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Original Contribution

Anesthesia-induced electroencephalogram oscillations and perioperative outcomes in older adults undergoing cardiac surgery

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HIGHLIGHTS

- Secondary analysis of 394 participants in the MINDDS Study.
- Intraoperative alpha power varied with measures of preoperative cognitive and physical health.
- Intraoperative alpha power also predicted postoperative delirium, 30-day readmission, but not non-home discharge.
- On adjusted analysis, intraoperative alpha power robustly predicted non-home discharge.
- Intraoperative EEG oscillations change as a function of cognitive and physical health and predict perioperative outcomes.

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ABSTRACT

Background: Electroencephalogram oscillations during general anesthesia may change as a function of cognitive and physical health. This study aimed to characterize associations between anesthesia-induced oscillations and postoperative outcomes in cardiac surgery patients over 60 years.

Methods: This was a prespecified secondary data analysis from the Minimizing Intensive Care Unit Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) study. Participants were admitted from home for elective cardiac surgery with cardiopulmonary bypass. The primary outcome was postoperative delirium obtained using the Confusion Assessment Method. Secondary outcomes were non-home discharge and 30-day readmission. The exposure of interest was alpha power measured during the maintenance phase of isoflurane-general anesthesia. Confounding cognitive and physical health variables were collected.

Results: Of 394 participants in the MINDDS study, 302 had analyzable electroencephalograms. The incidence of postoperative delirium was 11.1 %. Odds of postoperative delirium decreased by 14 % for every decibel increase in alpha power (OR 0.86, 95 % CI: 0.78 to 0.95; $P = 0.004$). This finding was not significant in adjusted analysis (OR_{adj} 0.92, 95 % CI: 0.81 to 1.03; $P = 0.154$). Non-home discharge setting findings were not associated with alpha power. The odds of 30-day readmission decreased by 20 % for every decibel increase in alpha power (OR_{adj} 0.80, 95 % CI: 0.71 to 0.91; $P < 0.001$). Findings were conserved in exploratory and sensitivity analyses.

Conclusions: In this study anesthesia-induced oscillations were associated with postoperative outcomes; however, these were not independently associated with delirium or discharge disposition after considering preoperative cognitive and physical health. These oscillations were robustly associated with 30-day readmission however, which may help anesthesiologists identify high-risk patients, offering benefits beyond the operating room.

Clinical trial registration: Registration Number: NCT02856594

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1. Introduction

General anesthesia and sedative states are associated with electroencephalogram (EEG) oscillations that exhibit anesthetic drug class and dose-dependent features [1]. Delta (0.5 to 3 Hz), frontal theta (3 to 8 Hz), and frontal alpha (8 to 12 Hz) oscillations are consistent features of isoflurane general anesthesia [2]. Sedation is associated with beta (13 to 25 Hz) oscillations. Computational models suggest beta and alpha oscillations share an underlying mechanism—they result from varying degrees of gamma-aminobutyric acid-A (GABA-A) current potentiation in thalamocortical circuits [3–5]. These and other anesthesia-induced oscillations are informing the design of closed-loop control systems [6] and putative circuit mechanisms underlying anesthetic states [7]. In clinical settings, these oscillations are advancing our quest to personalize anesthetic care [8].

Postoperative delirium is common in patients over 60 years recovering from cardiac surgery. [9–16] It is a cause of distress to patients, families, and caregivers [17]. It is also associated with discharge to non-home settings and readmission [18–21]. While low alpha power has been associated with postoperative delirium or subsyndromal delirium after non-cardiac surgery [22–24], suggesting that this EEG feature could be used to pre-emptively identify patients at high risk for postoperative delirium, uncertainty about this relationship remains. Low alpha power has been associated with normal aging [25–32], cognitive impairment or cognition [27,33–36], and comorbidities [37]. Thus, associations between alpha power and postoperative delirium may be confounded by underlying cognitive and physical health (i.e., delirium risk factors encoded in EEG oscillations). Further, whether alpha power is associated with discharge to a non-home setting and 30-day readmission is unclear.

Therefore, in this analysis of EEG recordings from the Minimizing Intensive Care Unit Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) study, we hypothesized the association between alpha power and postoperative delirium would not persist after adjusting for cognitive and physical health information. We also hypothesized the same for discharge to non-home settings and 30-day readmission.

2. Materials and methods

This MINDDS study was a single-center, parallel-arm, randomized, placebo-controlled superiority trial of nighttime dexmedetomidine for postoperative delirium prevention performed at Massachusetts General Hospital. Patients were randomized to a primary treatment postoperatively in the ICU, namely a short nighttime dose of intravenous dexmedetomidine (1 μg/kg over 40 min) or placebo. Patients were recruited in the parent trial between March 2017 and July 2021. The study was registered on ClinicalTrials.gov on August 5, 2016 (NCT02856594). The Mass General Brigham Institutional Review Board approved the study (Protocol 2016P000742). Study participants gave verbal informed consent for cognitive and physical assessments, followed by written informed consent before surgery. In this study, a prespecified secondary analysis was performed using data from a nested cohort of patients from within the parent trial.

2.1. Study population

The study protocol, including inclusion and exclusion criteria and results from the primary dexmedetomidine analyses, have been previously published [38,39]. Briefly, participants were eligible for inclusion if they were 60 years or older and scheduled to undergo a cardiac surgical procedure with cardiopulmonary bypass and planned admission to the ICU postoperatively. Participants were excluded if they were allergic to dexmedetomidine, had renal or liver failure, were on chronic benzodiazepine or antipsychotic therapies, had severe deficit(s) due to structural or anoxic brain damage, were admitted to the intensive care unit (ICU) for more than two days in the month before surgery, previously underwent cardiac surgery within one year of surgery, were undergoing a surgical procedure requiring total circulatory arrest, or were SARS-CoV-2 positive or symptomatic. Participants who were blind, deaf, or unable to communicate in English were excluded due to their inability to complete the cognitive assessments. Following enrollment and in accordance with prespecified criteria, participants were dropped from the study if they were scheduled to undergo a second surgical procedure during their hospital stay, intubated for more than twelve hours postoperatively, or became SARS-CoV-2 positive or symptomatic.

2.2. Definition of exposure and outcome measures

The primary exposure was isoflurane-general anesthesia alpha power. Data were recorded using the SedLine monitor (Masimo Inc., Irvine, CA). SedTrace electrode arrays were placed on the forehead at approximately Fp1, Fp2, F7, and F8, the ground electrode at approximately Fpz, and the reference electrode approximately one centimeter above Fpz. Data were recorded with a sampling frequency of 250 Hz. Electroencephalogram data segments were selected using information from the electronic medical record and spectral analysis.

For each patient, a continuous two-minute EEG segment without significant electrographic or mechanical artifact, burst-suppression, or hypotension (defined as mean arterial pressure < 65 mmHg) was visually selected from each spectrogram that corresponded with the maintenance phase of general anesthesia at least 15 min after the induction of general anesthesia, after surgical incision, and before the onset of cardiopulmonary bypass. The epochs were the first such artifact-free segment after surgical incision and before cardiopulmonary bypass selected by a single author (Z.Q.K. or I.T.) by visual spectrogram inspection and reviewed and approved by a third author (I.G.F.). Disagreements on the artefactual content and suitability of a segment were decided by a fourth author (O.A.).

Data from each channel was segmented into partially overlapping (95 %) 3 s epochs. Spectral power was estimated within each epoch using the MNE library of Python by means of 7 DPSS multitapers [40]. Then, alpha power was calculated as the median value within the canonical alpha frequency range (8-12 Hz). Afterwards, data from all epochs and electrodes was collapsed (median) to obtain a single value per patient. Sensitivity analysis was performed with normalized EEG data. Normalization was performed by dividing power from a given passband (e.g., alpha) by the total power or, equivalently in decibels, by subtracting the passband power in decibels by the total power in decibels.

The primary outcome was postoperative delirium, defined as any occurrence of delirium within three days after surgery. Delirium was assessed by trained members of the study team using the Long Form Confusion Assessment Method (CAM), a tool that evaluates the four features of delirium, namely acute onset and fluctuating course, inattention, disorganized thinking, and an altered level of arousal [41]. Delirium assessment training is described elsewhere. Briefly, initial training was led by a neuropsychologist and member of the team that created the CAM while subsequent trainings consisted of practice scoring videos of both delirious and non-delirious patients, observing CAM interviews conducted by previously trained team members, agreeing with the trainer's CAM scoring on a minimum of six observed interviews, and having a previously trained team member observe newly trained team member's first CAM assessment of a MINDDS patient at minimum [39]. Delirium was assessed twice daily (morning and afternoon, with at least six hours separating assessments) for the first three days postoperatively or until hospital discharge, whichever came first. On each study day, delirium was defined as present if it occurred during either the morning or afternoon assessment.

The secondary outcomes were non-home discharge, and 30-day hospital readmission abstracted from the Society of Thoracic Surgeons database after study completion.

2.3. Covariates

Cognitive function was assessed using the Telephonic Montreal Cognitive Assessment (t-MoCA), whereas physical and cognitive health variables were evaluated using the Patient-Reported Outcomes Measurement Information System® Short Forms (PROMIS) Global Health, PROMIS Physical Function, PROMIS Pain Interference, PROMIS Applied Cognition Abilities, and PROMIS Sleep Disturbance questionnaires. The t-MoCA ranges from 0 (worst) to 22 (best) points, does not require visual cues or writing, and can be administered over the phone. [42,43] PROMIS scores were converted to a T-score for analysis with a mean of 50 and a standard deviation of 10 with a higher T-score indicates better health in positively worded domains (e.g., physical function), whereas a lower T-score indicates better health in the negatively worded domains (e.g., pain interference). The PROMIS Global Health score was automatically transformed into Global Physical Health and Global Mental Health T-scores by construct.

2.4. Statistical methods

Data are presented as mean (standard deviation, SD), median (interquartile range, IQR), or frequency (proportion) depending on variable type and distribution. The normality of continuous variables was confirmed with a visual inspection of the data and the Shapiro-Wilk test for normality. This analysis was performed on randomized participants who did not meet a prespecified dropout criterion and had electroencephalogram data collected. Given that this study was nested within a randomized controlled trial, the sample size was fixed, and no a priori power calculation was performed. Given the observational nature of the present study, cases were analysed using a complete case framework.

To evaluate the association between covariates and alpha oscillations, separate linear regression models were fit for alpha power and the following in univariable analysis: age, body mass index, sex, t-MOCA, PROMIS Global Health Mental, PROMIS Global Physical, PROMIS Physical Function, PROMIS Pain Interference, PROMIS Applied Cognition Abilities, and PROMIS Sleep Disturbance. Final models were adjusted for age, body mass index, sex, t-MoCA, PROMIS Physical Function, and PROMIS Sleep Disturbance based on clinical relevance and given they represent distinct constructs. Variables temporally occurring after the intraoperative EEG epochs of interest were not included in models of intraoperative EEG characteristics. These include surgical characteristics, clinical characteristics, and randomization assignments. Results were presented as a mean difference (MD) and its associated 95 % confidence interval (CI).

Multivariable logistic regression was employed to assess the association between alpha power and dichotomous outcomes. These models were adjusted for age, body mass index, sex, t-MOCA, physical function, sleep disturbance, and treatment assignment. Treatment assignment, defined as randomization to dexmedetomidine or placebo postoperatively in the modified intention-to-treat cohort, was included because results of the primary trial indicated dexmedetomidine reduced the incidence of delirium, and it was thought necessary to appropriately account for this confounder in the present outcome analysis. A sensitivity analysis for treatment assignment was performed using adjustment for actual receipt of dexmedetomidine instead of treatment assignment. To mitigate the risk of model overadjustment given the set number of primary and secondary events, all multivariate models were further pruned using a recursive feature elimination (RFE) procedure with $P > 0.20$ as criterion for covariate exclusion (Supplemental Digital Content 6) [44]. As an additional sensitivity analysis, Saturated Models were generated including intraoperative alpha power and every significant covariate listed in Table 1 (Supplemental Digital Content 6). Effect estimates are presented as an adjusted odds ratio (OR_{adj}) with an associated 95 % CI. A sensitivity analysis for multiple comparisons was performed appraising primary and secondary results with a Bonferroni-

Table 1
Participant Characteristics Stratified by Delirium Status.

	Entire Cohort	No Delirium	Delirium[a]	*P*-Value
	N = 302	*N = 233*	*N = 29*	
Demographics				
Age, *years*	69 [64, 74]	68 [63, 73]	73 [68, 78]	0.001
Body Mass Index, kg/m^2	28.00 [24.97, 31.57]	27.8 [25.08, 30.96]	27.05 [23.20, 31.63]	0.904
Female Sex	75 (24.83)	51 (21.89)	13 (44.83)	0.007
White Race	292 (96.69)	224 (96.14)	29 (100.00)	0.603
Highest Level of Education				0.038
High School or Less	45 (14.90)	27 (11.59)	9 (31.03)	
Some College/ Associate Degree	66 (21.85)	50 (21.46)	4 (13.79)	
Bachelor's Degree	90 (29.80)	73 (31.33)	7 (24.14)	
Master's or Doctorate Degree	101 (33.44)	83 (35.62)	9 (31.03)	
Comorbidities and Past Medical History				
Diabetes	64 (21.19)	50 (21.46)	7 (24.14)	0.742
Hypertension	236 (78.15)	181 (77.68)	24 (82.76)	0.532
Prior Myocardial Infarction	34 (11.26)	25 (10.73)	3 (10.34)	0.950
Previous Cardiac Intervention	102 (33.77)	73 (31.33)	13 (44.83)	0.144
Peripheral Arterial Disease	23 (7.62)	13 (5.58)	7 (24.14)	0.003
Cerebrovascular Disease	34 (11.26)	20 (8.58)	9 (31.03)	0.002
Liver Disease	8 (2.65)	8 (3.43)	0 (0)	0.604
Syncope	10 (3.31)	10 (4.29)	0 (0)	0.608
Sleep Apnea	65 (21.52)	49 (21.03)	7 (24.14)	0.700
Chronic Lung Disease	48 (15.89)	37 (15.88)	4 (13.79)	0.771
Smoking Status				0.033
Current Smoker	9 (2.98)	6 (2.58)	2 (6.90)	
Former Smoker	143 (47.35)	106 (45.49)	19 (65.52)	
Never Smoked	150 (49.67)	121 (51.93)	8 (27.59)	
Baseline Neurocognitive and PROMIS Scores				
Telephonic MoCA	19.0 [17.0, 20.0]	19.0 [18.0, 20.0]	18.0 [15.0, 20.0]	0.033
PROMIS Scores [b]				
Applied Cognition	51.7 [45.9, 62.7]	53.0 [46.8, 62.7]	50.6 [41.6, 54.6]	0.029
Global Health – Physical	50.8 [42.3, 57.7]	50.8 [44.9, 57.7]	44.9 [39.8, 50.8]	0.002
Global Health – Mental	56.0 [50.8, 62.5]	56.0 [50.8, 62.5]	50.8 [43.5, 59.0]	0.010
Physical Function	45.5 [40.1, 52.5]	46.4 [40.8, 59.7]	41.5 [35.5, 46.4]	0.002
Pain Interference	40.7 [40.7, 53.2]	40.7 [40.7, 53.2]	47.9 [40.7, 55.8]	0.117
Sleep Disturbance[c]	50.5 [43.8, 54.3]	50.5 [43.8, 55.2]	46.2 [41.1, 52.4]	0.390
Surgical Characteristics				
Cardiopulmonary Bypass Time, *minutes*	128 [96, 162]	123 [94, 160]	148 [101, 191]	0.030
Cross Clamp Time, *minutes*[d]	92 [71, 116]	87 [70, 115]	102 [73, 141]	0.126
Clinical Characteristics				
Randomized to Receive Dexmedetomidine	141 (46.69)	110 (47.21)	8 (27.59)	0.045
Length of Hospital Stay, *days*	6 [5, 7]	6 [5, 7]	6 [6, 8]	0.023
Length of ICU Stay, *hours*	25.4 [23.0, 45.5]	25.0 [22.8, 31.0]	37.0 [24.0, 70.0]	0.005
Total Ventilation Time, *hours*	4.96 [3.95, 6.88]	4.80 [3.92, 6.45]	6.85 [4.42, 8.75]	0.003

Data is presented as mean ± standard deviation, median [quartile 1, quartile 3] or n (%) depending on variable type and distribution.
Abbreviations: MoCA (Montreal Cognitive Assessment), PROMIS (Patient-Reported Outcomes Measurement Information System), EEG (electroencephalogram), ICU (intensive care unit).
[a] Delirium is defined as present if it occurred within three days postoperatively following surgery. A total of 40 patients were missing delirium assessments and are included only in the entire cohort column.
[b] All PROMIS scores are translated to t-scores for reporting.

[c] Sleep disturbance was added after initiation of the trial, therefore this value is missing for nine participants.
[d] Cross clamp time was missing for one participant.

corrected $P < \alpha' = \frac{\alpha}{N}$ where N is the number of univariate comparisons. A sensitivity analysis using multivariate correction with false discovery rate-optimized model q-values was also performed.

Statistical analysis was performed with R statistical software (Version 4.2.3, R Core Team, Vienna, Austria, 2023). All tests were two-sided and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study cohort and characteristics

A total of 2695 participants were screened, 1229 of whom met at least one exclusion criterion. Of the remaining 1466 eligible participants, 469 consented to the MINDDS study. Seventy-five participants met at least one prespecified drop criterion before the study intervention leaving 394 participants in the final study cohort. Electroencephalogram data was not retrievable in 71 participants, and 21 had poor tracings. Ultimately 302 participants had analyzable electroencephalogram data (Fig. 1). Overall, participants were 69 (IQR 64, 74) years old and predominantly white males. Postoperative delirium was associated with worse performance on the baseline t-MoCA, and PROMIS Applied Cognition, Global Health Physical, Global Health Mental, and Physical Function questionnaires (Table 1).

3.2. Age-dependent spectrogram changes

Changes in the spectrogram were observed with increasing age (Fig. 2A). These changes were visually evident as decreased power in theta and alpha bands. However, marked differences were noticeable in the spectrogram of some participants, despite similarities in chronological age and sex. As an example, Fig. 2B illustrates the spectrogram of a 60-year-old female participant with an t-MOCA score of 18 (normal cognitive function), and PROMIS scores at or better than the PROMIS reference population mean for the concept being measured [45]. In contrast, Fig. 2C illustrates the spectrogram of a 60-year-old female participant with a t-MOCA score of 15 (cognitive impairment) and PROMIS scores at or worse than the population mean for the measured concept. When evaluating this in adjusted analyses, alpha power was associated with age, body mass index, sex, cognition, physical function, and sleep disturbance (Table 2). Thus, body mass index, female sex, t-MOCA, physical function, and sleep disturbance may explain the differences observed in these spectrograms.

3.3. Primary analysis

Of the 262 patients who had complete delirium status information, 11 % (29/262) of participants screened positive for postoperative delirium using the CAM (Table 3). Every decibel increase in alpha power was associated with 14 % lower odds of developing postoperative delirium (OR: 0.86, 95 % CI: 0.78 to 0.95; $P = 0.004$). However, this finding was not conserved (OR_{adj}: 0.92, 95 % CI: 0.81 to 1.03; $P = 0.154$) when adjusting for confounding variables (Table 3). Similar results were observed in a post-hoc sensitivity analysis considering whether the patient actually received dexmedetomidine per protocol (Supplemental Digital Content 1) and in Bonferroni-corrected analysis.

3.4. Secondary analyses

Of the 298 patients with complete discharge destination information, 15.8 % (47/298) of participants were discharged to non-home settings, and 8.8 % (26/296) of participants were readmitted within 30 days of hospital discharge (Table 3). The association between alpha power and discharge location was insignificant (OR_{adj}: 0.96, 95 % CI: 0.86 to 1.07; $P = 0.476$). Every decibel increase in alpha power was associated with 20 % lower odds (OR_{adj}: 0.80, 95 % CI: 0.71 to 0.91; $P < 0.001$) of 30-day readmission, which was significant to Bonferroni-corrected analysis for multiple comparisons ($\alpha' = \frac{0.05}{4} = 0.0125$).

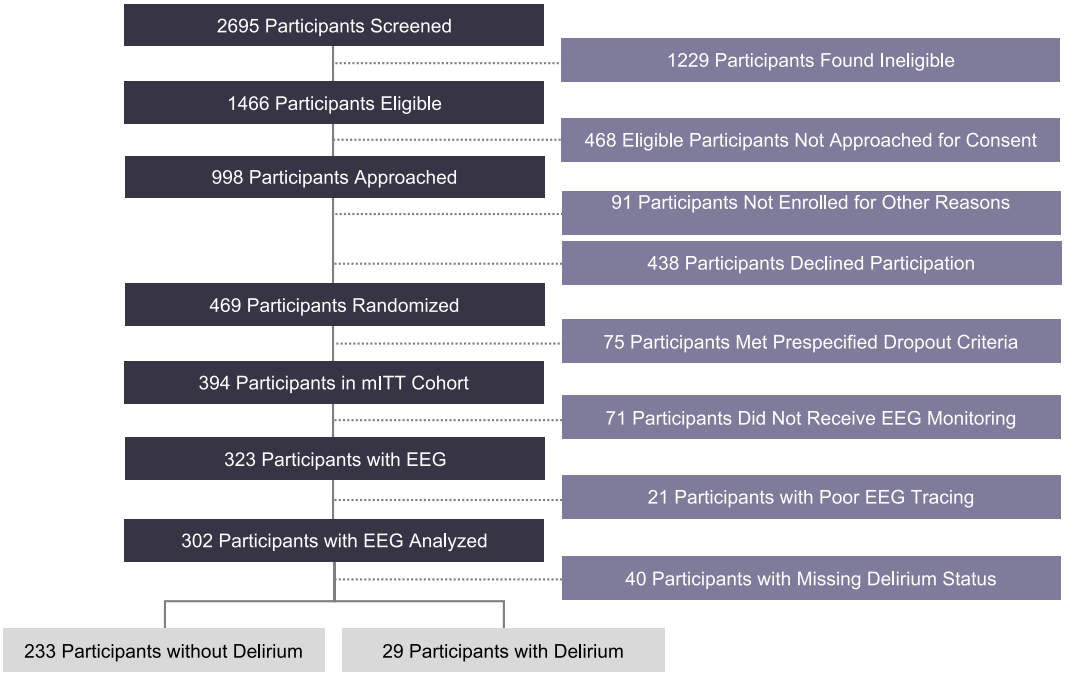

Fig. 1. Flow of participants in the study. Of 2695 participants initially screened for the MINDDS study, 394 were included in the modified intention to treat cohort. Of those, 302 had artifact-free, two-minute electroencephalogram segments in their intraoperative electroencephalogram (EEG) recordings during the maintenance phase of isoflurane-general anesthesia. Postoperative delirium was assessed in 262 of the 302 participants.

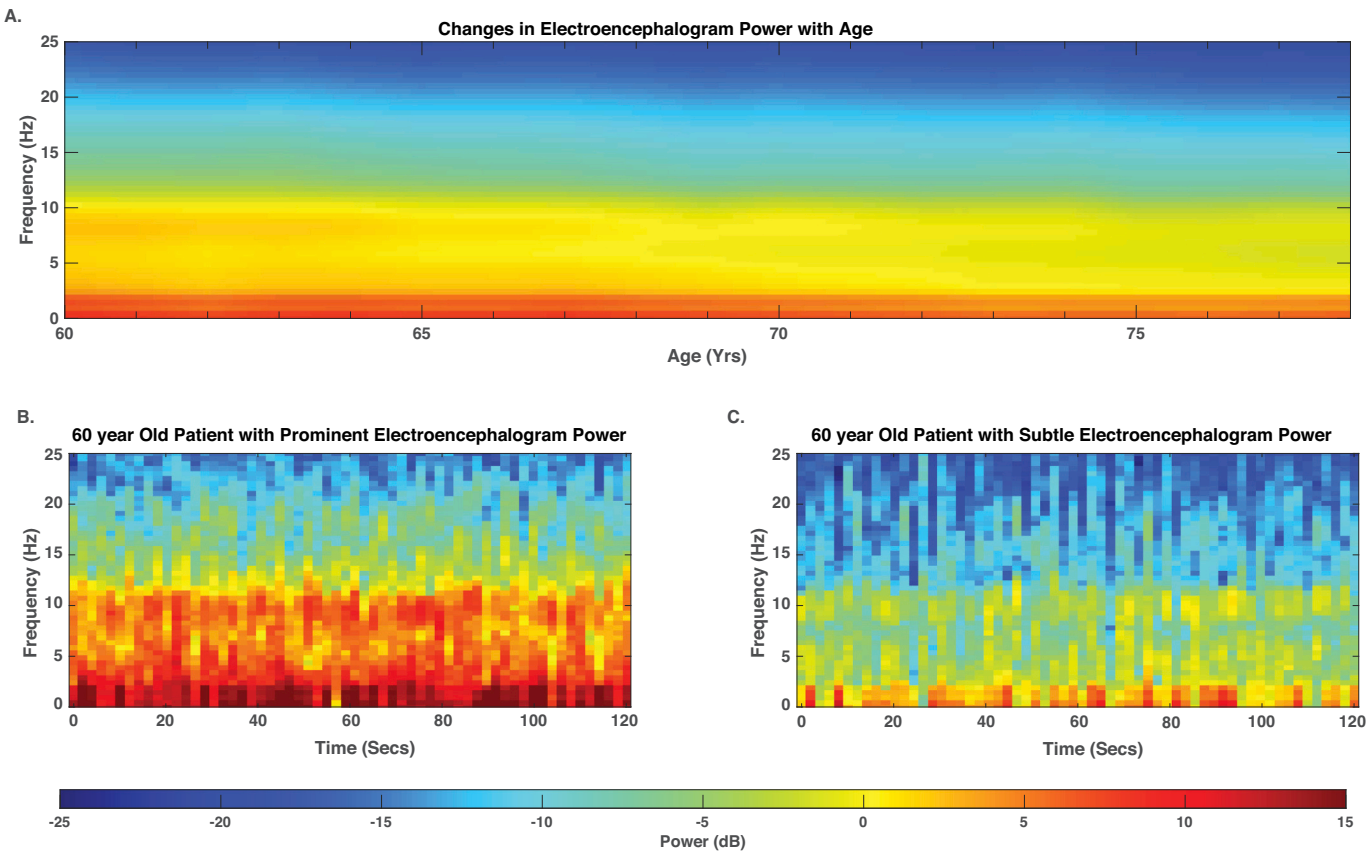

Fig. 2. Multitaper spectrograms of intraoperative electroencephalogram data demonstrating age-dependent changes in power (A) and intra-age variability (B and C). (A) age dependence of EEG during isoflurane-general anesthesia. Changes were observed with increasing age, including decreased alpha and theta power. (B) Typical spectrogram of a 60-year-old with a t-MOCA score of 18 (normal cognitive function) and PROMIS score at or better than the PROMIS reference population mean for each measured concept. (C) Typical spectrogram of a different 60-year-old female participant with a t-MOCA score of 15 (cognitive impairment) and PROMIS scores at or worse than the population mean for each measured concept.

3.5. Exploratory analysis

In adjusted analyses, delta power was associated with age and female sex; theta power with age, body mass index, female sex, and physical function; and beta power with age, female sex, physical function, and sleep disturbance (Supplemental Digital Content 2). Delta, theta, and beta power were not associated with postoperative delirium in adjusted analyses (Supplemental Digital Content 3–5). However, our findings suggested 28 % lower odds of readmission for every decibel increase in theta power (OR_{adj}: 0.82, 95 % CI: 0.70 to 0.95; $P = 0.010$), and 14 % lower odds of readmission for every decibel increase (OR_{adj}: 0.86, 95 % CI: 0.75 to 0.97; $P = 0.016$) in beta power.

3.6. Sensitivity analysis

Consistent with the primary interpretations, although crude models suggested an association between normalized alpha power and the outcomes of interest (Supplemental Digital Content 6), these associations did not always persist after adjustment. In adjusted models, when controlling for potential confounders, normalized alpha power was associated with neither postoperative delirium (OR_{adj}: 0.90, 95 % CI: 0.76 to 1.06; $P = 0.200$) nor non-home discharge (OR_{adj}: 0.93, 95 % CI: 0.80 to 1.07; $P = 0.300$), though it remained associated with readmission. Every decibel increase in alpha power was associated with 26 % odds decrease in readmission (OR_{adj}: 0.74, 95 % CI: 0.62 to 0.88; $P < 0.001$).

4. Discussion

In this secondary analysis, the odds of developing postoperative delirium decreased for every decibel increase in alpha power in unadjusted models. However, this finding was not conserved after adjusting for confounding variables, suggesting researchers and clinicians should consider prognostic covariates—such as age, preoperative physical and cognitive health measures—before drawing conclusions about the relationship between intraoperative alpha power and postoperative delirium. In contrast, the odds of 30-day readmission decreased for every decibel increase in alpha power. This finding was conserved in adjusted, exploratory, and sensitivity analyses.

The association we describe between alpha power and postoperative delirium or subsyndromal delirium is consistent with findings from non-cardiac surgery [22–24]. However, our adjusted analysis showed that cognitive and physical health information encoded in alpha oscillations might explain this finding. This implies that alpha power may not improve interpretable postoperative delirium prediction algorithms beyond the cognitive and physical health variables described in our manuscript. However, these cognitive and physical health variables may be leveraged using laboratory and computational models to study properties of the thalamocortical circuits underlying alpha oscillations (e.g., cellular changes associated with physical function).

It is important to note that the frontal anesthesia-induced alpha oscillation associations described may not be evident from baseline EEG recordings, given the distinct and large amplitude (high signal-to-noise ratio) oscillations associated with anesthetic drugs. This is consistent with findings that patients with early and late-stage Alzheimer's-type dementia demonstrated a significant reduction in frontal beta power in

Table 2
Association Between EEG and Clinical Characteristics.

	Alpha (8 to 12 Hz) Power, dB	
	MD (95 % CI)	*P-Value*
Unadjusted Models[a]		
Age, *years*	−0.15 (−0.21, −0.09)	**<0.001**
Body Mass Index, kg/m2	−0.09 (−0.17, −0.01)	**0.022**
Female Sex	1.71 (0.78, 2.64)	**<0.001**
Telephonic MoCA	0.35 (0.18, 0.52)	**<0.001**
PROMIS Scores [b]		
Global Health – Mental	0.02 (−0.03, 0.07)	0.402
Global Health – Physical	0.02 (−0.02, 0.06)	0.318
Physical Function	0.04 (−0.00, 0.09)	0.061
Pain Interference	−0.01 (−0.06, 0.05)	0.851
Applied Cognition	0.02 (−0.03, 0.06)	0.457
Sleep Disturbance	0.05 (0.00, 0.10)	**0.048**
Adjusted Model[c]		
Age, *years*	−0.14 (−0.2, −0.08)	**<0.001**
Body Mass Index, kg/m2	−0.07 (−0.15, −0.00)	**0.040**
Female Sex	1.92 (1.00, 2.84)	**<0.001**
Telephonic MoCA	0.21 (0.04, 0.38)	**0.016**
PROMIS Scores [b]		
Physical Function	0.06 (0.02, 0.11)	**0.008**
Sleep Disturbance	0.06 (0.01, 0.10)	**0.022**

Abbreviations: dB (decibel) Hz (hertz), MD (mean difference)MoCA (Montreal Cognitive Assessment), PROMIS (Patient-Reported Outcomes Measurement Information System), CI (confidence interval).

[a] Unadjusted models evaluate the association between clinical covariates and the primary and sensitivity electroencephalogram power band exposures in separate, univariate models.

[b] All PROMIS scores are translated to t-scores for reporting.

[c] Adjusted models include all covariates listed and report the effect estimate (MD) from the multivariable model including age, sex, telephonic MoCA, and PROMIS scores, as specified above.

Table 3
Primary and Secondary Outcome Models.

Outcomes	Unadjusted Models[d]		Adjusted Models[e]	
	OR (95 % CI)	*P-Value*	*OR (95 % CI)*	*P-Value*
Postoperative Delirium[a] (29/262)	0.86 (0.78, 0.95)	0.004	0.92 (0.81, 1.03)	0.154
Non-home Discharge[b] (47/298)	0.92 (0.85, 1.00)	0.057	0.96 (0.86, 1.07)	0.476
Readmission[c] (26/296)	0.80 (0.72, 0.90)	<0.001	0.80 (0.71, 0.91)	<0.001

Abbreviations: dB (decibel), MoCA (Montreal Cognitive Assessment), PROMIS (Patient-Reported Outcomes Measurement Information System), EEG (electroencephalogram), CI (confidence interval).

[a] Delirium is defined as present if it occurred within three days postoperatively following surgery. Delirium status was missing for 40 participants.

[b] Discharge status was missing for four participants (one non-delirious patient, one delirious patient, and two with missing delirium status).

[c] Readmission status was missing for six participants (three non-delirious patients, one delirium patient, and two patients with missing delirium status).

[d] Unadjusted models evaluate the association between alpha power and each outcome in separate models.

[e] Models are adjusted for age, body mass index, sex, telephonic MoCA, PROMIS Physical Function, PROMIS Sleep Disturbance, and treatment assignment (randomization to dexmedetomidine or placebo). Separate models were created for each combination of outcome and normalized alpha power.

response to a sedative dose of thiopental [46,47]. This difference in power was not discernable from baseline recordings [46,47].

Whether the incidence of postoperative delirium can be reduced by carefully targeting "light" anesthesia via electroencephalographic or other clinical measures is an open question in anesthesiology. Some studies suggest that electroencephalographic correlates of "deep" anesthesia (i.e., low power, burst suppression) predispose patients to postoperative delirium [48,49], while others suggest patient vulnerabilities and not general anesthesia per se underlie postoperative delirium [50,51]. The present results suggest a nuanced interpretation of deep anesthesia-postoperative delirium findings is warranted (e.g., patients exhibiting correlates of deep anesthesia are independently at risk for postoperative delirium). Thus, associations between correlates of deep anesthesia and postoperative delirium are confounded by physical and cognitive health variables that double as postoperative delirium risk factors.

The relationship between postoperative delirium and intraoperative EEG has been the subject of multiple studies [52,53] and meta-analyses [54–56] and the utility of EEG-guided anesthesia for reducing postoperative delirium remains a subject of active debate [55]. Few studies of a similar size and quality have been conducted using the Long Form Confusion Assessment Method (CAM)—a highly validated instrument for evaluating delirium—and few have included a physiologically relevant frontal EEG metric, such as alpha-band power. In a recent single-center prospective observational study of 220 patients who underwent cardiac surgery in an academic hospital in Belgium between 2019 and 2021, Khalifa, et al. found that lower intraoperative frontal alpha-band power was associated with a higher incidence of postoperative delirium after cardiac surgery independently of age, but not when controlling for cognitive status [53]. Though the study design differs from the present work in several ways—including location (United States vs. Belgium), design (prespecified analysis of prospective randomized controlled trial vs. prospective observational), incidence of delirium (29.5 % vs. 11.0 %), and calculation of intraoperative alpha power (median vs. mean)—the findings of the present study are consistent with those of Khalifa, et al. [53] Furthermore, the present study is consistent with recent work from our group demonstrating that cognitive function may mediate the association between chronological age and oscillatory-specific intraoperative frontal alpha power [57]. Together, these results beg the question: is intraoperative alpha power is a mediator of the association between preoperative cognition and postoperative delirium? Further studies may elucidate the causal relationship between these important clinical factors.

Readmission within 30 days is an important measure of coordination of care, communication, discharge planning, and quality that is measured in the United States as part of the Hospital Readmissions Reduction Program (HRRP) as required by Section 1886(q) of the Social Security Act [58]. Despite being exploratory, the 30-day readmission finding was preserved in direction and magnitude after adjusting for cognitive and physical health information, and comorbidities (Table 3). Although the pathophysiology underlying the relationship between intraoperative EEG and readmission remains unclear, it is posited that unmeasured variables (e.g., immunological state or neurological injury) encoded in the electroencephalogram may underly this finding. In cardiac surgery, intraoperative EEG has long been discussed as a potential method for recognizing or predicting postoperative neurological disorders, such as stroke [59], which may lead to readmission. Previous studies have found associations between intraoperative EEG and other postoperative outcomes in specific populations, such as EEG during carotid endarterectomy and 30-day perioperative stroke [60]. In non-cardiac surgery, multiple studies have also found an association between preoperative cognitive impairment, age, body mass index, and comorbidities outcomes including postoperative delirium and 30-day readmission in older non-cardiac surgery patients [61,62]. However, future studies that carefully characterize readmission diagnoses are necessary.

This study has some notable limitations. The present study is a prespecified secondary analysis of the MINDDS study [38], which demonstrated a decrease in the incidence of delirium for patients randomized to receive a short nighttime dose of intravenous dexmedetomidine as compared to placebo. In the present analysis, randomization to dexmedetomidine served as a potential confounder when assessing the relationship between alpha power and delirium. While our statistical analysis adjusted for randomization assignment, future studies would be

needed to confirm this analysis, as it is possible there that there is some residual confounding introduced with half of the patients receiving an intervention that reduces delirium, namely dexmedetomidine. Second, this study did not evaluate frailty, a risk factor for postoperative delirium. However, we used validated measures to characterize clinically relevant a priori defined cognitive and physical health measures. Further, a recent study did not find associations between alpha power and frailty [63]. Third, isoflurane was administered per empirical clinical practice. However, this analysis studied suppression-free two-minute electroencephalogram epochs with stable electroencephalogram dynamics. This was especially important given transient alpha power loss has been associated with nociceptive stimulus [64]. Fourth, the number of events for each outcome, such as 30-day readmission, was modest relative to the number of variables in our adjusted and exploratory models. It is also important to note that the sample size for this secondary analysis of a completed randomized controlled trial was fixed; therefore, the possibility of type II error cannot be fully excluded. Given the demonstrated power in significant univariate associations and use of a prognostic model, it is reassuring that this is unlikely to negate our findings, however we cannot exclude this possibility. Additionally, the use of frontal EEG may limit our conclusions, as may any bias introduced by the clinical decision to use or not EEG for any particular surgical case, as well as the quality of that recording. However, these limitations are shared in the literature and are, in part, a result of the widespread clinical use of these devices for monitoring brain states during anesthetics by anesthesiologists. Although high-definition, whole-scalp EEG would undoubtably provide another rich dataset for neuroscientists to understand the relationships between brain states during anesthesia and perioperative clinical outcomes, other EEG motifs are not in widespread use at this time and are less clinically practical and applicable to the anesthesiologist. The current analysis has the benefit of providing both neuroscientific and clinical information to the practicing clinician who may immediately translate these findings by informing their clinical judgement in patient care. Finally, our findings may not be generalizable, or there may be residual confounding introduced by differences in intraoperative or postoperative management that was not accounted for in this prespecified secondary analysis.

In this study of patients aged 60 years or older undergoing elective cardiac surgery with cardiopulmonary bypass, anesthesia-induced oscillations were associated with postoperative outcomes however these were not independently associated with delirium or discharge disposition after considering preoperative cognitive and physical health. In secondary analyses these oscillations were robustly associated with 30-day readmission in both unadjusted and adjusted analyses however. Equipped with this information, anesthesiologists may better identify which patients are at the greatest risk for postoperative delirium and other perioperative outcomes and personalize their anesthesia care to mitigate these risks. Further, anesthesia-induced oscillations may enable inferences on health outcomes that extend beyond the operating room.

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CRediT authorship contribution statement

Isaac G. Freedman: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gonzalo Boncompte:** Writing – review & editing, Formal analysis, Conceptualization. **Jason Z. Qu:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Zain Q. Khawaja:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Isabella Turco:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Ariel Mueller:** Writing – review & editing, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Kwame Wiredu:** Writing – review & editing, Formal analysis, Data curation. **Tina B. McKay:** Writing – review & editing, Methodology, Conceptualization. **M. Brandon Westover:** Writing – review & editing, Methodology, Conceptualization. **Juan C. Pedemonte:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Oluwaseun Akeju:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

A.M. reports receiving funding from Roche Diagnostics and the University of Chicago for statistical consulting projects related to biomarkers in preeclampsia. O.A. is listed as an inventor on patents assigned to Massachusetts General Hospital related to brain monitoring.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2025.111770.

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