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Original Contribution

Lower alpha frequency of intraoperative frontal EEG is associated with postoperative delirium: A secondary propensity-matched analysis

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HIGHLIGHTS

- Delirium remains a serious postoperative complication, that is difficult to treat and predict.
- Negative correlation of frontal alpha frequency and end-tidal anesthetic exists.
- Low frontal alpha frequency serves as a predictor for postoperative delirium.
- Anesthetic titration on alpha frequency might help reduce postoperative delirium.

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ABSTRACT

Background: Postoperative delirium (POD) is a serious complication of surgery, especially in the elderly patient population. It has been proposed that decreasing the amount of anesthetics by titrating to an EEG index will lower POD rate, but clear evidence is missing. A strong age-dependent negative correlation has been reported between the peak oscillatory frequency of alpha waves and end-tidal anesthetic concentration, with older patients generating slower alpha frequencies. We hypothesized, that slower alpha oscillations are associated with a higher rate of POD.

Method: Retrospective analysis of patients` data from a prospective observational study in cardiac surgical patients approved by the Bernese Ethics committee. Frontal EEG was recorded during Isoflurane effect-site concentrations of 0.7 to 0.8 and peak alpha frequency was measured at highest power between 6 and 17 Hz. Delirium was assessed by chart review. Demographic and clinical characteristics were compared between POD and non-POD groups. Selection bias was addressed using nearest neighbor propensity score matching (PSM) for best balance. This incorporated 18 variables, whereas patients with missing variable information or without an alpha oscillation were excluded.

Result: Of the 1072 patients in the original study, 828 were included, 73 with POD, 755 without. PSM allowed 328 patients into the final analysis, 67 with, 261 without POD. Before PSM, 8 variables were significantly different between POD and non-POD groups, none thereafter. Mean peak alpha frequency was significantly lower in the POD in contrast to non-POD group before and after matching (7.9 vs 8.9 Hz, 7.9 vs 8.8 Hz respectively, SD 1.3, $p < 0.001$).

Conclusion: Intraoperative slower frontal peak alpha frequency is independently associated with POD after cardiac surgery and may be a simple intraoperative neurophysiological marker of a vulnerable brain for POD. Further studies are needed to investigate if there is a causal link between alpha frequency and POD.

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1. Introduction

Delirium, a syndrome characterized by acute changes in attention, awareness and cognition is a frequent complication in patients undergoing surgery [1]. The prevalence of postoperative delirium (POD) following surgery is reported to be up to 20% of patients [2,3]. Patient specific risk factors for developing POD include advanced age, preexisting cognitive impairment or dementia, frailty, and cardiovascular- and renal disease. These predisposing factors are further influenced by the duration and invasiveness of the procedure, as well as duration and dose of anesthesia [4].

Patients suffering from delirium exhibit increased morbidity, higher rates of long-term cognitive deficits and higher postoperative mortality [5–8]. Furthermore, POD is associated with increased length of hospitalization and higher costs [2,4]. Therefore POD has emerged as a significant public health concern, causing additional annual health care costs for patients in the US undergoing elective major surgery of an estimated $32.9 billion [9].

Effective preventive perioperative measures include avoidance of perioperative polypharmacy and prolonged fluid fasting, careful perioperative pain and blood pressure management, intraoperative dexmedetomidine infusion, multimodal opioid sparing analgesia and monitoring the hypnotic depth of anesthesia to decrease the amount of anesthetics given intraoperatively [3,10].

While consensus is still lacking, current evidence suggests that the duration of electroencephalogram (EEG) burst suppression - an EEG pattern of deep general anesthesia - and the presence of specific EEG emergence trajectories may predict POD [11–16]. Despite the important negative result of the ENGAGES trial [17], titration of anesthesia dosing according to the EEG is recommended by several guidelines [18,19].

Commonly used anesthesia monitors transform the EEG signal into a single numerical value (index) purportedly reflecting the likelihood of consciousness, and claim to help maintain the patient in a state of unconsciousness with minimal suppression of vital functions without allowing surgical discomfort or pain. Nonetheless, there is a long-standing discussion if these monitors are up to this task, as systematic inaccuracies have been reported for the fragile and older population when using the BIS® monitor [20], where older patients show higher BIS values despite an increased age-adjusted MAC, an effect likely due to a more ‘awake’ looking EEG [21].

A promising approach is the renewed current focus on the alpha (8–12 Hz) oscillation in the frontal EEG. To date, associations have been observed between low intraoperative alpha power and subsequent delirium [22,23], but it remains unknown if alpha frequency is also associated with delirium [24]. Thus, with this secondary analysis of prospectively collected data we wanted to test the hypothesis if higher or lower peak alpha frequency is associated with postoperative delirium.

2. Materials and methods

The ethics committee of the canton of Bern, Switzerland, approved the original prospective observational study (KEK#210/15). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational studies was used to guide the methods of the study and to structure the manuscript [25].

2.1. Patient selection

A total of 1072 adult patients requiring general anesthesia for cardiac surgery with cardiopulmonary bypass (CPB) were enrolled between July 2016 and January 2018 as part of a prospective observational single-center study (ClinicalTrials.gov identifier: NCT02976584). For inclusion in this secondary analysis of the dataset we required the use of isoflurane for general anesthesia, complete data including pre-bypass EEG and endtidal anesthesia gas concentrations, as well as comorbidities. Strictly pre-bypass data were used with the aim to decrease confounding by CPB factors (e.g., cooling, inflammation, hemodilution). Due to the setup of our induction rooms, EEG recording started approximately an hour after induction of anesthesia in the operating room. Brain effect-site concentrations of isoflurane were estimated using a simple diffusion model with a half-time equilibrium constant (Keo) of 120, and named CeMAC. End tidal concentrations (and thus CeMAC values) were available every second. To reduce systematic bias through changing CeMAC levels, only EEG measurements that were recorded at CeMAC levels between of 0.7 to 0.8 were used for the final analysis.

2.2. EEG recordings

EEG signals (sampling frequency of 125 Hz) were recorded using the Narcotrend® monitor (MonitorTechnik, Bad Bramstedt, Germany) which provides a bipolar derivation (FP1-TP9 in the 10–20 system, with FpZ as the common reference). The Narcotrend monitor also has built-in high (0.5 Hz) and low (45 Hz) pass filters. Some electrocardiogram artifact was present in the EEG, and we used an ECG minimization method as detailed elsewhere [26]. Periods of EEG where burst suppression was present (defined as amplitudes <5 μV for more than half a second) were not included in the analysis. As in previous analyses, EEG activity with absolute slopes >50 mV per 8 ms was excluded from the analysis as noise [26].

2.3. Spectral analyses

Successive spectra were created from artifact and burst suppression-free sections of EEG of 20 s length with a 1 s offset using spectrogram.m in Matlab R2017b (The MathWorks Inc., Natick, MA, USA). We chose to use 625 FFT points (nfft), to allow a frequency resolution of 0.1 Hz. Alpha frequency was calculated as the frequency (in Hz) where spectral power was maximal within the extended alpha (6 to 17 Hz) range, when the underlying aperiodic power had been subtracted (as estimated using a linear regression on the spectra until 35 Hz without the power in the delta (0.5–4 Hz) and extended alpha ranges, see [27] for details. We chose the lower alpha range of 6 Hz after examination of the data, as we noted that the classic alpha oscillation could reach this low in our group of primarily elderly patients, and because isoflurane does not have such a prominent theta peak as with sevoflurane and desflurane. The median of all alpha frequency values for each patient was used in this analysis.

2.4. Independent variables

Demographics and comorbidities were prospectively collected. Comorbidities were recorded according to the EuroScore system [28]. Pulmonary disease was regarded as relevant at equal or more than a GOLD III [29]. Sodium blood levels were divided into normal and low range, as the maximal reported sodium value was 145 mmol/L.

2.5. Dependent variable – postoperative delirium (POD)

For detection of POD, the validated chart review method was used as a systematic retrospective approach [30]. Its sensitivity is known to be limited in comparison to the Confusion Assessment Method, but due to the study design a retrospective methodology had to be chosen.

2.6. Statistics

Demographic and clinical characteristics were compared between the delirium and non-delirium groups by using univariable and multivariable regression. Possible selection bias was addressed by performing propensity score matching (PSM) and by restricting brain concentrations to a CeMAC between 0.7 and 0.8, minimizing isoflurane dose effects. The propensity score for each individual is defined as the probability of developing POD given the patient’s baseline characteristics and comorbidities (Table 1). This incorporated 18 variables, including

Table 1
Independent variables summary – *before* propensity score matching.

Dependent: Delirium (no/yes)		NO n = 755	YES n = 73	OR (univariable)	OR (multivariable)
Age (years)	Mean (SD)	64.3 (11.7)	70.1 (7.2)	0.00 (0.00 to 0.01, $p <$ 0.001)	0.00 (−0.00 to 0.00, $p =$ 0.193)
Peak Alpha Frequency (Hz)	*Mean (SD)*	*8.9 (1.2)*	*7.9 (1.3)*	*−0.05 (−0.07 to − 0.04, p < 0.001)*	*−0.04 (−0.06 to − 0.03, p < 0.001)*
Gender (male/female)	0	571 (91.2)	55 (8.8)	–	–
	1	184 (91.1)	18 (8.9)	0.00 (−0.04 to 0.05, $p =$ 0.957)	−0.01 (−0.05 to 0.04, $p =$ 0.798)
CKD Stage (1–4)	1	189 (96.4)	7 (3.6)	–	–
	2	406 (90.4)	43 (9.6)	0.06 (0.01 to 0.11, $p =$ 0.013)	0.03 (−0.02 to 0.08, $p =$ 0.293)
	3	111 (92.5)	9 (7.5)	0.04 (−0.02 to 0.10, $p =$ 0.227)	−0.01 (−0.08 to 0.06, $p =$ 0.842)
	4	49 (77.8)	14 (22.2)	0.19 (0.11 to 0.27, p < 0.001)	0.10 (0.01 to 0.18, $p =$ 0.028)
CVI (none/TIA or Stroke without/with hemiplegia)	0	685 (92.1)	59 (7.9)	–	–
	1	56 (83.6)	11 (16.4)	0.08 (0.01 to 0.16, $p =$ 0.019)	0.06 (−0.01 to 0.13, $p =$ 0.111)
	2	14 (82.4)	3 (17.6)	0.10 (−0.04 to 0.23, $p =$ 0.162)	0.01 (−0.12 to 0.14, $p =$ 0.889)
Arteriopathy (none/peripheral/carotid)	0	642 (92.4)	53 (7.6)	–	–
	1	57 (85.1)	10 (14.9)	0.07 (0.00 to 0.14, $p =$ 0.044)	0.04 (−0.03 to 0.11, $p =$ 0.319)
	2	56 (84.8)	10 (15.2)	0.08 (0.00 to 0.15, $p =$ 0.039)	0.04 (−0.03 to 0.12, $p =$ 0.224)
Diabetes (none/NIDDM/IDDM)	0	608 (91.0)	60 (9.0)	–	–
	1	90 (93.8)	6 (6.2)	−0.03 (−0.09 to 0.03, $p =$ 0.378)	−0.04 (−0.10 to 0.02, p = 0.224)
	2	57 (89.1)	7 (10.9)	0.02 (−0.05 to 0.09, $p =$ 0.599)	−0.02 (−0.10 to 0.05, $p =$ 0.560)
Sodium (normal/low)	1	729 (91.5)	68 (8.5)	–	–
	2	26 (83.9)	5 (16.1)	0.08 (−0.03 to 0.18, $p =$ 0.144)	0.08 (−0.02 to 0.18, $p =$ 0.125)
BMI	Mean (SD)	27.4 (4.8)	27.5 (4.8)	0.00 (−0.00 to 0.00, $p =$ 0.770)	0.00 (−0.00 to 0.01, $p =$ 0.391)
Liver Disease (no/yes)	0	673 (90.9)	67 (9.1)	–	–
	1	82 (93.2)	6 (6.8)	−0.02 (−0.09 to 0.04, $p =$ 0.485)	−0.01 (−0.07 to 0.05, $p =$ 0.682)
Alcohol abuse (no/yes)	0	639 (91.9)	56 (8.1)	–	–
	1	116 (87.2)	17 (12.8)	0.05 (−0.01 to 0.10, $p =$ 0.078)	0.04 (−0.01 to 0.10, $p =$ 0.101)
Reduced LVEF (no/yes)	0	560 (92.7)	44 (7.3)	–	–
	1	195 (87.1)	29 (12.9)	0.06 (0.01 to 0.10, $p =$ 0.011)	0.03 (−0.01 to 0.07, $p =$ 0.192)
Pulmonary Hypertension (no/yes)	0	653 (91.8)	58 (8.2)	–	–
	1	102 (87.2)	15 (12.8)	0.05 (−0.01 to 0.10, $p =$ 0.099)	0.02 (−0.04 to 0.07, $p =$ 0.600)
Weight Intervention (isolated CABG or Valve/2 procedures/3 procedures)	0	270 (92.8)	21 (7.2)	–	–
	1	210 (95.9)	9 (4.1)	−0.03 (−0.08 to 0.02, $p =$ 0.217)	−0.03 (−0.08 to 0.03, $p =$ 0.322)
	2	201 (88.2)	27 (11.8)	0.05 (−0.00 to 0.10, $p =$ 0.063)	0.00 (−0.05 to 0.06, $p =$ 0.871)
	3	74 (82.2)	16 (17.8)	0.11 (0.04 to 0.17, $p =$ 0.002)	0.02 (−0.07 to 0.11, $p =$ 0.686)
Pulmonary Disease (no/yes)	0	671 (91.9)	59 (8.1)	–	–
	1	84 (85.7)	14 (14.3)	0.06 (0.00 to 0.12, $p =$ 0.042)	0.02 (−0.04 to 0.08, $p =$ 0.540)
Previous Surgery (no/yes)	0	689 (92.1)	59 (7.9)	–	–
	1	66 (82.5)	14 (17.5)	0.10 (0.03 to 0.16, $p =$ 0.004)	0.05 (−0.02 to 0.12, $p =$ 0.132)
Acute Endocarditis (no/yes)	0	727 (91.4)	68 (8.6)	–	–
	1	28 (84.8)	5 (15.2)	0.07 (−0.03 to 0.16, $p =$ 0.191)	0.05 (−0.05 to 0.15, $p =$ 0.289)
Recent MI (no/yes)	0	661 (91.4)	62 (8.6)	–	–
	1	94 (89.5)	11 (10.5)	0.02 (−0.04 to 0.08, $p =$ 0.522)	0.03 (−0.03 to 0.09, $p =$ 0.350)
Aneurysmatic Thoracic Ao (no/yes)	0	634 (93.2)	46 (6.8)	–	–
	1	121 (81.8)	27 (18.2)	0.11 (0.06 to 0.16, p < 0.001)	0.09 (0.02 to 0.16, $p =$ 0.009)

Data are expressed as mean and standard deviation, or as count and percentage as appropriate. OR = odds ratio; CKD = chronic kidney disease; CVI = cerebrovascular insult; TIA = transient ischemic attack; NIDDM/IDDM = non-insulin dependent diabetes mellitus/insulin dependent diabetes mellitus; BMI = body-mass-index; LVEF = left ventricular ejection fraction; CABG = coronary artery bypass grafting; MI = myocardial infarction; Ao = aorta.

demographic variables and comorbidities. Peak alpha frequency was not matched on, as this was the variable of interest.

Multiple matching models with different matching ratios and calipers were evaluated to select a matching model with the overall best balance and the smallest reduction in the number of POD patients. Nearest-neighbor matching without replacement with up to five non-POD for each POD patient was used with a caliper of 0.2 SD of a patient's predicted propensity score.

The nearest-neighbor matching method selects, for each treated individual i, the control individual with the smallest distance in propensity score from individual i. Following propensity score matching, the balance of the matched treated and control groups was evaluated by calculating variance ratios and absolute values of the standardized differences in means as well as by performing a MANOVA, which is used in multivariate hypothesis testing [31–33]. To depict the influence of propensity score matching on the differences in POD, univariable and multivariable regression was used before matching; *t*-test and chi-square tests were used after matching as deemed appropriate. A p value of <0.05 was considered significant in all applied tests. R was used for data handling (R version 4.2.2 (2022−10−31); Institute of Statistics and Mathematics, R Foundation of Statistical Computing) and for further analysis the finalfit, MatchIt and vioplot package [34].

3. Results

Of the 1072 cardiac surgical patients in the database, 244 patients were excluded from further analysis. In 17 patients EEG data was missing, and in 109 patients, the end-tidal volatile concentrations were not stable long enough to determine an accurate effect site concentration. In 53 patients no frontal alpha oscillation could be detected and another 65 patients had either one or more missing comorbidity values or a history of dementia (which has known EEG alterations at baseline). This resulted in a total of 828 patients for the final analysis – 73 with POD and 755 without (Fig. 1).

Table 1 presents continuous data as mean and standard deviations or counts and percentages, per level for categorical data prior to propensity matching, as well as odds ratios. At the univariable level, 10 of the 19 independent variables show a significant association with the dependent variable POD before performing PSM. On the multivariable level only three variables presented a significant association with POD: Peak alpha frequency, chronic kidney disease (CKD) and an aneurysmatic thoracic aorta requiring surgery.

Following PSM there were no significant differences remaining between the matched groups of POD versus non-POD, with the standardized mean difference not exceeding 0.25, no variance ratio outside the range of 0.5–2, and a non-significant MANOVA test ($P = 0.996$) (Fig. 2). Of the 755 non-POD patients, 494 were not suitable for matching, whereas only 6 POD patients could not be matched of the 73 POD patients. After correcting for the group imbalances through matching the findings of the difference in peak alpha frequency persisted (Table 2). The detailed distribution of peak alpha frequencies for matched patients

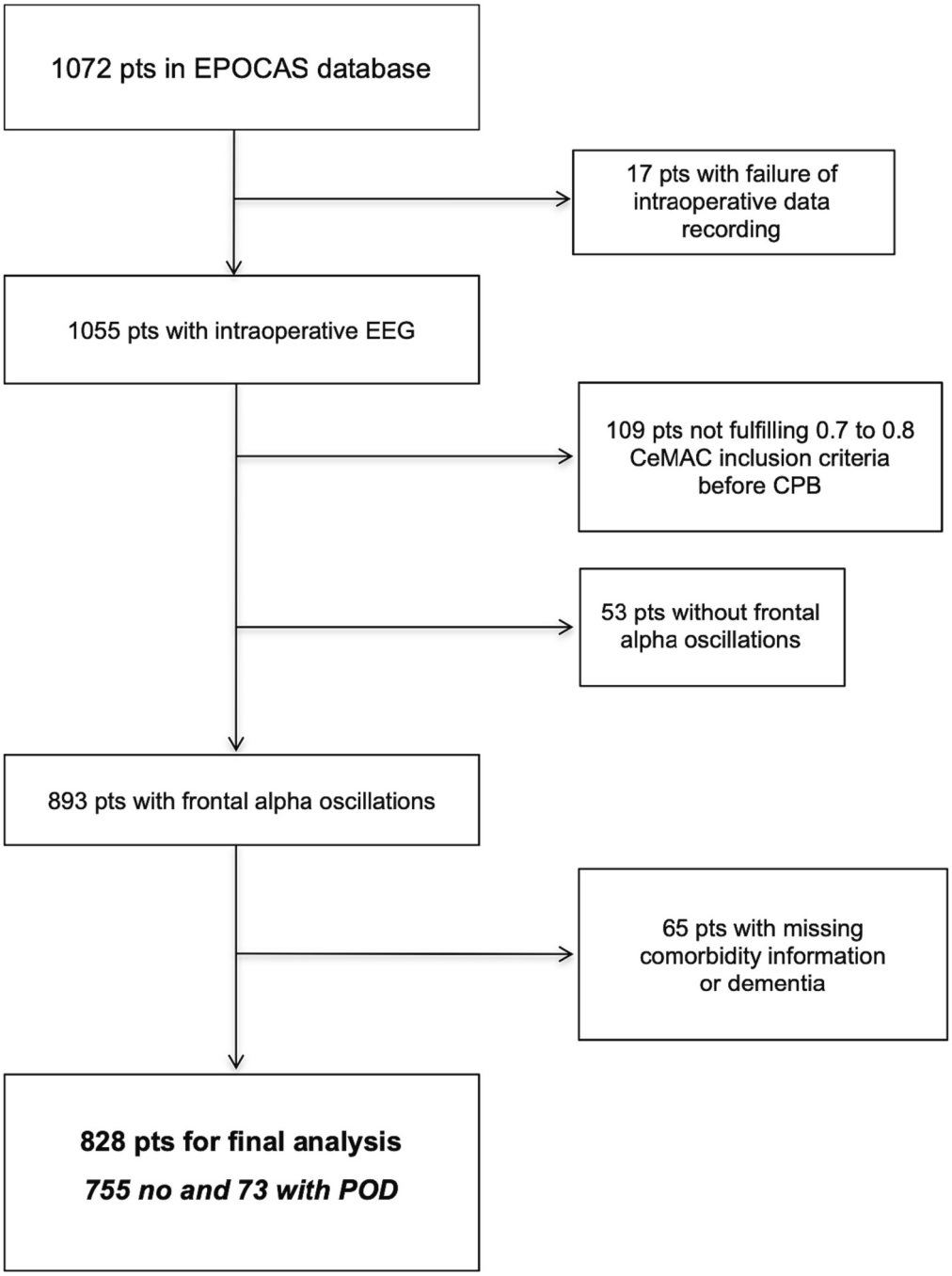

Fig. 1. Flow chart of data selection.

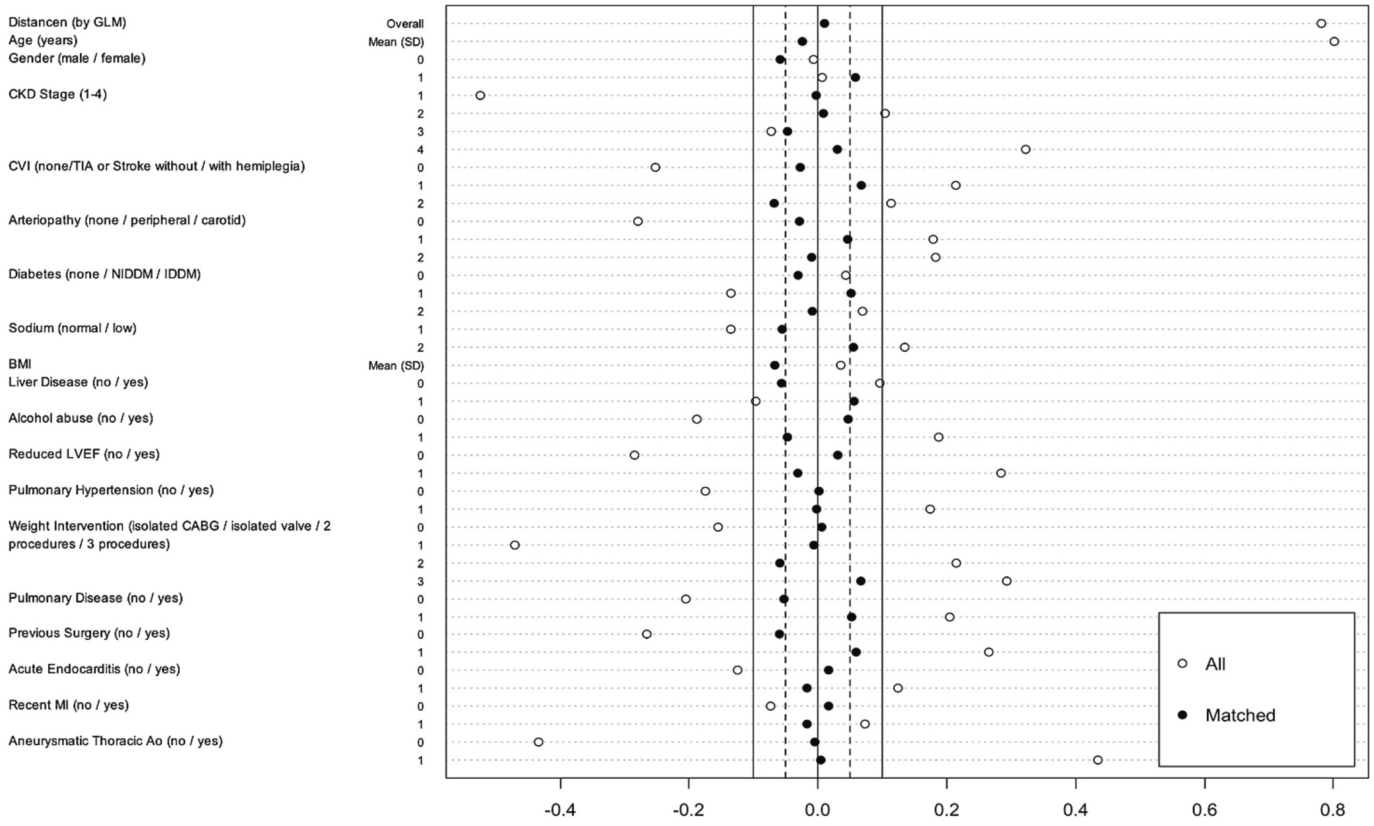

Fig. 2. Balance of independent variables before and after propensity score matching.

are presented in Fig. 3.

Hence, our main finding demonstrates that patients with POD have lower intraoperative peak alpha frequencies (mean 7.9 Hz) than non-POD patients (mean 8.8 Hz). This intraoperative pattern of peak alpha is statistically significant before and after performing PSM.

The white dot represents the median, the thick black bar in the center the interquartile range, the black line the rest of the distribution. On each side of the black line is a kernel density estimation to show the distribution shape of peak alpha frequency. Wider sections of the violin plot represent a higher probability that members of the population will take on the given value; the thinner sections represent a lower probability.

4. Discussion

We detected a clinically important association of lower peak alpha frequencies in frontal EEGs of patients undergoing isoflurane anesthesia who subsequently developed POD. The effect was present at univariable and multivariable levels, as well as before and after PSM adjusting for clinically important confounding factors known to be associated with POD [35]. These encompass consistent risk factors such as increasing age, history of stroke, CKD, and especially end stage renal disease [36]. All these independent variables were significantly differently distributed between POD and non-POD groups in our patient population before PSM, but not afterwards.

Several risk factors for POD are also part of the EuroScore, a predictive score for mortality risk after cardiac surgery [28]. EuroScore factors had been prospectively collected for the primary study and could be used to create the matching pairs for this secondary analysis. The mean age of patients with POD in previous studies ranges from 68 to 78 years [37,38]. Likewise, prevalence of delirium increases with worsening CKD, increasing up to approximately 40% in surgical patients, depending on surgical discipline and procedure [39–43] and up to over 60% in non-surgical patients suffering CKD in stage IV-V [44,45].

Another known risk factor of POD is cardiovascular surgery itself, supposedly stemming from inflammatory responses to the invasive procedure [35,46–49]. Decreased brain function or reserve and a higher vulnerability for cerebral hypoperfusion may be possible mechanisms [38].

Prolonged periods of burst suppression activity in the intraoperative EEG has been associated with higher incidence of POD in mostly retrospective studies [50–53]. In contrast, RCTs have reported varying results, with the most recent and largest study not supporting a causal link between burst suppression and POD [17]. Interestingly, in this study 30-day mortality and use of vasopressors was significantly higher in the group with more burst suppression. Although recommended by several medical societies, the intraoperative use of EEG anesthesia monitors and the proposed index guided anesthesia management – with the aim of avoiding or reducing low index levels or burst suppression and subsequent POD – is being critically questioned by some authors [13,18,19,54]. Given that the main commercially available DOA monitors exhibit markedly discordant index values when provided with identical raw EEG traces that show clear patterns of emergence [55], this criticism is not without warrant.

There is an increasing focus on the relationship between the alpha oscillation and POD, although to date this has focused on alpha power, not frequency. Lower power has been associated with an increased rate of POD [56–58] as have low levels of alpha connectivity [59]. Moreover, low frontal alpha power is also associated with an increased propensity for burst suppression, independent of patient's chronological age and therefore representing a higher likelihood for postoperative neurocognitive disorders like POD [23].

With regards to frequency, the alpha oscillation is known to slow to both increasing anesthetic dose and with age [24,60,61]. Although not the same as the frontal alpha during anesthesia, the occipital alpha oscillation that occurs during the awake state is clearly slower in

Table 2
Independent variables summary – *after* propensity score matching.

Dependent: Delirium (no/yes)		NO	YES	*p*-value
		$n = 261$	$n = 67$	
Age (years)	Mean (SD)	68.9 (9.0)	69.6 (7.2)	0.555
Peak Alpha Frequency (Hz)	Mean (SD)	8.8 (1.3)	7.9 (1.3)	<0.001
Gender (male/female)	0	201 (77.0)	50 (74.6)	0.803
	1	60 (23.0)	17 (25.4)	
CKD Stage (1–4)	1	32 (12.3)	7 (10.4)	0.662
	2	163 (62.5)	41 (61.2)	
	3	37 (14.2)	8 (11.9)	
	4	29 (11.1)	11 (16.4)	
CVI (none/TIA or Stroke without/ with hemiplegia)	0	219 (83.9)	54 (80.6)	0.568
	1	31 (11.9)	11 (16.4)	
	2	11 (4.2)	2 (3.0)	
Arteriopathy (none/peripheral/ carotid)	0	207 (79.3)	50 (74.6)	0.629
	1	22 (8.4)	8 (11.9)	
	2	32 (12.3)	9 (13.4)	
Diabetes (none/NIDDM/IDDM)	0	217 (83.1)	56 (83.6)	0.996
	1	20 (7.7)	5 (7.5)	
	2	24 (9.2)	6 (9.0)	
Sodium (normal/low)	1	248 (95.0)	62 (92.5)	0.621
	2	13 (5.0)	5 (7.5)	
BMI	Mean (SD)	27.7 (4.9)	27.4 (4.8)	0.626
Liver Disease (no/yes)	0	242 (92.7)	61 (91.0)	0.839
	1	19 (7.3)	6 (9.0)	
Alcohol abuse (no/yes)	0	205 (78.5)	53 (79.1)	1.000
	1	56 (21.5)	14 (20.9)	
Reduced LVEF (no/yes)	0	172 (65.9)	43 (64.2)	0.904
	1	89 (34.1)	24 (35.8)	
Pulmonary Hypertension (no/yes)	0	211 (80.8)	53 (79.1)	0.883
	1	50 (19.2)	14 (20.9)	
Weight Intervention (isolated CABG or Valve/2 procedures/3 procedures)	0	84 (32.2)	20 (29.9)	0.719
	1	39 (14.9)	9 (13.4)	
	2	102 (39.1)	25 (37.3)	
	3	36 (13.8)	13 (19.4)	
Pulmonary Disease (no/yes)	0	224 (85.8)	54 (80.6)	0.384
	1	37 (14.2)	13 (19.4)	
Previous Surgery (no/yes)	0	231 (88.5)	57 (85.1)	0.578
	1	30 (11.5)	10 (14.9)	
Acute Endocarditis (no/yes)	0	251 (96.2)	64 (95.5)	1.000
	1	10 (3.8)	3 (4.5)	
Recent MI (no/yes)	0	219 (83.9)	56 (83.6)	1.000
	1	42 (16.1)	11 (16.4)	
Aneurysmatic Thoracic Aorta (no/ yes)	0	194 (74.3)	45 (67.2)	0.306
	1	67 (25.7)	22 (32.8)	

Data are expressed as mean and standard deviation, or as count and percentage as appropriate. CKD = chronic kidney disease; CVI = cerebrovascular insult; TIA = transient ischemic attack; NIDDM/IDDM = non-insulin dependent diabetes mellitus/insulin dependent diabetes mellitus; BMI = body-mass-index; LVEF = left ventricular ejection fraction; CABG = coronary artery bypass grafting; MI = myocardial infarction; Ao = aorta.

patients with various cognitive disorders such as Alzheimer's disease, depression, and anxiety [62–64]. Slower awake alpha frequency has also been associated with higher postoperative pain [65]. Of interest, a slower alpha frequency during propofol anesthesia has been associated with altered cerebral autoregulation [66] but to our knowledge our current analysis is the first to examine possible associations between alpha slowing during anesthesia and POD.

Besides guiding anesthesia by rather unreliable processed EEG indices [55], investigators are examining other EEG markers, such as slow wave saturation [67–70], maximizing alpha power [22,23,27,52,71,72], or avoiding burst suppression [17]. Our approach of looking into peak alpha frequency is founded on the well described effects of changes of the anesthetic concentration on our target organ, the brain [24] and the pathophysiological background of surgery triggered neuroinflammation [73–75], neurotransmitter imbalances (especially acetylcholine) [76–83], disruption of neural networks [84–86] and microvascular dysfunction [87] resulting in inadequate oxygen and nutrient supply to brain cells, affecting their function [88,89] and leading to slower brain waves. This slowing of the alpha oscillation in POD suffering patients may be interpreted as a sign of a vulnerable brain or as a real causal influencing factor that could be approached to lower the incidence of POD [57].

4.1. Limitations

It should be noted that our results are derived from a secondary analysis of prospectively collected data and not a randomized clinical trial (RCT). This implies an overestimated effect of peak alpha frequency on POD, which has been shown in multiple studies comparing the results of retrospective versus prospective randomized studies [90–92]. However, by including a larger number of patients of a vulnerable cardiac surgical population with a high event rate for delirium and taking care of study bias and confounding factors through creating well balanced groups through propensity score matching, we were able to simulate conditions similar to a RCT.

The diagnosis of POD in our patients was based on chart review. This approach may underestimate the true event rate as discussed in detail by Inouye and colleagues and translates into a predictable uncertainty not significantly effecting our hypothesis creation [30]. When pre-existing neurological disorders such as Alzheimer's disease are followed by POD, this method proves to be less reliable than the direct detection of delirium using the CAM test. As a consequence, patients with such comorbidities were excluded from this analysis.

It is also known that changes in the slope of the aperiodic component of the EEG can cause shifts in alpha frequency [93] but the magnitude of changes are far less than the clinical effect of around 1 Hz that we observed.

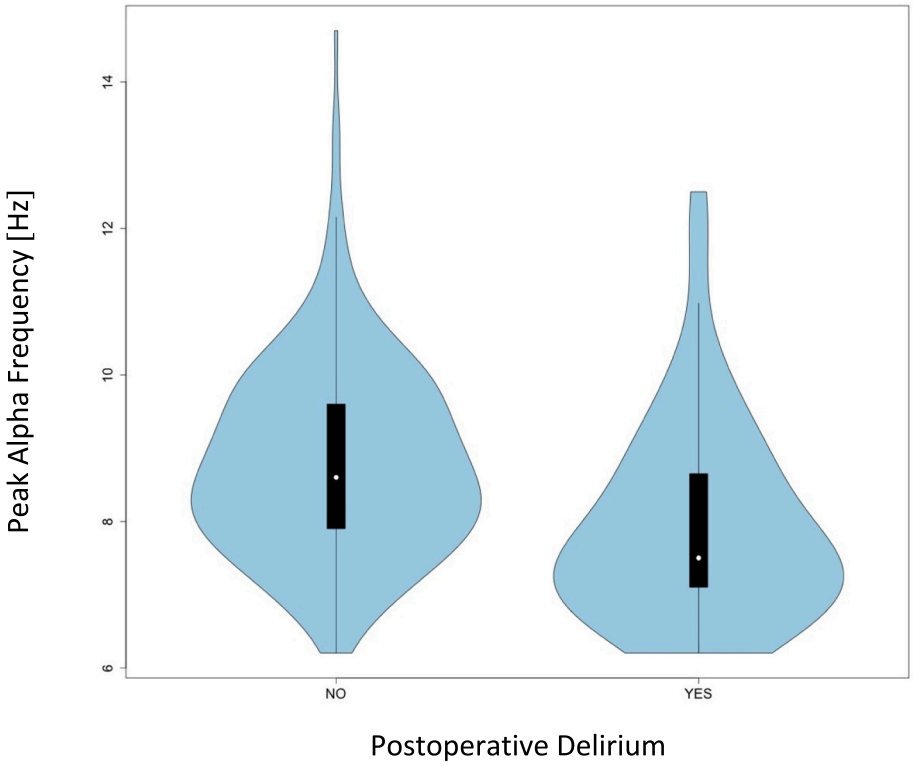

Fig. 3. Violin plot of Peak Alpha Frequencies in the non-POD and POD groups after Propensity Score Matching.

5. Conclusions

In this cardiac surgical patient population, a slower frontal alpha frequency under general anesthesia with isoflurane was independently associated with postoperative delirium and might be a simple intra-operative pathophysiological marker of a vulnerable brain for ultimately developing POD, or a potential tool for anesthesiologists to lower the incidence of POD.

Author statement

On behalf of all authors, I confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. I further confirm that the order of authors listed in the manuscript has been approved by all authors.

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Declaration of Competing Interest

The authors have no competing interests to declare.

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