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Associations between anaesthetic dose-adjusted intraoperative EEG alpha power, processing speed, and postoperative delirium: analysis of data from three prospective studies

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Abstract

Background: We previously have shown that low intraoperative EEG alpha power is associated with impaired preoperative cognition, a delirium risk factor, and that intraoperative anaesthetic-dose-adjusted EEG bispectral index values were associated with a four-fold increased risk of postoperative delirium (POD). Yet, associations between intraoperative anaesthetic-dose-adjusted alpha power and delirium or delirium risk factors have yet to be quantified.

Methods: We examined cerebrospinal fluid (CSF) Alzheimer's disease (AD)-related biomarkers, cognitive scores, EEG recordings, and delirium data from 82 noncardiac, non-neurologic surgical patients ≥60 yr in age. Based on prior work, each participant's intraoperative frontoparietal EEG alpha power was anaesthetic dose-adjusted by dividing it by (2.5 minus the age-adjusted end-tidal minimum alveolar concentration), and then analysed for its association with POD and delirium risk factors, preoperative CSF AD-related biomarkers, and preoperative cognition.

Results: Lower anaesthetic-dose-adjusted frontoparietal alpha power was associated with increased odds of POD (odds ratio [95% confidence interval (CI)]: 1.44 [1.09, 1.89], P=0.009) and moderate-to-severe delirium (odds ratio [95% CI]: 1.44 [1.04, 2.00], P=0.030). Anaesthetic-dose-adjusted frontoparietal alpha power was not associated with pathologic concentrations of CSF pTau-181, Aβ1–42, or pTau-181/Aβ1–42 (P>0.05). In multivariable cognitive models, anaesthetic-dose-adjusted frontoparietal alpha power was associated with preoperative timed processing speed/executive function performance (β [95% CI]: 0.27 [0.06, 0.49], P=0.014), but not with untimed attention/memory performance (β [95% CI]: 0.12 [−0.13, 0.37], P=0.349).

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Conclusions: Lower intraoperative anaesthetic-dose-adjusted frontoparietal alpha power was associated with delirium and delirium-predisposing factors (impaired preoperative processing speed/executive function in timed attention tasks). Larger studies are warranted to confirm these associations after further adjustment for covariates.

Keywords: alpha power; Alzheimer's disease; anaesthesia; cerebrospinal fluid; EEG; perioperative neurocognitive disorder

Editor's key points

- Patients who develop postoperative delirium are at increased risk of developing Alzheimer's disease and related dementias, and *vice versa*.
- Low intraoperative EEG alpha power is associated with impaired preoperative cognition, a delirium risk factor, but associations with delirium or delirium risk factors have yet to be quantified.
- Low intraoperative frontoparietal alpha power was associated with delirium and certain delirium-predisposing factors, but not with CSF concentrations of Alzheimer's disease biomarkers.
- Larger studies are warranted to confirm these associations and to identify underlying neurophysiological mechanisms.

Up to 50% of older Americans who undergo surgery each year develop postoperative delirium (POD),[1–4] characterised by fluctuating inattention and altered levels of consciousness. Patients who develop POD are at increased risk of developing Alzheimer's disease (AD) and related dementias (ADRD),[1] and *vice versa*, individuals with preclinical/prodromal AD (e.g. with no apparent cognitive deficits but abnormally low cerebrospinal fluid [CSF] amyloid beta [Aβ] or high CSF phosphorylated tau [pTau-181])[1] and those with preoperative cognitive impairment are more likely to develop POD.[1,2,5] However, preoperative cognitive testing is not performed[6] and AD-related CSF biomarker measurements are not obtained before surgery at most US hospitals. Alternatively, many anaesthesiologists monitor intraoperative electroencephalography (EEG) for titration of anaesthetics,[7] meaning EEG biomarkers of POD could prove clinically useful for identifying patients for resource-intensive delirium prevention programmes.[1] Further, identifying EEG biomarkers of POD could elucidate the neurophysiological mechanisms that underlie POD itself.

A recent pilot study found a relationship between subsyndromal POD and intraoperative frontal EEG alpha power.[8] Compared with cognitively normal patients, patients with mild cognitive impairment (MCI) or AD have lower volatile anaesthetic-induced processed (e.g. bispectral index [BIS]-based) EEG metrics,[9] suggesting that their brain activity might be less resistant[10] (or more sensitive[11]) to inhaled anaesthetics. In line with the idea that brain vulnerabilities might increase anaesthetic sensitivity, we recently found that low anaesthetic brain resistance based on EEG BIS scores (anaesthetic resistance index = BIS/[2.5 minus the age-adjusted minimum alveolar concentration]) was independently associated with ~four-fold increased odds of POD, whereas BIS values alone were not associated with POD.[10] This formula adjusts BIS values by the difference between the maximum anaesthetic dose likely to be given in typical clinical practice (an age-adjusted minimum alveolar concentration [aaMAC] of ~2.5 based on >17 000 anaesthetic patients[7]) and the actual anaesthetic dose a patient received.[10] Accordingly, we hypothesised that abnormal anaesthetic-dose-adjusted raw (rather than processed) EEG metrics (e.g. alpha power) could help identify preclinical/prodromal ADRD neuropathology or other latent (clinically silent or undiagnosed) neurologic impairments that might predispose some patients to POD. Thus, we investigated the relationship between anaesthetic-dose-adjusted EEG alpha power, POD, and preoperative POD risk factors, including preclinical/prodromal CSF AD pathology and preoperative cognitive impairment.

Methods

This study included data from three prospective studies conducted at Duke University Medical Center (Durham, NC, USA): Markers of Alzheimers Disease and Cognitive Outcomes After Perioperative Care (MADCO-PC; NCT01993836), Investigating Neuroinflammation Underlying Postoperative Cognitive Dysfunction (INTUIT; NCT03273335), and Modulating ApoE Signalling to Reduce Brain Inflammation, deLirium and postopErative Cognitive Dysfunction (MARBLE; NCT03802396). These studies were registered with clinicaltrials.gov and approved by the Duke Institutional Review Board; all study subjects or legally authorised representatives gave written informed consent before participation. These studies enrolled patients aged ≥60 yr who were scheduled to undergo elective noncardiac, non-neurologic surgery lasting ≥2 h with a planned postoperative overnight hospitalisation (see Supplementary material for additional study-specific information). MADCO-PC and INTUIT were prospective observational cohort studies. MARBLE was a randomised clinical trial; however, only participants who received placebo were used in the current study.

Neurocognitive testing and delirium assessment

Neurocognitive assessments were completed ≤1 month before surgery using a well-established neurocognitive test battery[12–14] that included the Hopkins Verbal Learning Test,[15] the Digit Span Test from the revised Wechsler Adult Intelligence Scale (WAIS-R),[16] the WAIS-R Digit Symbol Test,[16] and the Trail Making Test (A and B).[17] Trails A and B scores were truncated at 300 s and negative log-transformed to reduce skewness and match the directionality of other cognitive test scores (such that larger values indicate better performance). The z-scores of individual tests were summed to generate two cognitive domain scores for timed processing speed/executive function tests (Digit Symbol and Trails A and B) and untimed attention/memory tests (Hopkins Delayed Recognition and Recall, Digit Span Forwards and Backwards).

Delirium incidence was measured using the Confusion Assessment Method (CAM)[18] in MADCO-PC and the 3-Minute

Diagnostic Confusion Assessment Method (3D-CAM)[19] in INTUIT and MARBLE, and via validated chart review in all three studies.[20] POD severity and delirium feature analyses were assessed with the 3D-CAM for INTUIT and MARBLE participants and were unavailable for the MADCO-PC participants given that the task was aborted if the inattention domain was not present (per CAM protocol). See the Supplementary material for additional delirium details by study.

CSF collection

Preoperative CSF samples were collected via lumbar puncture as described in the Supplementary material. In MADCO-PC, CSF Aβ1–42, tau, and pTau-181 were assayed in duplicate using Innogenetics immunoassay reagents (INNO-BIA AlzBio3; Ghent, Belgium), whereas INTUIT and MARBLE assays were assayed in duplicate using the Roche Diagnostics Elecsys platform (Indianapolis, IN, USA) because the Alzbio3 assay was no longer commercially available at the time the INTUIT and MARBLE samples were analysed (see Supplementary material for additional details). Personnel performing these assays were blinded to patient information. CSF Aβ1–42 or pTau-181 pathology was determined based on previously published cut-off values for the AlzBio3 platform (Aβ1–42 $\leq$249 pg ml^{-1},[21] pTau-181 >23 pg ml^{-1},[22] pTau-181/Aβ1–42 >0.10[22]) and Roche Elecsys platform (Aβ1–42 $\leq$1000 pg ml^{-1},[23] pTau-181 >27 pg ml^{-1},[24] pTau-181/Aβ1–42 >0.024[23]).[25]

EEG recordings

Thirty-two-channel EEG data (Brain Products GmbH, Gilching, Germany) were collected on a subset of MADCO-PC, INTUIT, and MARBLE patients (see Supplementary material for study-specific EEG details). Electrode impedances generally <20 kΩ were obtained before data collection by light abrasion of scalp locations with coarse electrode paste. EEG was sampled at $\geq$500 Hz with a 0.016–250 Hz band-pass filter.

EEG preprocessing and variable calculation

EEG processing was performed in MATLAB R2023a (The MathWorks, Inc., Natick, MA, USA) using EEGLAB v2021.0 (Swartz Center for Computational Neuroscience, San Diego, CA, USA) and custom scripts. After acquisition, the EEG data were band-pass filtered from 1 to 55 Hz to remove high-frequency noise, drift, and other artifacts and then down-sampled to 250 Hz. Epochs with highly variable amplitudes were removed (i.e. within-subject $\log_{10}$ (standard deviation [μV]) $\leq$ -0.5 or $\geq$ 1.8, as this likely reflected poor signals or large high-frequency distortions from electrocautery or head movement). EEG epochs contaminated by excessive artifacts in more than five channels were excluded. When more than five channels were contaminated, they were each interpolated via spherical splines.[26] Once pre-processed, the EEG data were re-referenced to the average signal of the TP9 and TP10 electrodes near the mastoid bone (i.e. standard 10–20 left and right mastoid electrode sites), as previously reported.[27]

After initial preprocessing, intraoperative left and right hemispheric frontal and parietal alpha (7–13 Hz) power (dB) was computed for each minute of the intraoperative EEG recording using custom scripts, starting from $\geq$5 min after anaesthesia began (anaesthesia start note) until $\geq$5 min before the case ended (anaesthesia stop note). Regions of interest (ROIs) were the average signal from electrode sites Fp1 + F3 (left frontal ROI), Fp2 + F4 (right frontal ROI), P3 + P7 (left parietal ROI), and P4 + P8 (right parietal ROI). Activity across these ROIs was averaged to calculate mean frontoparietal alpha power. Minutes of artifact or non-volatile gas anaesthetic use (per anaesthetic record) were excluded from the analysis. To minimise potential confounding, EEG data were excluded during case minutes corresponding to extreme aaMAC doses (<0.5 or $\geq$2.5), >10% nitrous oxide, and for 30 min after ketamine or dexmedetomidine administration (because of the differential effects of these drugs on the EEG *vs* those of volatile anaesthetics[28]). When ketamine or dexmedetomidine was given before the start of the combined inhaled anaesthesia and EEG recordings, the 30-min rejection window started at the first recorded minute of combined gas and EEG. Patients with <15 min of EEG data per these criteria were removed from further analyses.

After data processing, anaesthetic-dose-adjusted alpha power was calculated on a minute-by-minute basis using the formula: frontoparietal alpha power at a given minute/(2.5 − aaMAC at that minute), where aaMAC is the age-adjusted end-tidal minimum alveolar concentration fraction of volatile anaesthetic received by each individual participant.[29] The denominator reflects the difference between the maximum anaesthetic dose given in typical clinical practice (i.e. 2.5 aaMAC)[7] and the actual anaesthetic dose a patient received.[10] These values were then summarised across the surgical case as the mean of the median alpha power values over a sliding 5-min window (with 4-min overlap) to reduce the impact of artifacts in the EEG data.[7] Thus, every participant had a single case summary value for dose-adjusted frontoparietal alpha power for the analyses.

Statistical analysis

Univariable analyses were performed between intraoperative alpha power and POD incidence and severity, CSF AD biomarkers, and preoperative processing speed/executive function and attention/memory function scores. Data normality was evaluated using the Shapiro–Wilk test; analyses were performed with either parametric or nonparametric methods as appropriate.

The relationships between anaesthetic-dose-adjusted frontoparietal alpha power and POD incidence, delirium severity, and the presence (or absence) of each of the four 3D-CAM delirium features were analysed with univariable logistic regression. Delirium severity was dichotomised as previously described[30] to account for a potentially nonlinear relationship between dose-adjusted frontoparietal alpha power and delirium severity. We acquired odds ratios and area under the curve (AUC) values from these models to compare the performance and utility of dose-adjusted frontoparietal alpha power for these delirium metrics *vs* AUC values for delirium biomarkers from prior studies.[31] All logistic models were Firth-corrected to account for the small imbalanced sample sizes for delirium incidence, delirium severity classification, and delirium feature presence.

Relationships between numeric measures (e.g. preoperative processing speed/executive function, attention/memory function) were analysed via univariable and multivariable regression models. Given the small sample size of our cohort, a limited number of covariates (age, sex, and years of education) could be included in our numeric analyses. Relationships between ordinal measures (e.g. POD severity scores) were analysed via Spearman correlations. *T*-tests were used to compare

brain sensitivity to anaesthetics (i.e. intraoperative dose-adjusted frontoparietal alpha power) among participants with normal *vs* pathological concentrations of the CSF AD-related biomarkers pTau-181, Aβ1–42, or pTau-181/Aβ1–42 based on previously published CSF biomarker thresholds.[21–25] *P*-values were not corrected for multiple comparisons across these biomarkers given the exploratory nature of these analyses.

Results

Across the three cohorts, 202 participants underwent 32-channel intraoperative EEG recordings; seven were excluded because of file errors and 75 because of receiving the investigational drug CN-105 during the MARBLE clinical trial. An additional 11 files were excluded for having <15 min of usable data after preprocessing. Of the remaining 109 participant datasets, 27 participants did not have gas anaesthesia for ≥80% of their surgical case. Thus, 82 participant datasets remained for analysis. Preoperative and intraoperative/postoperative characteristics of this cohort are presented in Table 1 and Supplementary Table S1, respectively. All references to dose-adjusted frontoparietal alpha power refer to intraoperative data. A summary of EEG data removed before analysis, per the minute-by-minute intraoperative exclusion criteria, is presented in Supplementary Table S2.

We first tested whether delirium incidence or severity was associated with anaesthetic-dose-adjusted frontoparietal alpha power. Participants with lower anaesthetic-dose-adjusted frontoparietal alpha power had increased POD risk and *vice versa* (odds ratio [95% confidence interval (CI)]: 1.44 [1.09, 1.89], *P*=0.009, Fig. 1a). The area under the receiver-operating characteristic (AUROC) curve (95% CI) of the association between dose-adjusted frontoparietal alpha power and patients with *vs* without POD was 0.71 (0.55, 0.87) (Supplementary Fig. S1a). Similarly, moderate-to-severe delirium severity (*vs* zero-to-mild delirium severity) was inversely associated with frontoparietal anaesthetic-dose-adjusted alpha power (odds ratio [95% CI]: 1.44 [1.04, 2.00], *P*=0.030; Fig. 1b; AUC [95% CI]: 0.69 [0.47, 0.90]; Supplementary Fig. S1b). Raw 3D-CAM delirium severity scores were not significantly associated with frontoparietal anaesthetic-dose-adjusted alpha power (Spearman's $\hat{\rho}$ [95% CI]: −0.21 [−0.42, 0.03], *P*=0.081; Fig. 1c).

Although the 3D-CAM is a subset of items commonly used when administering the larger CAM assessment, follow-up analyses were done to determine whether the combination of CAM and 3D-CAM data influenced our results for delirium incidence. The CAM was only used in the small subset of eight participants from the MADCO-PC study. When these eight participants were excluded, the association between dose-adjusted frontoparietal alpha power and 3D-CAM delirium incidence remained significant (odds ratio [95% CI]: 1.59 [1.15, 2.19], *P*=0.005).

Next, we analysed Firth-corrected logistic regression models of the association between anaesthetic-dose-adjusted frontoparietal alpha power and the four 3D-CAM features used to identify POD (acute/fluctuating mental status, inattention, disorganised thinking, and altered consciousness). Anaesthetic-dose-adjusted frontoparietal alpha power was inversely associated with acute/fluctuating mental status and altered level of consciousness, but was not significantly associated with inattention or disorganised thinking (Supplementary Table S3, Fig. 2).

Table 1 Preoperative patient characteristics of the overall cohort. Values are mean (standard deviation [SD]), median (Q1, Q3), or *n* (%). *Two participants had missing *APOE* genotype, quality of life, or cognitive testing scores. †One participant had missing IADL, Mental Abilities, or Hopkins Verbal Learning Test scores. ‡Eighteen participants had missing MMSE scores. ¶Raw Trails scores were truncated to 300 s and negative log-transformed to reduce skewness and match the directionality of other cognitive test scores (such that larger values indicate better performance). §Seven participants had missing CSF Aβ1–42 and pTau-181 data. Aβ1–42 and pTau positivity was determined by published thresholds for Aβ1–42 and pTau-181 pathology, respectively, in Alzheimer's disease for the AlzBio3 assay platform (A+ if Aβ1–42 ≤249 pg ml^{-1},[21] T+ if pTau-181 >23 pg ml^{-1},[22] pTau-181/Aβ1–42 >0.10[22]) and the Roche Elecsys assay platform (A+ if Aβ1–42 ≤1000 pg ml^{-1},[23] T+ if pTau-181 >27 pg ml^{-1},[24] pTau-181/Aβ1–42 >0.024[23]).

Preoperative participant data	Overall (*n*=82)
Age, yr	68 (65, 72)
Male sex	44 (53.66%)
Non-White race	19 (23.17%)
Years of education	16 (13, 17)
Body mass index	29.68 (5.11)
Apolipoprotein E4 (*APOE4*) Carrier*	23 (28.75%)
Hypertension	47 (57.32%)
American Society of Anesthesiologists (ASA) physical status	3 (2, 3)
Duke Activity Status Index (DASI) score*	25.08 (13.45, 42.7)
Center for Epidemiological Studies-Depression (CES-D) score*	7.68 (4, 13.5)
State-Trait Anxiety Inventory (STAI) score*	28 (23, 40)
Independent Activities of Daily Living (IADL) score†	6 (6, 6)
Mental Abilities score†	70.82 (60, 81.08)
Mini-Mental State Exam (MMSE) score‡	28 (26.5, 29)
Digit Span Forwards score*	7.5 (6, 10)
Digit Span Backwards score*	6.44 (2.42)
Trails A score*, ¶	−3.43 (−3.66, −3.18)
Trails B score*, ¶	−4.44 (−4.75, −4.13)
Digit Symbol score*	45 (37, 52)
Hopkins Delayed Recall score†	9 (7, 10)
Hopkins Delayed Recognition score†	11 (10, 12)
Cerebrospinal fluid pTau-181/Aβ1–42 pathology§	8 (10.67%)
Cerebrospinal fluid pTau-181 pathology§	7 (9.33%)
Cerebrospinal fluid Aβ1–42 pathology§	14 (18.67%)

Next, we examined the association between intraoperative anaesthetic-dose-adjusted frontoparietal alpha power (dB) and preoperative vulnerabilities potentially associated with increased POD risk, including the CSF AD-related biomarkers Aβ1–42, pTau-181, and the pTau-181/Aβ1–42 ratio. In univariable analyses, dose-adjusted frontoparietal alpha power did not significantly differ between participants with low *vs* normal preoperative CSF Aβ1–42 concentrations (mean difference [95% CI]: −0.46 dB [−1.85, 0.93], *P*=0.510; Fig. 3a), nor among those with high *vs* normal preoperative pTau-181 concentrations (mean difference [95% CI]: −1.21 dB [−3.05, 0.63], *P*=0.194; Fig. 3b). Similarly, participants with high pTau-

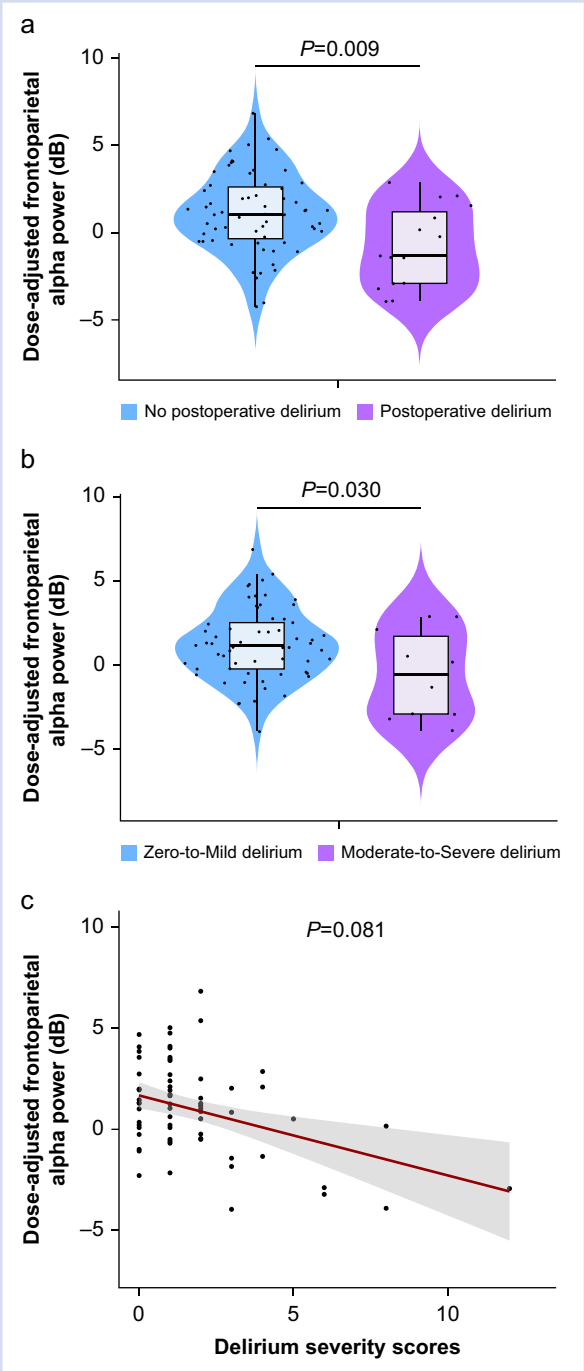

Fig 1. Plots of dose-adjusted frontoparietal alpha power by delirium incidence and severity. (a) Violin plot of dose-adjusted frontoparietal alpha power by delirium incidence (n=15 with delirium, 63 without delirium). (b) Violin plot of dose-adjusted frontoparietal alpha power by delirium severity group (n=61 with zero-to-mild delirium severity, n=10 with moderate-to-severe delirium). (c) Scatterplot of dose-adjusted frontoparietal alpha power by delirium severity from the 3-Minute Confusion Assessment Method (3D-CAM) (n=71). For (a) and (b), the black dots represent the data distribution of dose-adjusted frontoparietal alpha power. Boxplots within the outlines show the median (middle black line), 25% and 75% quartiles (lower and upper box edges, respectively), whiskers (1.5 * the 25%–75% interquartile range), and outliers (dots beyond the whisker range). For (a) and (b), P-values from Firth-corrected logistic regression models are shown. For (c), the line and grey shaded region represents a linear trend line and the 95% confidence interval, respectively. The P-value from the Spearman's correlation is shown.

181/Aβ1–42 ratios (a more specific indicator of AD pathology[32]) did not have lower anaesthetic-dose-adjusted frontoparietal alpha power than participants with normal levels of this ratio (mean differences [95% CI]: −0.64 dB [−2.39, 1.11], P=0.469; Fig. 3c). Among the 13 participants who experienced delirium in this cohort and who had available CSF AD biomarker data, eight participants (61.5%) had normal concentrations of CSF Aβ1–42, and 11 participants (84.6%) had normal concentrations of CSF pTau181 and CSF pTau181/Aβ1–42.

Next, because preoperative cognitive impairment has been associated with altered intraoperative EEG alpha power, we examined the relationship between anaesthetic-dose-adjusted frontoparietal alpha power and cognitive tests completed before surgery. Analyses showed that dose-adjusted frontoparietal alpha power was associated with scores on time-sensitive tests of processing speed/executive function (Trails A, Trails B, and Digit Symbol scores; Fig. 4) and Hopkins Delayed Recognition, although it was not associated with scores on non-time-sensitive tests of verbal attention/working memory (Digit Span Forwards/Backwards, Hopkins Delayed Recall; Fig. 4). Figure 4h–i shows univariable analyses of summary z-scores for the timed processing speed/executive function (Fig. 4a–c) and untimed attention/memory (Fig. 4d–g) tests. After covariate adjustment for age, sex, and years of education, anaesthetic-dose-adjusted alpha power remained significantly associated with timed, but not untimed, cognitive test summary z-scores (Table 2). Relationships were similar for unadjusted alpha power and anaesthetic-dose-adjusted alpha power between these EEG metrics and POD, preoperative CSF AD-related biomarkers, and preoperative cognitive performance. However, dichotomised delirium severity and untimed attention/working memory summary scores were not significantly associated with unadjusted frontoparietal alpha power (Supplementary Figs. S2–S5, Supplementary Table S4).

Discussion

We observed that anaesthetic-dose-adjusted frontoparietal alpha power is associated with POD risk and impaired timed task performance but might not be associated with preclinical/prodromal CSF AD biomarkers. These findings are in line with prior studies, which have shown that decreased frontal intraoperative alpha power and brain anaesthetic sensitivity (and its inverse, brain anaesthetic resistance) are associated with preoperative cognitive impairments[27,33] and POD,[10,11] respectively.

Our univariable analyses showed that patients with low frontoparietal anaesthetic-dose-adjusted intraoperative alpha power had increased odds of POD and moderate-to-severe delirium severity, similar to other studies of intraoperative EEG alpha power and POD risk.[8,34] Particularly, our cohort showed associations between frontoparietal anaesthetic-dose-adjusted alpha power and both acute/fluctuating mental status changes and altered levels of consciousness (core features of delirium). The underlying neurologic mechanisms of fluctuations in mental status and alterations in the level of consciousness among patients with POD are unclear,

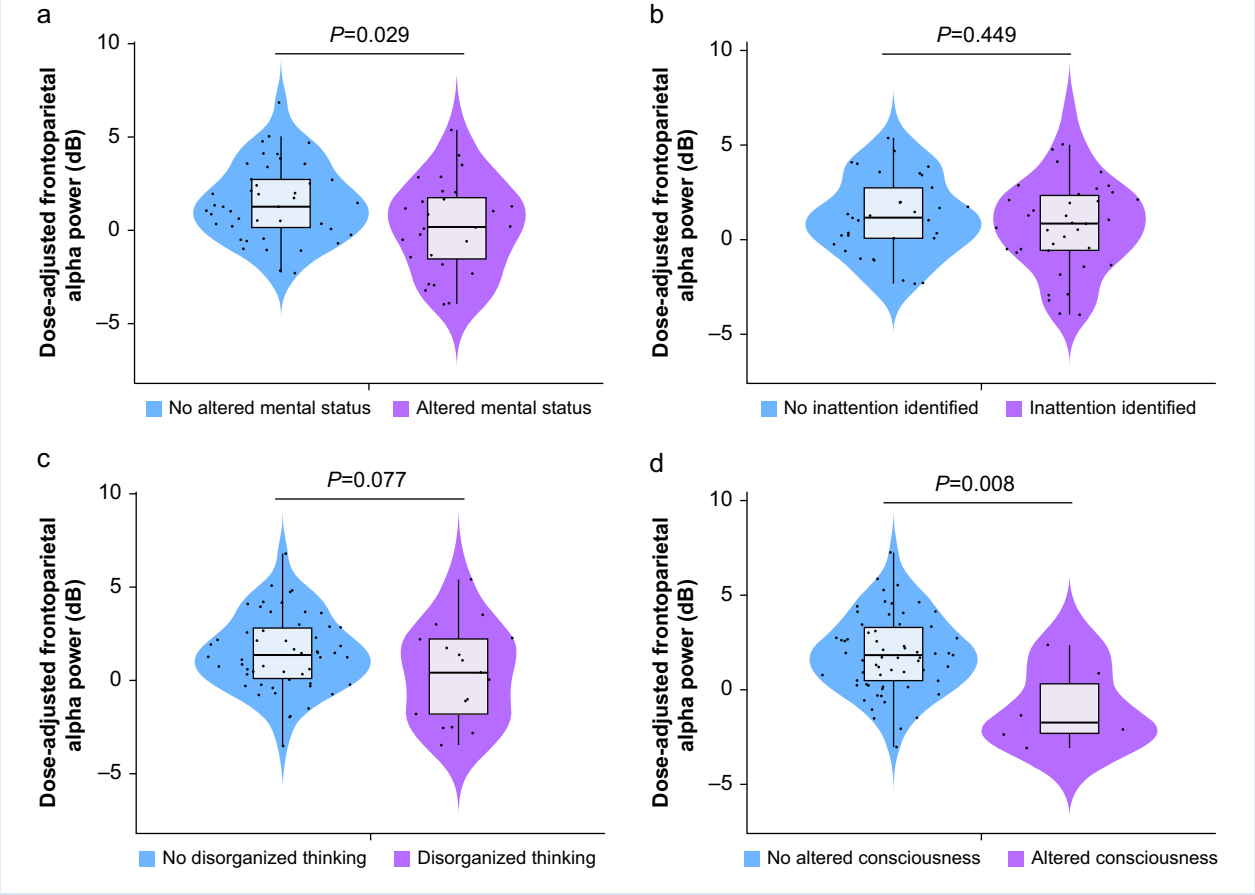

Fig 2. Plots of dose-adjusted frontoparietal alpha power by 3-Minute Confusion Assessment Method (3D-CAM) delirium feature presence at any postoperative timepoint (n=71). The panels correspond to the following delirium features: (a) altered (acute or fluctuating) mental status (n=28 with this feature), (b) inattention (n=38 with this feature), (c) disorganised thinking (n=17 with this feature), and (d) altered level of consciousness (n=6 with this feature). The black dots represent the data distribution of dose-adjusted frontoparietal alpha power. Boxplots within the outlines show the median (middle black line), 25% and 75% quartiles (lower and upper box edges, respectively), whiskers (1.5 * the 25%–75% interquartile range), and outliers (dots beyond the whisker range). Firth-corrected logistic regression P-values are reported for each of the 3D-CAM features (for their association with anaesthetic-dose-adjusted intraoperative frontoparietal alpha power).

though patients with POD have been shown to have preoperative structural dysconnectivity between several brain areas including the thalamus,[35,36] which is critical for regulating consciousness (e.g. under anaesthesia[37,38]) and for generating alpha oscillations.[36,37,39]

The association between dose-adjusted frontoparietal alpha power and POD in this cohort had a moderate AUC of 0.71, which is similar or higher than previously observed AUC delirium prediction values for preoperative Mini-Mental Status Examination scores (AUC: 0.64), serum albumin (AUC: 0.61), age-adjusted Charlson Comorbidity Index (AUC: 0.79), and postoperative pain scores (AUC: 0.71).[31] Although the cohort studied here was too small to combine these and other terms[40,41] into one model for delirium risk, future studies should examine whether dose-adjusted frontoparietal alpha power in combination with these other predictors would improve delirium risk prediction.

Additionally, the AUC of 0.71 of anaesthetic-dose-adjusted frontoparietal alpha power observed here was slightly higher than the AUC of 0.69 of unadjusted frontoparietal alpha power in this cohort. Although anaesthetic-dose-adjusted frontoparietal alpha power generally had larger effect sizes than the unadjusted frontoparietal alpha power metric, a larger study is needed to directly compare these EEG metrics to determine which has a stronger association with POD and its risk factors (i.e. preoperative CSF AD-related biomarkers and cognitive performance).

We did not find significantly lower intraoperative anaesthetic-dose-adjusted frontoparietal alpha power among participants with elevated (*vs* normal) CSF pTau-181, Aβ1–42, or pTau-181/Aβ1–42. There are few papers quantifying associations between brain, CSF, or plasma AD-related biomarkers and EEG metrics.[42] One study found that the degree of brain tau pathology (but not Aβ) negatively modulates occipital and temporoparietal alpha connectivity in the awake resting state, with regional deficits varying by AD phenotype.[43] Based on this, there are several potential explanations for why dose-adjusted frontoparietal alpha power was not significantly associated with pTau-181 in this cohort. Firstly, our frontoparietal electrode subset might have missed other regional (e.g.

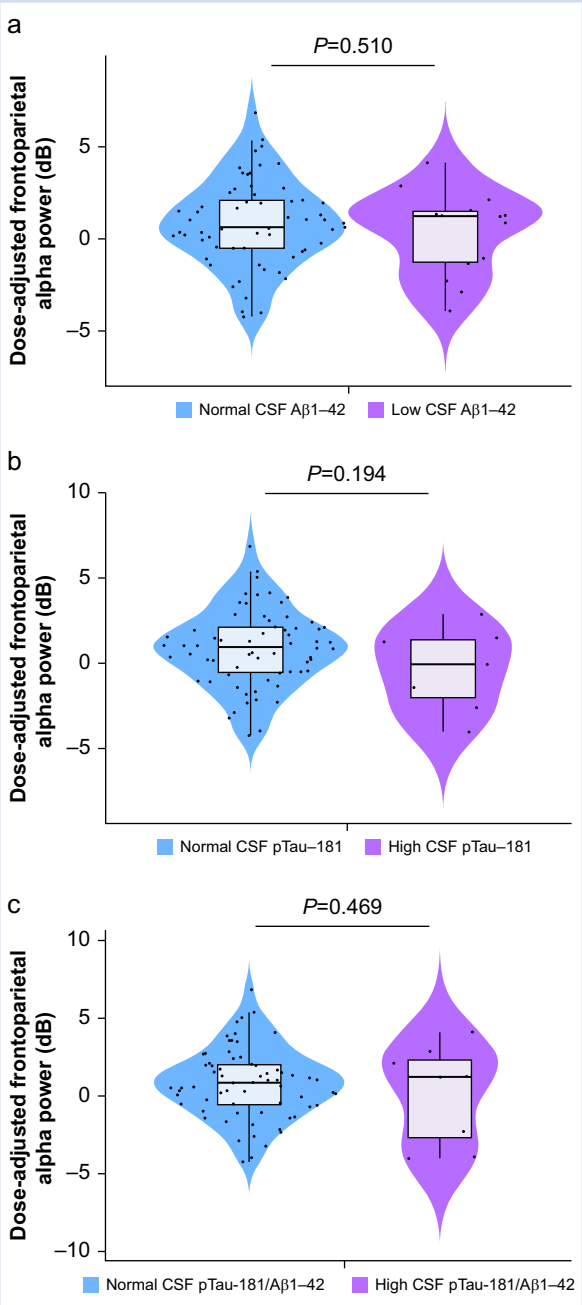

Fig 3. Violin plots of dose-adjusted frontoparietal alpha power by preoperative cerebrospinal fluid (CSF). (a) Aβ1–42 pathology (n=14 positive for this pathology), (b) pTau-181 pathology (n=7 positive for this pathology), and (c) pTau-181/Aβ1–42 ratio pathology (n=8 positive for this pathology). In total, n=75 patients had available CSF Alzheimer's disease (AD) biomarker data. The black dots represent the data distribution of dose-adjusted frontoparietal alpha power. Boxplots within the outlines show the median (middle black line), 25% and 75% quartiles (lower and upper box edges, respectively), whiskers (1.5*the 25%–75% interquartile range), and outliers (dots beyond the whisker range). T-test P-values are reported for each of the CSF AD biomarkers (for their association with intraoperative anaesthetic-dose-adjusted frontoparietal alpha power).

occipital, temporoparietal) changes in alpha oscillations. Secondly, there are potential differences between associations with alpha in the resting state *vs* under general anaesthesia, e.g. arising from intraoperative alpha anteriorisation, which is thought to reflect a silencing of occipital–parietal-oriented thalamocortical neurones and activation of frontal-oriented thalamocortical neurones.[44] Differences in the neuronal generators of alpha during anaesthesia *vs* the awake state could lead to correspondingly different associations between preoperative *vs* intraoperative alpha with either CSF pTau181 or Aβ1–42. Thirdly, the resting-state literature generally exhibits more robust results with alpha connectivity metrics *vs* alpha power for AD-related pathology,[42] and this could be true in the anaesthetised state as well. Thus, larger studies are needed to determine whether this study is underpowered to detect the effect of CSF AD-related biomarkers on anaesthetic-dose-adjusted frontoparietal alpha power *vs* whether alternative dose-adjusted metrics (e.g. from other brain regions, with alpha functional connectivity) might be associated with these CSF AD biomarkers and their corresponding brain impairments (e.g. neuronal damage, tissue atrophy,[45] impaired synaptic function[46]). The overlap between dose-adjusted EEG features of pathologic CSF AD-related biomarkers and EEG features of POD is a related, important topic of future study, though our data suggest that only a small subset of participants who developed POD had pathologic CSF AD biomarker concentrations.

Lastly, after multivariable adjustment for age, sex, and years of education, low anaesthetic-dose-adjusted frontoparietal alpha power was associated with impaired preoperative timed cognitive test performance using summary z-scores from the Trails A, Trails B, and Digit Symbol tests, which depend on elements of executive function, attention, and processing speed. Similarly, prior studies have found that patients who developed POD after surgery had preoperative abnormalities in the corpus callosum, cingulum, and temporal lobes, which themselves were associated with preoperative cognitive impairment.[35] Additionally, impairments in Trails A performance and processing speed have been associated with atrophy of the corpus callosum,[47] and abnormalities in cingulum microstructure have been associated with worse performance on the Trails B and Digit Symbol tests and other processing speed-related tasks.[48] This suggests that that the integrity of the corpus callosum, cingulum, and other brain regions involved in Trail Making and Digit Symbol performance might be related to the function of the cortico–thalamic loops that generate intraoperative frontoparietal alpha power, such as via disrupted information processing in prefrontal–thalamocortical circuits.[49] Furthermore, there was no evidence of an association between intraoperative frontoparietal alpha power and untimed attention/memory tasks such as the delayed recall portion of the Hopkins Verbal Learning Test, for which performance is hippocampal-dependent[50,51] unlike the Trail Making and Digit Symbol tasks. Future work should examine these relationships and perform mediation analyses to test the extent to which delirium-predisposing factors (impaired preoperative timed attention performance) are related to POD risk via their effects on intraoperative dose-adjusted frontoparietal alpha power *vs* independently of this EEG measure of brain activity in response to inhaled anaesthetics. Future work should also investigate the potential differential effects of injected anaesthetics on these associations.

The main limitation of this study is that it is an exploratory analysis of a limited-size cohort from prior studies designed

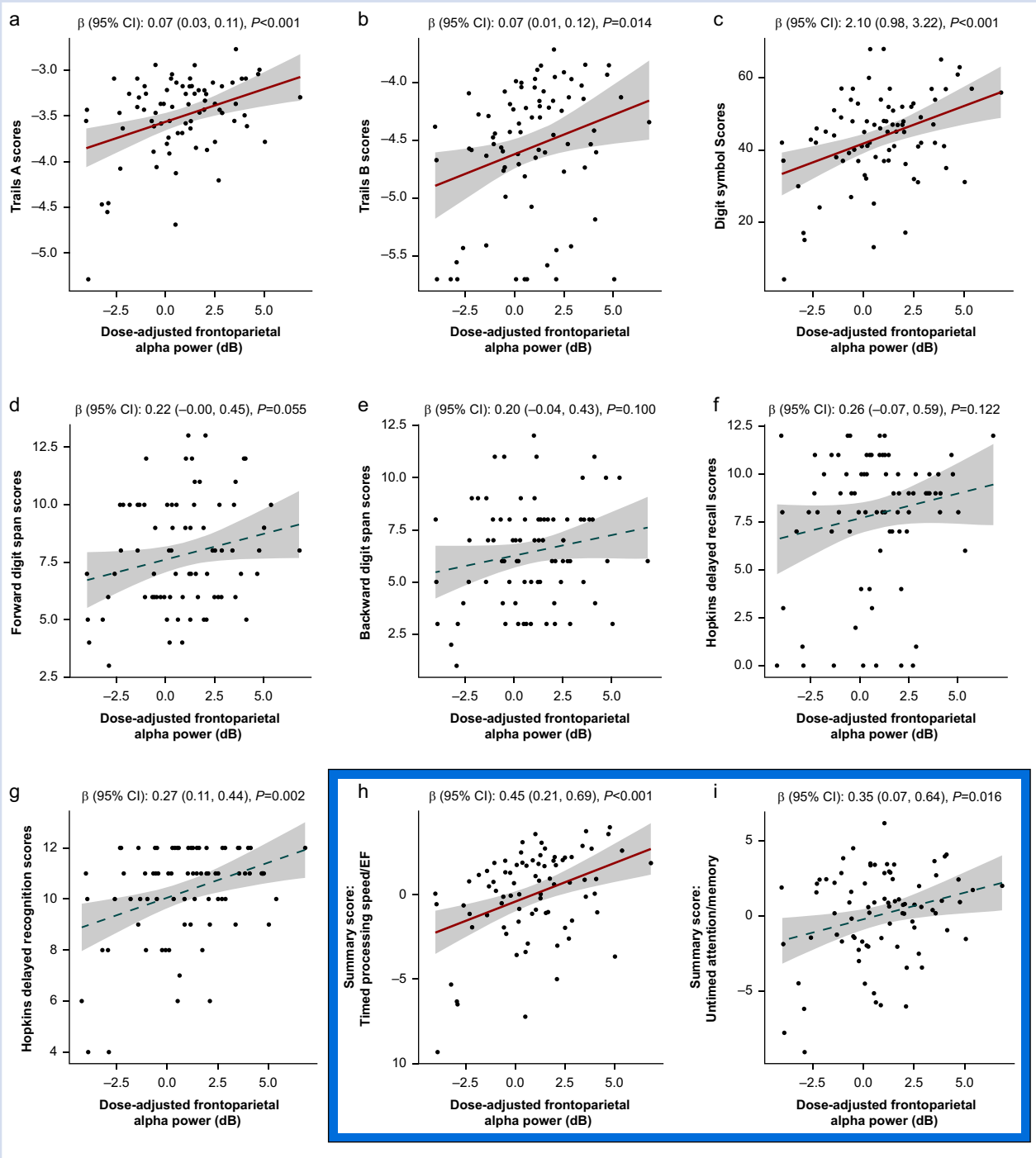

Fig 4. Scatterplots of preoperative cognitive test scores by dose-adjusted alpha power. Beta coefficients, 95% confidence intervals, and P-values are reported for each of the tests (for their association with anaesthetic-dose-adjusted intraoperative frontoparietal alpha power). Panels (h) and (i) show correlations between summary z-scores for the respective preoperative timed processing speed/executive function (a–c) and untimed attention/memory (d–g) tests, colour-coded by cognitive domain as red and blue–green and lines, respectively. The lines and shaded regions represent linear trend lines and 95% confidence intervals, respectively. *N*=80 participants had available preoperative cognitive test scores for panels a–e. *N*=81 participants had available preoperative scores for the Hopkins Verbal Learning Test (f–g). EF, executive function.

for other purposes. An appropriately powered study is needed to apply multiple comparison corrections and covariate adjustment to assess the predictive capacity (and potential clinical utility) of dose-adjusted intraoperative frontoparietal alpha power for delirium risk prediction, and for identifying patients with preclinical/prodromal ADRD or cognitive

Table 2 Multivariable linear models of preoperative timed processing speed/executive function and untimed attention/memory summary z-scores by anaesthetic-dose-adjusted frontoparietal alpha power, adjusted for the covariates age, sex, and years of education (n=80). The timed processing speed/executive function summary z-score was generated from scores on the Digit Symbol and Trails A and Trails B tests. The untimed attention/memory summary z-score was generated from scores on the Hopkins Delayed Recognition and Recall and Digit Span Forwards and Backwards tests. CI, confidence interval.

Timed processing speed/executive function model	**β [95% CI]**	***P*-value**
Anaesthetic-dose-adjusted alpha power	0.27 [0.06, 0.49]	0.014
Age, yr	−0.20 [−0.28, −0.11]	<0.001
Male sex	−0.39 [−1.34, 0.57]	0.422
Years of education	0.32 [0.17, 0.48]	<0.001
Untimed attention/memory model	**β [95% CI]**	***P*-value**
Anaesthetic-dose-adjusted alpha power	0.12 [−0.13, 0.37]	0.349
Age, yr	−0.23 [−0.33, −0.13]	<0.001
Male sex	−0.85 [−1.97, 0.26]	0.131
Years of education	0.43 [0.25, 0.61]	<0.001

impairment. Our group is currently conducting a 250-subject prospective cohort study to address these questions, titled Low Neurophysiologic Resistance to Anesthetics as a Marker of Preclinical/ProdromaL Alzheimer's Disease and Neurovascular Pathology, Delirium Risk and INattention (ALADDIN).[52] When complete, ALADDIN will allow for multivariable (and mediation) testing of associations between intraoperative anaesthetic-dose-adjusted EEG metrics and POD, and with POD predisposing factors such as CSF and functional MRI (fMRI) biomarkers of preclinical/prodromal AD or preoperative cognitive impairment. The larger cohort will also provide greater statistical power to determine the nature of the relationships (continuous, threshold-based, etc.) between intraoperative anaesthetic-dose-adjusted EEG metrics and the aforementioned outcomes of interest.

Secondly, this cohort included a highly educated sample of older adults, which might limit the generalisability of the results to the broader population of older noncardiac, non-neurologic surgical patients. Furthermore, there might be potential differential effects of sex, race, ethnicity, and apolipoprotein E4 (*APOE4*) genotype status on the conclusions. These and other covariates will be considered in the ALADDIN study.

Thirdly, this cohort included participants from three prospective studies from the same medical centre, which all had the same main inclusion and exclusion criteria (age ≥60 yr, scheduled for noncardiac, non-neurologic surgery of ≥2 h duration with a planned overnight hospital stay). However, the INTUIT study had extra exclusion criteria for patients taking immunosuppressants and anti-inflammatory drugs. Although unlikely to have an impact on the outcomes in the current study, the combination of cohorts is a potential limitation.

Fourthly, CSF AD biomarker data were collected from Alz-Bio3 and Roche Elecsys assays, which could not be combined as numerical data given differences in calibration between the two different assay platforms. Thus, we were limited to analysing these variables according to established cut-offs for classifying preclinical prodromal AD pathology with each assay. Importantly, there could also be uncertainty regarding the optimal pathologic cut-point for these CSF biomarkers, which are indirect markers of AD-related neuropathologic progression.[53] Although the sample sizes for these comparisons were relatively small, the findings are novel; to our knowledge, no prior study has investigated associations between intraoperative anaesthetic-adjusted EEG alpha power and CSF AD-related biomarkers. Similarly, delirium data were collected using either the CAM or 3D-CAM. Use of two different assessments could introduce bias, although our results held up in follow-up analyses when removing the eight participants with CAM data from our analysis of dose-adjusted frontoparietal alpha power and 3D-CAM-based delirium assessments.

Fifthly, patients were excluded from the analyses if they did not meet the criteria for exposure to gas anaesthetics or if they had <15 min of usable EEG data after processing. Our EEG artifact removal process was strict: if >5 of 32 electrodes had an artifact in an epoch, including electrodes outside of the frontal and parietal ROIs, then all electrodes in that epoch were rejected. Modification of our data inclusion requirements could be pursued in future studies to investigate their impact and include more data. Larger studies should also assess whether the results hold in a smaller subset of frontal or parietal electrodes to potentially improve the feasibility of using these metrics in clinical practice without 32-channel EEG. These frontal or parietal intraoperative dose-adjusted EEG features could, if validated, improve routine anaesthesia care for patients without available cognitive screening tests or ADRD biomarkers by enabling anaesthetists to make inferences about a patient's preoperative neurocognitive status and delirium risk based on EEG data routinely obtained in the operating room.

Sixthly, we summarised our dose-adjusted frontoparietal alpha power metric across the surgical case for each participant. Future studies could consider the impact of time on the outcomes studied here, for instance by using time series analyses of the anaesthetic and EEG data over the full surgical case.

Lastly, there may be alternative anaesthetic-dose-adjusted EEG formulas to better characterise brain sensitivity to anaesthetics. An optimal formula would maximise separation between individuals who are highly sensitive to the neurophysiologic effects of volatile anaesthetics (such as those who receive a low aaMAC and have low alpha power) *vs* those who are highly resilient to volatile anaesthetic effects (such as those who receive a high aaMAC and have high alpha power).[9] We would expect that an improved dose-adjustment formula would strengthen associations between dose-adjusted frontoparietal alpha power and POD and predisposing factors *vs* unadjusted frontoparietal alpha power.

Conclusions

These results suggest that intraoperative anaesthetic-dose-adjusted frontoparietal alpha power is associated with POD and certain POD risk factors, such as impaired timed processing speed/executive function performance. Future studies

are warranted to confirm these findings in a larger cohort and to discover the underlying neurophysiological mechanisms.

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Declarations of interest

MB has received material support (EEG monitor loan) for a postoperative recovery study in older adults from Masimo and has participated in Masimo peer-to-peer educational sessions, for which his honorarium was donated at his request to the Foundation for Anesthesia Education and Research. MB also acknowledges private legal consulting fees related to postoperative neurocognitive function in older adults. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EEG data processing and analysis: MR, KCR, LA, MGW
Statistical analysis: MR, MCW
Data interpretation: MR, MCW, MBW, MGW, MBerger
Manuscript preparation: MR, MCW, MBennett, MBW, MGW, MBerger
Manuscript review and final approval: all authors

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2024.12.041.

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