9 (3.4)	−0.91 (−2.26 to 0.44; 0.186)	8.4 (4.4)	0.35 (−1.45 to 2.15; 0.704)
Pulmonary hypertension (no/yes)	0	518	7.4 (4.4)	—	6.9 (2.9)	—	8.3 (3.9)	—
	1	71	4.9 (4.3)	−2.43 (−3.51 to −1.35; <0.001)	6.2 (3.2)	−0.71 (−1.44 to 0.02; 0.057)	6.3 (3.5)	−1.99 (−2.95 to −1.02; <0.001)
Pulmonary disease (no/yes)	0	516	7.2 (4.4)	—	6.8 (2.9)	—	8.2 (4.0)	—
	1	73	6.4 (4.4)	−0.79 (−1.87 to 0.30; 0.156)	6.6 (3.2)	−0.21 (−0.94 to 0.51; 0.561)	7.5 (3.7)	−0.68 (−1.65 to 0.28; 0.166)
GFR (ml min^{-1})	—	75.5 (20.4)	7.1 (4.4)	0.04 (0.03–0.06; <0.001)	6.8 (3.0)	0.02 (0.01–0.03; 0.003)	8.1 (3.9)	0.04 (0.03–0.06; <0.001)
Diabetes mellitus (none/NIDDM/IDDM)	0	476	7.4 (4.3)	—	6.9 (2.9)	—	8.4 (3.9)	—
	1	70	6.1 (4.6)	−1.33 (−2.43 to −0.24; 0.017)	6.6 (3.2)	−0.29 (−1.03 to 0.45; 0.438)	7.1 (3.4)	−1.36 (−2.33 to −0.38; 0.006)

Continued

Table 1 Continued

Independent variable	Level	Count or mean of independent variable (SD)	Peak alpha power		Oscillatory alpha power		Broadband power	
			Mean (dB) (SD)	Univariable coefficient (CI; P-value)	Mean (dB) (SD)	Univariable coefficient (CI; P-value)	Mean (dB) (SD)	Univariable coefficient (CI; P-value)
	2	43	4.8 (4.2)	−2.68 (−4.04 to −1.31; <0.001)	5.8 (2.7)	−1.11 (−2.03 to −0.18; 0.019)	6.0 (3.8)	−2.41 (−3.62 to −1.20; <0.001)
Liver disease (no/yes)	0	521	7.1 (4.4)	—	6.8 (2.9)	—	8.0 (3.9)	—
	1	68	7.2 (4.6)	0.15 (−0.97 to 1.27; 0.798)	6.7 (3.4)	−0.08 (−0.83 to 0.67; 0.830)	8.4 (4.0)	0.35 (−0.64 to 1.35; 0.485)

comorbidities on intraoperative frontal EEG alpha and broadband power during isoflurane anaesthesia. Interestingly, the effect of age, comorbidities, and MAC on alpha power with the broadband effect removed (oscillatory alpha power) was low and could explain about 10% of variance only (Table 3). In contrast, the effect of age, comorbidities, and MAC on a broadband EEG measure was stronger, either with age alone (accounting for 15% variance) or combined with comorbidities and MAC (accounting for 37% variance). Any interpretation of frontal alpha power measures during anaesthesia has to take into consideration whether the underlying broadband effect was included during its calculation. Age and comorbidities both have a significant negative effect on peak or oscillatory alpha power, but comorbidities seem to have a relatively larger influence on the underlying broadband power.

Table 2 Multivariable effects of comorbidities and neurophysiological factors on intraoperative frontal EEG peak alpha, oscillatory alpha, and broadband power. The coefficients have been selected and calculated by least absolute shrinkage and selection operator regression. CAD, coronary artery disease; CVI, cerebrovascular insult; GFR, glomerular filtration rate; IDDM, insulin-dependent diabetes mellitus; LVEF, left ventricular ejection fraction; MAC, minimum alveolar concentration; NIDDM, non-insulin-dependent diabetes mellitus; TIA, transient ischaemic attack.

Independent variable	Level	Peak alpha power coefficients	Oscillatory alpha power coefficients	Broadband power coefficients
Gender (male/female)	0			
	1	0	0	0
Anaemia (no/yes)	0			
	1	-0.027	-0.064	-0.200
Temperature (°C)	—	-0.279	0.060	-0.811
MAC	—	7.952	-2.138	11.168
Sodium (mEq L^{-1})	—	0	0	0
Pulse pressure (mm Hg)	—	-0.004	-0.003	-0.011
Extra-cardiac arteriopathy (none/peripheral/carotid)	0			
	1	-0.546	0	0
	2	-0.713	-0.412	-0.494
Aneurysmatic thoracic aorta (no/yes)	0			
	1	-0.298	0	0
CVI (none/TIA or stroke without [1]/with hemiplegia [2])	0			
	1	0	0	-0.112
	2	-2.662	-1.905	-0.257
Reduced LVEF (no/yes)	0			
	1	-0.299	-0.029	0
CAD (no/yes)	0			
	1	0	-0.193	0
Acute endocarditis (no/yes)	0			
	1	-0.761	0	0
Pulmonary hypertension (no/yes)	0			
	1	-1.273	-0.471	-0.477
Pulmonary disease (no/yes)	0			
	1	0	0	0
GFR (ml min^{-1})	—	0.024	0.004	0.017
Diabetes mellitus (none/NIDDM/IDDM)	0			
	1	-1.022	0	-0.892
	2	-1.344	-0.011	-0.901
Liver disease (no/yes)	0			
	1	0	0	0
Intercept	—	11.093	6.188	29.723

Table 3 R squares of regression analysis of age, least absolute shrinkage and selection operator (LASSO), and score of comorbidities and minimum alveolar concentration with age *vs* specific anaesthesia-related EEG measures. na, not available.*Model explains significantly more of peak alpha power variation than age alone ($P<0.001$); †Both models explain significantly more of broadband power variation than age alone ($P<0.001$).

Model	Peak alpha power (dB)	Oscillatory alpha power (dB)	Broadband power (dB)
Age	0.19	0.1	0.15
LASSO regression	0.19	0.09	0.31†
Score and age	0.29*	na	0.37†

As frontal alpha power is sometimes used to calculate DoA in clinically used monitors, these findings should inform the design of any future algorithms purporting to determine a patient's level of sedation or put their use into question in patients with high comorbidity load.[30,31] This result might be an explanation for a frequent clinical finding of falsely elevated readings of DoA monitors when used in patients with many comorbidities,[32,33] especially, as this vulnerable population would benefit most from a reliable interpretation of the EEG through DoA monitors to try and reduce delirium[34] or even death.[35] Our analysis showed that isoflurane concentration had a significant independent association with frontal alpha and broadband power. To our knowledge, there are no systematic studies showing that comorbidities have a

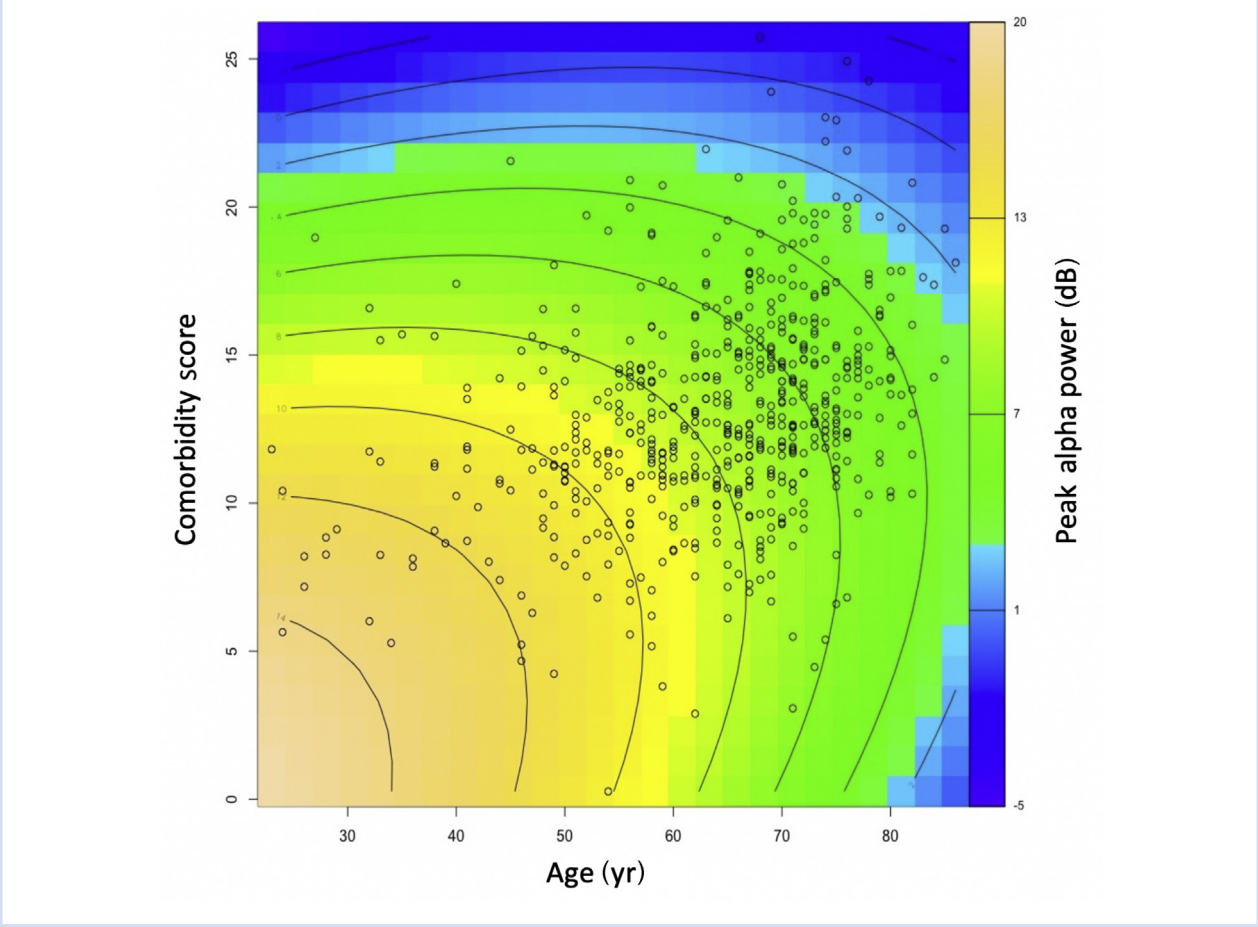

Fig 3. Contour plot of age, a score of comorbidities and minimum alveolar concentration (MAC), and the effect on frontal peak alpha power. Age (in yr) is shown on the *x*-axis, the score is shown on the *y*-axis, and alpha power (in dB) is displayed with lines and in colour bands (colder colours [blue and green] for lower power and warmer colours [orange and yellow] for higher power). It can be appreciated that young patients with higher comorbidity load can have low alpha power, and older patients with low comorbidity load reaching higher alpha power. The lowest alpha power is seen in old patients with accompanying high scores (based on multiple comorbidities and a low MAC).

significant influence on intraoperative frontal alpha or broadband power. Age is described as being negatively correlated with frontal (average) alpha power during sevoflurane and propofol anaesthesia in otherwise healthy patients.[4] However, most people undergoing surgery suffer from an increasing number of comorbidities when they get older; hence, EEG power loss may be a manifestation of the combined effect of comorbidities on the brain.[36] Interestingly, the previously reported R^2 of age and alpha power was 0.46 under sevoflurane general anaesthesia, and is much stronger than our result of R^2=0.19. This might be explained by the much higher variability of frontal alpha power in our population, possibly exaggerated by the higher comorbidity load of our cardiac surgery patients.[37]

It is interesting that comorbidities and MAC are more strongly associated with broadband EEG measures than they are with narrowband alpha oscillations. Our finding that increasing age is associated with decreasing overall broadband power is in agreement with previous research,[4] but that comorbidities can have a similar effect is a novel finding. Whilst the biological origins of broadband EEG remain unclear,[12] oscillatory alpha power is thought to be a measure of thalamocortical system integrity. Our results suggest that this system can degrade to a large degree independent of age and comorbidity progression.

Oxidative stress and inflammation are important factors for brain ageing and also play a central role in many of the diseases that we found to be significant contributors to the multivariable model[38] (e.g. diabetes,[39] cardiovascular,[18] or renal disease[16]). In addition, cytokine signalling has been shown to be involved in the modulation of EEG patterns during volatile anaesthesia.[40]

The EEG is believed to be caused predominantly by postsynaptic electric activity in the cortex.[1] The comorbidity-induced decrease in EEG power we observed might be attributable to a reduction of the synaptic density of the cortex along with an accompanying decline in neurotransmitter synthesis and electrical current formation.

Nonetheless, there are older patients with preserved neuroanatomy of certain brain regions (e.g. hippocampus and anterior temporal cortex), which is associated with better memory function, named 'super-agers'.[41] However, it is not known if these patients started out with supernormal cortical thickness, or if the ageing process of the brain was slower because of other factors (e.g. education, health, and physical activity). Unfortunately, there are no definitive EEG recordings to confirm this, but it is suggestive that a reduced intraoperative frontal (average) alpha power correlates well with patients' preoperative cognitive function.[10]

A few limitations of this study should be discussed. First, as the alpha oscillation frequency slows with both increasing age and increasing volatile anaesthetic concentration,[42] decreasing alpha power with age might be to some degree caused by the oscillation slipping below the predefined extended 7–17 Hz target range. When we completed an additional analysis allowing the alpha oscillation to range down to 6 Hz (see Supplementary section), the effect of comorbidities and MAC was minimally weaker and identical for age. Secondly, depending on the structure and resistivity variations of the human skull, the previously reported filtering effect on EEG power and frequency might be variable.[43] Thus, the decreasing alpha power with age described by Purdon and colleagues[4] could be explained by an increased resistivity of the skull with ageing. Additionally, the effect of comorbidity on alpha and broadband EEG power might depend on how long the patient has had that specific comorbidity. Although this was a prospective study, it was not possible to accurately determine the year of primary detection for every comorbidity. Even then, the comorbidity might well have been present but undetected for years. Despite the thorough preoperative assessment of patients before undergoing cardiac surgery, there still is a chance that some comorbidities remain undetected. Other comorbidities have a low prevalence, so even with a quite large sample size as in our study their effect might be underestimated. Also, there is the possibility of introduction of selection bias, as many of the sickest patients may be excluded because of having burst suppression, or instability of the isoflurane dosing.

In conclusion, age and comorbidities are independently associated with decreased frontal alpha and broadband power during general anaesthesia with isoflurane. The association with peak alpha power is markedly reduced when the underlying broadband effect is subtracted. Broadband measures themselves are more strongly correlated with comorbidities than age, suggesting a mechanism affecting multiple frequency bands of the EEG. These findings might have significant clinical consequences as a result of possible misclassification by DoA monitors using automated computation in fragile patients with many comorbidities. Misclassification might pose the risk of under- or overdosing anaesthetics depending on the underlying algorithm, possibly leading to an increased postoperative incidence of delirium, awareness, or even death.

Authors' contributions

Study conception: HAK, VH, CR, DH
Study design: HAK, DH
Data acquisition: HAK, TH, DR, VH, MS, DH
Data analysis: HAK, CS, CR, JS, DH
Data interpretation: HAK, TH, CR, JS, DH
Drafting of paper: HAK, DH
Critical revision of paper: all authors.
All authors approved the final version and agree to be accountable for all aspects of the work.

Declarations of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

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