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RESEARCH PAPER

Prediction of postoperative delirium in older adults from preoperative cognition and occipital alpha power from resting-state electroencephalogram

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Abstract

Background: Postoperative delirium is the most common complication following surgery amongst older adults, and has been consistently associated with increased mortality and morbidity, cognitive decline, loss of independence and increased health-care costs. We sought to identify preoperative predictors that could identify individuals at high risk for postoperative delirium, which could guide clinical decision-making and enable targeted interventions to potentially decrease delirium incidence and postoperative delirium-related complications.

Methods: Preoperative resting-state electroencephalograms (EEGs) and the Montreal Cognitive Assessment were collected from a prospective observational cohort of 85 older adults (12 cases of delirium) undergoing elective surgery. Four machine learning models were tested and the model with the highest f1-score was subsequently validated in an independent, prospective cohort of 51 older adults (6 cases of delirium) undergoing elective surgery.

Results: Occipital alpha powers have higher f1-score (0.57 ± 0.07) than frontal alpha powers (0.47 ± 0.07), EEG spectral slowing (0.48 ± 0.08), or modelling of EEG power spectral density into periodic and aperiodic components (0.44 ± 0.09) in the training cohort. Occipital alpha powers plus cognitive scores were able to predict postoperative delirium with area under the receiver operating characteristic curve (AUC) (0.94, 95% CI: [0.86–0.99]), sensitivity (0.83, 95% CI: [0.50–1.00]) and specificity (0.91, 95% CI: [0.82–0.98]) in the validation cohort, and outperformed models incorporating occipital alpha powers alone or cognitive scores alone.

Conclusions: Whilst the sample size is small and findings require confirmation in larger studies, our results suggest that the thalamocortical circuit exhibits different EEG patterns under stressors, with occipital alpha powers potentially reflecting baseline vulnerabilities.

Keywords: postoperative delirium; machine learning; resting-state EEG; Montréal Cognitive Assessment; alpha powers

Key Points

- Predict postoperative delirium using pre-operative EEG alpha power and MoCA scores.
- Prediction performance improves over cognitive assessment alone.
- ROC-AUC, specificity, accuracy >90% and sensitivity >80%, in a validation cohort.
- Abnormalities in baseline EEG are a risk factor for postoperative delirium.

Introduction

Delirium is a complex neuropsychiatric syndrome that is characterised by an acute, fluctuating disturbance in attention, level of consciousness and cognition [1]. Postoperative delirium is a common complication in older adults after surgery, occurring in 19%–32% of patients [2], and is associated with longer ICU and hospital stay, increased post-discharge institutionalisation, persistent cognitive decline and increased short- and long-term mortality [3–7]. Postoperative delirium has an estimated annual healthcare cost of over $30 billion in the USA alone [8].

Early and accurate identification of individuals at high risk could enable interventions to reduce the incidence, severity and duration of postoperative delirium. Such interventions might include a careful evaluation of the risk–benefit ratio for surgery; enabling brain health optimisation prior to surgery e.g. via elimination of medications that increase delirium risk or through pre-operative transcranial direct current stimulation [9]; modification of intraoperative anaesthesia [10]; postoperative treatment with acetaminophen [11]; and through targeted implementation of more intensive behavioural protocols before and after the surgery (e.g. the ABCDEF Bundle [12] and HELP [13, 14]). Many studies have shown that preoperative cognitive impairment is a strong predictor of postoperative delirium [15, 16]. Other risk factors include age, history of alcohol abuse, history of smoking, medical comorbidity and pre-existing impairment in activities of daily living [17, 18]. However, whilst these risk factors increase delirium risk at the group level, there are limited clinically useful tools to predict delirium at the individual level. Furthermore, despite studies linking abnormalities in cerebral oscillatory activity with delirium [19], the specific mechanisms by which risk factors for delirium are related to the underlying brain dysfunction and subsequent delirium symptoms are still not fully understood.

Whilst the aetiology of postoperative delirium is commonly accepted to be multifactorial [17], one ongoing theory is that baseline vulnerabilities or cognitive functions may play a larger role than anaesthetic or sedative depth in postoperative delirium [20]. In line with this theory, in a neurophysiological model of delirium [21], delirium is the result of impaired cognitive functions in individuals with pre-existing impairments in brain connectivity and plasticity exposed to a stressor, such as surgery. As such, EEG, a neuroimaging technology capable of measuring cortical connectivity, plasticity and impairment in cognitive functioning, is commonly used to study delirium [22]. EEG slowing, a shift in EEG spectral power from high frequency to low-frequency, has been reported in subjects with delirium [23–26]. EEG recorded during the intraoperative period also showed that lower frontal alpha powers are associated with baseline cognitive impairment [19, 27] and up to a 4-fold increase in delirium risk [28, 29]. Another EEG biomarker is based on modelling EEG power spectral density (PSD) as a combination of periodic and aperiodic components (FOOOF), with studies showing lower aperiodic offset correlated with postoperative delirium during anaesthesia [30] and emergence from anaesthesia [31]. So far, however, these findings have not been reported for the relationship between preoperative EEG and postoperative delirium. However, there are preliminary associations between preoperative resting-state EEG (rsEEG) power ratios and postoperative delirium [32–34].

Based on the conceptual model of delirium [21] and the studies described above, we hypothesised that machine learning applied to preoperative resting-state EEG features and baseline measures of cognitive function can both predict individual postoperative delirium risk and identify subclinical neurophysiological changes that may play a crucial role in the neuropathology of postoperative delirium. A range of models were developed based on both exploratory approach and a priori hypotheses approach based on both intraoperative period and during episode of delirium. We evaluated a range of models in one prospective cohort of older adults undergoing elective surgery, and the best-performing model was subsequently validated in a second independent prospective cohort of older adults undergoing surgery at another institution. We also assessed whether models combining EEG and cognitive function performed better than those using either EEG or cognitive testing alone.

Materials and method

Participants

The dataset from Successful Ageing after Elective Surgery renewal (SAGES II, NIH-NIA P01AG031720) study [35], a prospective observational cohort study of older adults scheduled for major elective non-cardiac surgery, was used for the model selection process. After rejecting ineligible participants, the analysis sample consists of 85 participants, 12 of whom developed postoperative delirium. Demographic and clinical information for the analytic sample is presented in Supplementary Table S1 (see Supplementary Table S3 for the excluded cohort). Written informed consent for study participation was obtained from all participants according to procedures approved by the institutional review boards of Beth Israel Deaconess Medical Center, Brigham and Women's Hospital and the Brigham and Women's Faulkner Hospital—the study hospitals, and Hebrew SeniorLife—the study coordinating center, all located in Boston, Massachusetts.

The dataset used for model validation is from Investigating Neuroinflammation Underlying Postoperative Cognitive Dysfunction (INTUIT) [36, 37], also a prospective observational cohort study registered on clinicaltrials.gov (NCT03273335). After rejecting ineligible participants, the analysis sample consists of 51 participants, 6 of whom developed postoperative delirium. Demographic and clinical information for this 51 patient cohort from the INTUIT/PRIME study is presented in Supplementary Table S2 (and Supplementary Table S4 for the excluded cohort). Written informed consent was obtained from all participants. The study was approved by Duke University Health System Institutional Review Board.

Clinical assessments

For the SAGES Study, delirium was assessed daily with the Confusion Assessment Method (CAM) long-form post-surgery, usually late morning. CAM is a standardised and internationally accepted tool that enables non-psychiatrically trained clinicians to identify and recognise delirium quickly and accurately in both clinical and research settings (sensitivity 94%–100%, specificity 90%–95%, interrater reliability 84%–100%) [38]. Baseline cognitive function was assessed with The Montréal Cognitive Assessment (MoCA, range 0–30, 0 = most impaired) [39]. MoCA were conducted either through video call over Zoom [40] or face-to-face in the patient's place of residence prior to surgery. Because the MoCA was administered after other neuropsychological assessments, the memory subdomain test of MoCA was corrected for possible interference effect from the previous memory tests.

For the INTUIT/PRIME Study, a short form of CAM, called the 3D-CAM, was used to identify delirium. It was assessed twice daily, one in the morning between 7 and 9 am, and another between 4 and 6 pm, by research staffs (see Supplementary Materials). The 3D-CAM has excellent overall agreement with the long-form CAM [41]. The Mini-Mental Status Examination (MMSE) was used in the INTUIT/PRIME study for assessment of baseline cognitive function (range 0–30, 0-most impaired). The MMSE was converted to MoCA scores based on an established cross-walk (sensitivity analysis showed stable scoring for MMSE $\geq$10) [42]. Since one MMSE score can be mapped to multiple MoCA scores, the median of multiple MoCA scores was used for our study following recommended conversion procedures (see Supplementary Table S5 for the conversion table).

EEG data collection & processing and analysis

EEG data collection and processing details are in the Supplementary Materials, including Supplementary Figure S1.

Features and transformation

EEG spectral power ratio (SPR) [23, 24], defined as (alpha+beta power)/(delta+theta power), frontal alpha relative powers [28, 29] and frontal FOOOF-modelling [30, 31], were hypothesised a priori to predict postoperative delirium. SPRs from all 59 channels in both eye conditions, plus MoCA, make up the SPR Feature Set. Relative alpha powers from Fp1, Fp2, F7 and F8 channels in both eye conditions, plus MoCA, make up the Frontal Alpha Powers Set. Relative alpha powers, offset and exponents from Fp1, Fp2, F7 and F8 channels in eyes-closed condition, plus MoCA, make up the FOOOF Set. In addition, for the preliminary data exploration on the SAGES cohort (Figure 1A), we systematically examined relative EEG spectral powers of several different frequency bands as well as ratios of frequency band powers from different regions of interest (ROIs) (Supplementary Table S6). Through this process, relative alpha powers (8–12 Hz) from the occipital region were identified as promising candidates for further analysis and model development. The feature set with the transformed occipital alpha powers and MoCA, with a total of 7 features, will be referred to throughout this paper as the Principal Feature Set, where the transformation is commonly used to separate two groups with similar means but different variances, and improve the predictive performance. More information, including transformation, is in the Supplementary Materials.

ML models and cross-validation

The SAGES cohort was used for the model selection step (Figure 1B). During the model selection step, the SAGES Data Set was cross-validated using 10 repetitions of 5-fold stratified CV (Figure 1D). The 95% confidence intervals were estimated using the student's t-distribution using the sample mean and standard deviation of 50 folds. The models were assessed with 8 metrics: accuracy, sensitivity, specificity, f1-score, area under the curve of the receiver operating characteristic curve (ROC-AUC), precision-recall curve (PR-AUC) and positive predictive value (PPV, also known as precision) and negative predictive value (NPV). To prioritise the minority class (delirium), f1-score was chosen as the deciding factor, defined as $\left(F_1 = \frac{2TP}{2TP+FP+FN} \right)$, (TP = true positive, FP = false positive, FN = false negative, positive case is defined as having delirium). The INTUIT/PRIME cohort was used for the model validation (Figure 1C). For the model validation step, the best performing model from the model selection step was chosen based on f1-score, retrained on the entire SAGES Data Set, and model parameters were then fixed and tested on the entire INTUIT/PRIME Data Set. Bootstrapping was used to compute the 95% confidence intervals, where the test set (INTUIT/PRIME Data Set) was re-sampled 2000 times, with each re-sampling set stratified to the class proportions of the original sample.

Feature importance

To quantify the contribution of each feature to the model's performance, feature importances are computed using permutation importance. It works by randomly shuffling the values of a single feature and observing the resulting change in the model's performance. To handle correlated features, only 3 uncorrelated features are tested (MoCA and alpha powers from POz channel in EO and EC conditions).

Result

Scatterplots of the untransformed (left panel) and transformed (right panel) resting state relative alpha powers from the O2 channel are shown in Figure 2. In the untransformed samples, the control group (blue) has similar means but much larger variances than the delirium group (purple) in both data sets and eye conditions, with no significant differences between groups. The variances of both SAGES and INTUIT/PRIME samples are remarkably similar within the same eye conditions and groups, suggesting that the EEG quality is consistent across both studies. After transformation, all of the group contrasts are significant (two-sample two-tailed Welch's t-test, $\alpha < 0.05$). Findings are similar for the resting state alpha powers in the other channels in the occipital region (Supplementary Figures S2 and S3). Whilst the alpha peaks for the O2 channel in both SAGES and INTUIT/PRIME Data Sets are consistent across both data sets within the same eye conditions and groups, the distributions of the powers within the delta, theta and beta frequency ranges are not consistent (Figure 3). Similar findings arise in O1 and POz channels (Supplementary Figures S4 and S5, respectively).

The cross-validation results of SAGES Data Set of the SPR Feature Set, Frontal Alpha Powers Set, FOOOF Set and the Principal Feature Set are shown in Supplementary Figure S6 and Supplementary Table S7. Out of the 36 models tested, linear discriminant analysis with Ledoit-Wolf estimator (LDA LW) model based on the Principal Feature Set has the highest f1-score (mean ± 95% confidence interval: 0.57 ± 0.07, sensitivity: 0.54 ± 0.08, specificity: 0.94 ± 0.02, ROC-AUC: 0.80 ± 0.04). With the Principal Feature Set selected, when retraining and then testing the LDA LW model on the entire INTUIT/PRIME Data Set (Figure 4A and Supplementary Table S7), the f1-score is 0.67 (95% CI [0.43, 0.92]), sensitivity and specificity are 0.83 (95% CI [0.50, 1.00]) and 0.91 (95% CI [0.82, 0.98]), respectively. The ROC and precision-recall curves are shown in Figure 4B and C. Their AUCs are 0.94, 95% CI [0.87, 0.99] and 0.70, 95% CI [0.46, 0.95], respectively. The 95% confidence intervals of all of its metrics are above chance levels (dark horizontal bars of Figure 4A). The feature importance result (Supplementary Figure S7) showed that MoCA has the highest contribution to the predictive performance, followed by alpha powers of POz channel in EO condition and EC condition. Importantly, none of the features have negative impact on the performance. Since LDA LW is a linear classifier trained on only 7 features, the risk of overfitting remains low. When compared to MoCA-Alone (Table 1), the Principal Feature Set outperformed MoCA alone in all metrics except for sensitivity (tied at 0.83). MoCA-Alone yielded sensitivity, specificity and ROC-AUC of 0.83 (95% CI [0.50, 1.00]), 0.80 (95% CI [0.67, 0.91]), 0.91 (95% CI [0.81, 0.98]) respectively. The biggest improvements from MoCA-Alone to the Principal Feature Set lie in PPV (0.20 increase) and specificity (0.11 increase). When compared to Alpha-Powers-Alone (Table 1), Alpha-Powers-Alone has

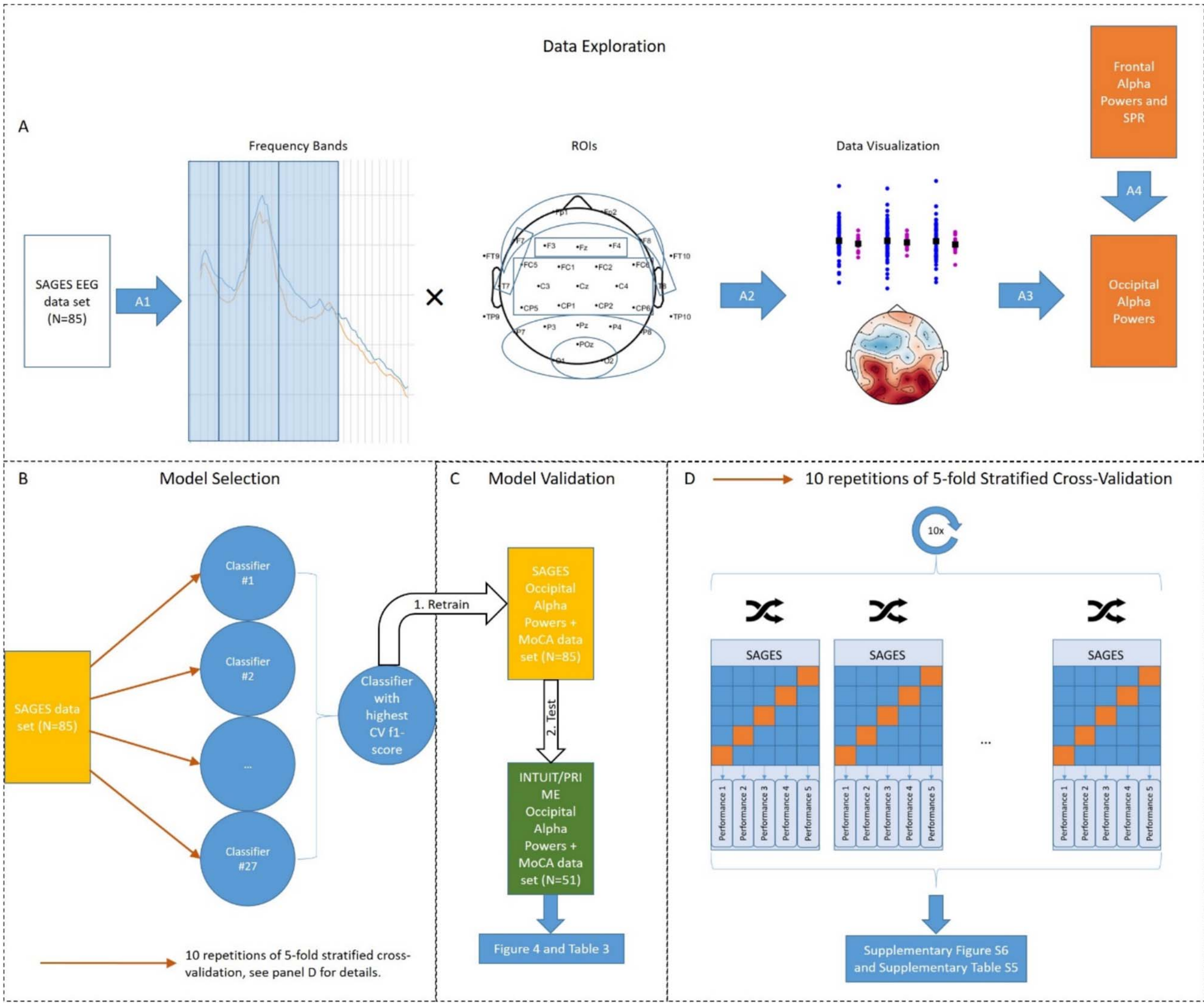

Figure 1. Schematic diagram of machine learning framework. (A) Data exploration. (A1) different band powers of different regions of interested (ROIs) were extracted from SAGES EEG Data Set. (A2) the results are visualised using scatter plots as well as EEG topographic plots. (A3) occipital alpha powers (and sub-alpha powers) from both eyes-open and eyes-closed condition was selected. Baseline cognition (MoCA) was selected a priori. (B) Model Selection. The feature sets consisting of EEG alpha (and sub-alpha) powers determined from data exploration (A), along with MoCA selected a priori, were tested using nine different classifiers using cross-validation (arrows). The details of the cross-validation is shown in (D). (C) After the classifier with the highest f1-score is determined in model selection step, the classifier was re-trained on the entire SAGES Data Set, then the parameters of the classifier were held fixed and independently validated on INTUIT/PRIME Data Set. The results are plotted in Figure 4 and tabulated in Table 1. (D) Details of the cross-validation used in model selection step. The CV performance are plotted in Supplementary Figure S6 and Supplementary Table S7.

very skewed performance between sensitivity (0.17, 95% CI [0, 0.50]) and specificity (1.00, 95% CI [1.00, 1.00]). Alpha-Powers-Alone's ROC-AUC is 0.77, 95% CI [0.57, 0.94].

Discussion

Using preoperative rsEEG and baseline cognitive functions collected from two independent cohorts of older adults undergoing elective surgeries, we trained and tested machine learning models to assess their performance in predicting post-operative delirium. In the model selection step, the Principal Feature Set, consisting of resting state EEG occipital relative alpha powers and baseline MoCA scores outperformed the SPR Feature Set and the Frontal Alpha Powers Set in the cross-validation of the SAGES Data Set. Using the Principal Feature Set, LDA LW, the model with the highest f1-score was selected and retrained on the entire SAGES Data Set and with the model parameters fixed, tested on an independently collected cohort, the INTUIT/PRIME Data Set. In the INTUIT/PRIME Data

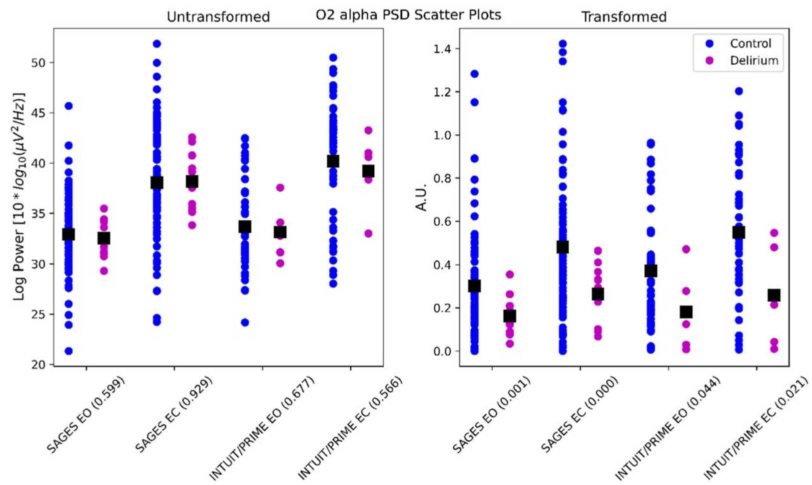

Figure 2. Scatter plots of individual EEG alpha powers in O2 channel. Scatter plot showing distributions of alpha powers in participants with post-operative delirium (dots on the right side) and without delirium (dots on the left side). Squares represent the mean of their respective groups. Left panel shows the untransformed alpha powers as seen in PSD plots (Figure 3) and right panel shows transformed alpha powers. Values enclosed in parentheses in the x axis represent the *P*-values of two-sample two-tailed Welch's t-test. This channel is representative of all channels in the occipital region and their scatter plots can be found in the Supplementary Figures S2 and S3.

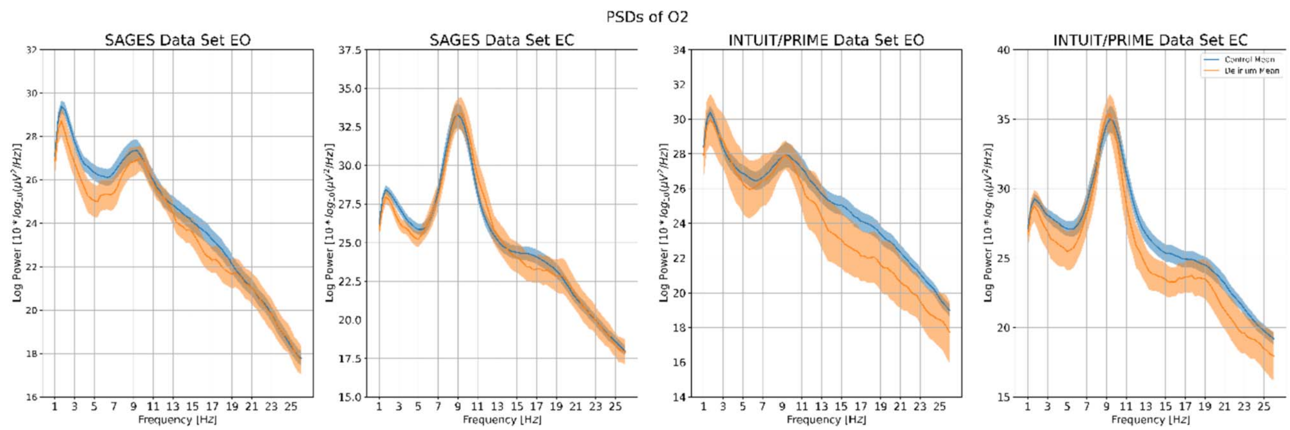

Figure 3. Power spectral densities of O2 channel. Power spectral densities of O2 channel from both SAGES and INTUIT/PRIME Data Sets in both eyes-open (EO) and eyes-closed (EC) conditions for [1, 26] Hz frequency range. Shaded regions represent standard error of the means. Blue represents control group and orange represents delirium group. PSDs for O1 and POz are shown in Supplementary Figures S4 and S5, respectively.

Set, LDA LW yielded ≥0.9 in accuracy, specificity and ROC-AUC and ≥ 0.8 in sensitivity. Importantly, it substantially outperformed MoCA-Alone, with the biggest improvements in PPV (0.20 increase) and specificity (0.11 increase). Whilst our limited sample sizes suggested caution, our results nevertheless support the theory that baseline vulnerability may play a major role in postoperative delirium and that occipital relative alpha powers are associated with baseline vulnerability [20, 21, 32].

The predictive performance seen above can be attributed to the difference in the variances of the resting state occipital relative alpha powers. One possible interpretation of the differences in the variances is that individuals within the control group exhibit greater fluctuation in the EEG powers over time relative to the delirium group and the greater fluctuation could be an indirect indication of cortical connectivity and plasticity [43]. Thus, greater fluctuation over time from one healthy individual could be translated to greater fluctuation across multiple healthy individuals from a fixed time point, relative to individuals with postoperative delirium. Whilst the variances of relative alpha power over time within one resting state recording session didn't show strong predictive performance for delirium (results not shown), we hypothesised that the variance over much longer range of time might better measure the integrity of cortical circuits. Indeed, one recent study found that patients without POD had fluctuations in the PSD during emergence from anaesthesia, whereas patients with POD exhibit nearly

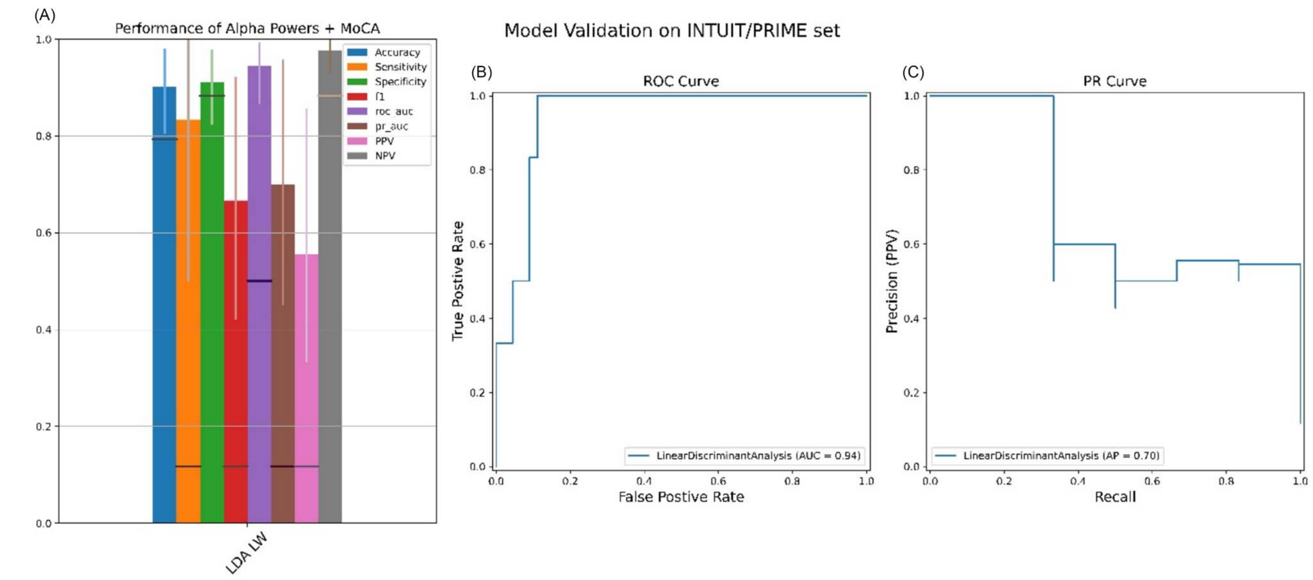

Figure 4. Model validation: performances using the Principal Feature Set (Alpha Powers + MoCA). (A) The performance of the model (LDA LW) selected from the model selection step. 95% confidence intervals are shown as thin vertical bars. Chance levels for each metric are shown as dark horizontal lines (details of chance levels in Supplementary Materials). Blue: accuracy, orange: sensitivity, green: specificity, red: f1 score, purple: AUC of ROC curve, brown: AUC of precision-recall curve, pink: positive predictive value (PPV, also known as precision), grey: negative predictive value (NPV). Values are tabulated in Table 1. ROC (B) and PR (C) curves are shown for the selected LDA LW model. The AUCs reported as mean and 95% CI are 0.94 [0.86, 0.99] for the ROC curve and 0.70 [0.44, 0.95] for the PR curve.

Table 1. Performances of (A) principal feature set (alpha-powers + MoCA), (B) MoCA-alone and (C) alpha-powers-alone on INTUIT/PRIME data set. Ranges enclosed in brackets represent 95% confidence intervals.

				A) Principal Feature Set (Alpha-Powers + MoCA)				
	Accuracy	Sensitivity	Specificity	F1	ROC AUC	PR AUC	PPV	NPV
LDA LW	0.90 [0.80, 0.98]	0.83 [0.50, 1.00]	0.91 [0.82, 0.98]	0.67 [0.43, 0.91]	0.94 [0.86, 0.99]	0.70 [0.44, 0.95]	0.56 [0.33, 0.86]	0.98 [0.93, 1.00]
				B) MoCA Alone				
	Accuracy	Sensitivity	Specificity	F1	ROC AUC	PR AUC	PPV	NPV
LDA LW	0.80 [0.69, 0.90]	0.83 [0.50, 1.00]	0.80 [0.67, 0.91]	0.50 [0.31, 0.71]	0.91 [0.81, 0.98]	0.54 [0.30, 0.88]	0.36 [0.21, 0.56]	0.97 [0.92, 1.00]
				C) Alpha-Powers Alone				
	Accuracy	Sensitivity	Specificity	F1	ROC AUC	PR AUC	PPV	NPV
LDA LW	0.90 [0.88, 0.94]	0.17 [0.00, 50]	1.00 [1.00, 1.00]	0.29 [0.00, 0.67]	0.77 [0.57, 0.94]	0.53 [0.21, 0.87]	1.00 [0.00, 1.00]	0.90 [0.88, 0.94]

constant PSD over the same period [31]. This could be tested with a longitudinal study with repeated measurements from the same individuals.

One recurring and consistent finding of EEG during episodes of delirium is the EEG slowing (decrease in SPR) [29, 44]. One consistent finding in the intraoperative setting is the association between lower frontal alpha powers [29] or lower aperiodic offset parameter [30] and postoperative delirium. However, we find that in the preoperative setting, EEG slowing, frontal alpha powers and FOOOF modelling all do not have the same predictive performance as occipital alpha powers. The link between occipital alpha powers and delirium is not new; most studies evaluating alpha activity during delirium have reported lower occipital alpha powers in patients with delirium compared to controls [26, 44, 45], although a few studies reported the opposite pattern [26, 34]. Furthermore, both Ostertag et al. [31] and Tanabe et al. [34] showed that the healthy control group showed significant changes in *frontal* alpha powers (decrease over the course of emergence from anaesthesia and increase between pre- and postoperative periods, respectively) whereas the delirium group showed no change in frontal alpha powers. Furthermore, Tanabe et al. [34] showed that the delirium group showed a significant decrease in *occipital* alpha powers between pre- and postoperative periods, whereas the control group showed no change in occipital alpha powers in the same period. More studies focusing on the temporal evolution of EEG band powers are needed to better understand the changes in spectral dynamics over time. Finally, another study showed that the significant decrease in intraoperative alpha powers observed in postoperative/subsyndromal delirium group versus healthy control group is independent of anaesthetic dose [29], supporting the idea that baseline vulnerabilities or cognitive impairment have greater influence on postoperative delirium than anaesthetic or sedative depths. Whilst the connection between EEG slowing during delirium, lower frontal alpha powers and lower aperiodic offset parameter during surgery, and the restricted range of occipital alpha powers observed preoperatively here is unclear, one possibility is that the thalamocortical connectivity responsible for the generation of the alpha rhythm in the occipital regions in the awake state [26, 34, 44, 45], and in frontal regions during anaesthesia [17], is particularly susceptible to different breakdowns during different stressors. If true, this implies that thalamocortical connectivity is a measure of baseline vulnerability, which, in turn, plays a bigger role in postoperative delirium than other factors and would explain the failure of studies targeting depth-of-anaesthesia to reduce the risk of post-operative delirium [29, 46]. Additionally, this could support the thalamocortical dysrhythmia hypothesis [47]. More research is needed to better understand the connection.

One main limitation of this study is the difference in the predictive performance in the SAGES and INTUIT/PRIME cohorts, especially in the sensitivity metric. One possible explanation is that the rsEEG for the INTUIT/PRIME cohort was recorded on the same day of the surgery, whereas the rsEEG for the SAGES cohort was recorded at least 2–3 days in advance of scheduled surgeries. Another possibility is that sub-types of anaesthesia and surgery types could affect the model performance. Another main limitation is the relatively small sizes of the training set (SAGES) and especially the test set (INTUIT/PRIME). The confidence intervals of sensitivity and precision are wide (Table 1) but are still above chance levels. A larger sample size is needed to confirm our findings. The third limitation is that the preprocessing of rsEEG involved manual rejection of ICA components, which can introduce subjectivity. In this study, we purposely focused on a limited feature set (spectral band power) that is simple, easy to calculate, well-established and has high test–retest reliability. However, this omits potentially informative temporal features such as alpha burst variability, and more explicit measures of functional connectivity between brain regions [43]. Indeed, several past studies showed that alpha band connectivity may play a role in the aetiology of delirium, with most studies showing decreases in functional connectivity in delirium group [48]. In contrast, Tanabe et al. [34] found that there was higher preoperative connectivity (weighted phase lag index) in the delirium group, suggesting that different connectivity measures may have varying results. Future studies could explore integration of these more complex and potentially informative features.

In conclusion, machine learning methods utilising preoperative rsEEG and MoCA features can predict postoperative delirium with performance and confidence intervals above chance-levels across all metrics. These findings suggest that pre-operative rsEEG can identify subclinical neurophysiological changes that may play a crucial role in the neuropathology of postoperative delirium. Independent confirmation in a larger sample size and with prospective application is needed to validate our proposals, and to potentially improve model performance by incorporation of measures of functional connectivity.

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Supplementary Data: Supplementary data is available at *Age and Ageing* online.

Declaration of Conflicts of Interest: Dr. E. Santarnecchi serves on the scientific advisory boards for BottNeuro, which has no overlap with present work; and is listed as an inventor on several issued and pending patents on brain stimulation solutions to diagnose or treat neurodegenerative disorders and brain tumours. Dr. A. Pascual-Leone is a co-founder of Linus Health and TI Solutions AG which have no overlap with present work. He serves on the scientific advisory boards for the ACE Foundation and the IT'IS Foundation, Neuroelectrics, TetraNeuron, Skin2Neuron, MedRhythms and Magstim Inc; and is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging, applications of noninvasive brain stimulation in various neurological disorders, as well as digital biomarkers of cognition and digital assessments for early diagnosis of dementia. Dr. M Berger has received private legal consulting fees related to perioperative neurocognitive disorders.

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Data Availability: Analysis codes are available on https://github.com/bacnbs/sages2_repo. Data will be available soon.

References

1. American Psychiatric Association, American Psychiatric Association, eds. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th edition. Washington, D.C: American Psychiatric Association, 2013.
2. Yan E, Veitch M, Saripella A *et al.* Association between postoperative delirium and adverse outcomes in older surgical patients: a systematic review and meta-analysis. *J Clin Anesth* 2023;**90**:111221. https://doi.org/10.1016/j.jclinane.2023.111221.
3. Dolan MM, Hawkes WG, Zimmerman SI *et al.* Delirium on hospital admission in aged hip fracture patients: prediction of mortality and 2-year functional outcomes. *J Gerontol A Biol Sci Med Sci* 2000;**55**:M527–34. https://doi.org/10.1093/gerona/55.9.M527.
4. Ely EW, Shintani A, Truman B *et al.* Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;**291**:1753–62. https://doi.org/10.1001/jama.291.14.1753.
5. Ouimet S, Kavanagh BP, Gottfried SB *et al.* Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med* 2007;**33**:66–73. https://doi.org/10.1007/s00134-006-0399-8.
6. Ní Chróinín D, Francis N, Wong P *et al.* Older trauma patients are at high risk of delirium, especially those with underlying dementia or baseline frailty. *Trauma Surg Acute Care Open* 2021;**6**:e000639. https://doi.org/10.1136/tsaco-2020-000639.
7. Sanchez D, Brennan K, Al Sayfe M *et al.* Frailty, delirium and hospital mortality of older adults admitted to intensive care: the delirium (deli) in ICU study. *Crit Care* 2020;**24**:609. https://doi.org/10.1186/s13054-020-03318-2.
8. Gou RY, Hshieh TT, Marcantonio ER *et al.* One-year Medicare costs associated with delirium in older patients undergoing major elective surgery. *JAMA Surg* 2021;**156**:462–42. https://doi.org/10.1001/jamasurg.2020.7260.
9. Tao M, Zhang S, Han Y *et al.* Efficacy of transcranial direct current stimulation on postoperative delirium in elderly patients undergoing lower limb major arthroplasty: a randomized controlled trial. *Brain Stimul* 2023;**16**:88–96. https://doi.org/10.1016/j.brs.2023.01.839.
10. Weinstein SM, Poultsides L, Baaklini LR *et al.* Postoperative delirium in total knee and hip arthroplasty patients: a study of perioperative modifiable risk factors. *Br J Anaesth* 2018;**120**:999–1008. https://doi.org/10.1016/j.bja.2017.12.046.
11. Subramaniam B, Shankar P, Shaefi S *et al.* Effect of intravenous acetaminophen vs placebo combined with propofol or dexmedetomidine on postoperative delirium among older patients following cardiac surgery: the DEXACET randomized clinical trial. *JAMA* 2019;**321**:686–96. https://doi.org/10.1001/jama.2019.0234.
12. Marra A, Ely EW, Pandharipande PP *et al.* The ABCDEF bundle in critical care. *Crit Care Clin* 2017;**33**:225–43. https://doi.org/10.1016/j.ccc.2016.12.005.
13. Inouye SK, Bogardus ST, Charpentier PA *et al.* A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;**340**:669–76. https://doi.org/10.1056/NEJM199903043400901.
14. Inouye SK, Bogardus ST, Baker DI *et al.* The hospital elder life program: a model of care to prevent cognitive and functional decline in older hospitalized patients. Hospital elder life program. *J Am Geriatr Soc* 2000;**48**:1697–706.
15. Wong CK, van Munster BC, Hatseras A *et al.* Head-to-head comparison of 14 prediction models for postoperative delirium in elderly non-ICU patients: an external validation study. *BMJ Open* 2022;**12**:e054023. https://doi.org/10.1136/bmjopen-2021-054023.
16. Cizginer S, Marcantonio E, Vasunilashorn S *et al.* The cognitive reserve model in the development of delirium: the successful aging after elective surgery study. *J Geriatr Psychiatry Neurol* 2017;**30**:337–45. https://doi.org/10.1177/0891988717732152.
17. Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. *Dement Geriatr Cogn Disord* 1999;**10**:393–400. https://doi.org/10.1159/000017177.
18. Bellelli G, Brathwaite JS, Mazzola P. Delirium: a marker of vulnerability in older people. *Front Aging Neurosci* 2021;**13**:626127. https://doi.org/10.3389/fnagi.2021.626127.
19. Giattino CM, Gardner JE, Sbahi FM *et al.* Intraoperative frontal alpha-band power correlates with preoperative neurocognitive function in older adults. *Front Syst Neurosci* 2017;**11**:24. https://doi.org/10.3389/fnsys.2017.00024.
20. Pandharipande PP, Whitlock EL, Hughes CG. Baseline vulnerabilities may play a larger role than depth of Anesthesia or sedation in postoperative delirium. *Anesthesiology* 2021;**135**:940–2. https://doi.org/10.1097/ALN.0000000000004039.
21. Shafi MM, Santarnecchi E, Fong TG *et al.* Advancing the neurophysiological understanding of delirium. *J Am Geriatr Soc* 2017;**65**:1114–8. https://doi.org/10.1111/jgs.14748.
22. Sanders RD, Watne L, Roberson SW *et al.* International Delirium Pathophysiology & Electrophysiology Network for data sharing (iDEPEND). *BJA Open* 2024;**11**:100304. https://doi.org/10.1016/j.bjao.2024.100304.
23. Zisook S, Braff DL. Delirium: recognition and management in the older patient. *Geriatrics* 1986;**41**:67–78.
24. Koponen H, Partanen J, Pääkkönen A *et al.* EEG spectral analysis in delirium. *J Neurol Neurosurg Psychiatry* 1989;**52**:980–5. https://doi.org/10.1136/jnnp.52.8.980.
25. Boord MS, Moezzi B, Davis D *et al.* Investigating how electroencephalogram measures associate with delirium: a systematic review. *Clin Neurophysiol* 2021;**132**:246–57. https://doi.org/10.1016/j.clinph.2020.09.009.

26. Wiegand TLT, Rémi J, Dimitriadis K. Electroencephalography in delirium assessment: a scoping review. *BMC Neurol* 2022;**22**:86. https://doi.org/10.1186/s12883-022-02557-w.
27. Koch S, Feinkohl I, Chakravarty S *et al.* Cognitive impairment is associated with absolute intraoperative frontal α-band power but not with baseline α-band power: a pilot study. *Dement Geriatr Cogn Disord* 2019;**48**:83–92. https://doi.org/10.1159/000502950.
28. Cooter Wright M, Bunning T, Eleswarpu SS *et al.* A processed electroencephalogram-based brain Anesthetic resistance index is associated with postoperative delirium in older adults: a dual Center study. *Anesth Analg* 2022;**134**:149–58. https://doi.org/10.1213/ANE.0000000000005660.
29. Gutierrez R, Egaña JI, Saez I *et al.* Intraoperative low alpha power in the electroencephalogram is associated with postoperative subsyndromal delirium. *Front Syst Neurosci* 2019;**13**:56. https://doi.org/10.3389/fnsys.2019.00056.
30. Pollak M, Leroy S, Röhr V *et al.* Electroencephalogram biomarkers from Anesthesia induction to identify vulnerable patients at risk for postoperative delirium. *Anesthesiology* 2024;**140**:979–89. https://doi.org/10.1097/ALN.0000000000004929.
31. Ostertag J, Engelhard A, Nuttall R *et al.* Development of Postanesthesia care unit delirium is associated with differences in aperiodic and periodic alpha parameters of the electroencephalogram during emergence from general Anesthesia: results from a prospective observational cohort study. *Anesthesiology* 2024;**140**:73–84. https://doi.org/10.1097/ALN.0000000000004797.
32. Acker L, Wong MK, Wright MC *et al.* Preoperative electroencephalographic alpha-power changes with eyes opening are associated with postoperative attention impairment and inattention-related delirium severity. *Br J Anaesth* 2024; **132**:154–63. https://doi.org/10.1016/j.bja.2023.10.037.
33. Kim J, Park S, Kim K-N *et al.* Resting-state prefrontal EEG biomarker in correlation with postoperative delirium in elderly patients. *Front Aging Neurosci* 2023;**15**:1224264. https://doi.org/10.3389/fnagi.2023.1224264.
34. Tanabe S, Mohanty R, Lindroth H *et al.* Cohort study into the neural correlates of postoperative delirium: the role of connectivity and slow-wave activity. *Br J Anaesth* 2020;**125**:55–66. https://doi.org/10.1016/j.bja.2020.02.027.
35. Ward M, Hshieh TT, Schmitt EM *et al.* Successful aging after elective surgery II: study cohort description. *J Am Geriatr Soc* 2024;**72**:209–18. https://doi.org/10.1111/jgs.18627.
36. Berger M, Oyeyemi D, Olurinde MO *et al.* The INTUIT study: investigating neuroinflammation underlying postoperative cognitive dysfunction. *J Am Geriatr Soc* 2019;**67**:794–8. https://doi.org/10.1111/jgs.15770.
37. Whitson HE, Crabtree D, Pieper CF *et al.* A template for physical resilience research in older adults: methods of the PRIME-KNEE study. *J Am Geriatr Soc* 2021;**69**:3232–41. https://doi.org/10.1111/jgs.17384.
38. Inouye SK, van Dyck CH, Alessi CA *et al.* Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;**113**:941–8. https://doi.org/10.7326/0003-4819-113-12-941.
39. Nasreddine ZS, Phillips NA, Bédirian V *et al.* The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;**53**:695–9. https://doi.org/10.1111/j.1532-5415.2005.53221.x.
40. Joffe Y, Liu J, Arias F *et al.* Adaptation, calibration, and validation of a cognitive assessment battery for telephone and video administration. *J Am Geriatr Soc* 2025;**73**:482–91. https://doi.org/10.1111/jgs.19275.
41. Marcantonio ER, Ngo LH, O'Connor M *et al.* 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. *Ann Intern Med* 2014;**161**:554–61. https://doi.org/10.7326/M14-0865.
42. Saczynski JS, Inouye SK, Guess J *et al.* The Montreal cognitive assessment: creating a crosswalk with the mini-mental state examination. *J Am Geriatr Soc* 2015;**63**:2370–4. https://doi.org/10.1111/jgs.13710.
43. Deco G, Jirsa VK, McIntosh AR. Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nat Rev Neurosci* 2011;**12**:43–56. https://doi.org/10.1038/nrn2961.
44. Guay CS, Kafashan M, Huels ER *et al.* Postoperative delirium severity and recovery correlate with electroencephalogram spectral features. *Anesth Analg* 2023;**136**:140–51. https://doi.org/10.1213/ANE.0000000000006075.
45. Thomas C, Hestermann U, Walther S *et al.* Prolonged activation EEG differentiates dementia with and without delirium in frail elderly patients. *J Neurol Neurosurg Psychiatry* 2008;**79**:119–25. https://doi.org/10.1136/jnnp.2006.111732.
46. Brown CH, Edwards C, Lin C *et al.* Spinal Anesthesia with targeted sedation based on Bispectral index values compared with general Anesthesia with masked Bispectral index values to reduce delirium: the SHARP randomized controlled trial. *Anesthesiology* 2021;**135**:992–1003. https://doi.org/10.1097/ALN.0000000000004015.
47. Llinás RR, Ribary U, Jeanmonod D *et al.* Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci USA* 1999;**96**:15222–7. https://doi.org/10.1073/pnas.96.26.15222.
48. Hanna A, Jirsch J, Alain C *et al.* Electroencephalogram measured functional connectivity for delirium detection: a systematic review. *Front Neurosci* 2023;**17**:1274837. https://doi.org/10.3389/fnins.2023.1274837.

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