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Association between preoperative frontal electroencephalogram alpha asymmetry and postoperative quality of recovery: an observational study

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Abstract

Background: Left-sided frontal alpha asymmetry on electroencephalograms, which indicates decreased relative left-hemispheric activity, has been associated with depression, anxiety, and stress responsivity. We aimed to evaluate the association between perioperative measures of frontal alpha asymmetry and quality of recovery (QoR) after surgery.
Methods: We enrolled 110 female patients undergoing thyroidectomy and recorded perioperative electroencephalograms. The power of the prefrontal alpha band (8–13 Hz) was measured in the Fp1 and Fp2 leads. Left-sided frontal alpha asymmetry was defined as a higher alpha band power in Fp1 than in Fp2 and vice versa. QoR was assessed using the QoR-15 score on the day before surgery and postoperative days 1 and 2. The primary study endpoint was a difference in postoperative global QoR-15 score between preoperative left-sided and right-sided alpha asymmetry groups. The predictability of frontal alpha asymmetry for poor QoR-15 score was also evaluated.
Results: The global QoR-15 score showed a significant group-by-time interaction, and *post-hoc* analysis revealed significantly lower scores on postoperative days 1 ($P=0.006$) and 2 ($P<0.001$) in the left-sided frontal alpha asymmetry group. In the multivariate logistic regression analysis, preoperative left-sided frontal alpha asymmetry was associated with a 3.3-fold increased risk of the lowest tertile for the postoperative day 1 QoR-15 score (95% CI: 1.31–8.24; $P=0.011$).
Conclusions: Preoperative left-sided frontal alpha asymmetry was independently associated with a lower postoperative QoR-15 score in female patients undergoing thyroidectomy, highlighting the potential role of preoperative frontal electroencephalography in predicting patient-centred outcomes after surgery.
Clinical trial registration: KCT0006586 (http://cris.nih.go.kr/).

Keywords: alpha asymmetry; electroencephalogram; general anaesthesia; thyroidectomy; quality of recovery

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Editor's key points

- There has been no relevant biological predictor for the quality of recovery (QoR) after surgery and anaesthesia.
- Electroencephalography frontal alpha asymmetry is well known to reflect affective processing, psychological illness, and stress response.
- In female patients undergoing thyroidectomy, preoperative frontal alpha asymmetry was closely associated with QoR-15 score and independently predicted poor QoR.
- The possible mediating/moderating role of perioperative frontal alpha asymmetry in the association of clinical factors and QoR needs to be further investigated in various surgical cohorts in order to optimise perioperative care for enhancing QoR.

Patient-reported quality of recovery is an important goal in post-surgical management and anaesthesia, which once focused only on adverse events or haemodynamic stability.[1] The quality of recovery (QoR) score is the most validated measure of patient-centred outcomes and encompasses multiple dimensions of the recovery process.[1,2] However, little is known about the risk factors for poor QoR scores. Although some mental health conditions, such as depression and anxiety, influence the QoR score,[3,4] no objective and easy-to-estimate predictors have been identified.

Frontal electroencephalography (EEG) asymmetry, a measure of the difference in EEG alpha power between homologous left and right frontal electrodes, is a marker of affective processing and psychopathology.[5] Since alpha oscillation has an inhibitory influence on cortical activity,[5] left-sided frontal alpha asymmetry (FAA), which indicates higher alpha power in the left versus right frontal lobe, reflects lesser left than right cortical activity, and vice versa.[6] Left-sided FAA has been recognised as a biological marker of trait and state anxiety and depression and as a potential predictor of future development of clinically significant mental disorders.[5] More recently, FAA has been reported to reflect and/or contribute to stress responsivity processes.[7–12] A few clinical trials have demonstrated the occurrence of FAA or its changes in reaction to social, emotional, and physical challenges.[8–12] Relatively greater left frontal activation (lower alpha power) versus right, namely right-sided FAA, is associated with a healthy response or resilience.[9,11]

Despite the same surgical and anaesthetic management, patients experience varying amounts of perioperative stress, which primarily influences patient-centred outcomes. Since stress-coping capacity and emotional traits and states that determine vulnerability to perioperative stress are reflected by FAA, our primary hypothesis was that patients who present with left-sided FAA before surgery may experience poor QoR. To test this hypothesis, we aimed to compare the postoperative QoR-15 scores between patients with preoperative left- and right-sided FAA. We also evaluated the predictability of left-sided FAA for poor QoR.

Methods

This prospective observational study was approved by the Institutional Review Board of Yonsei University Health System (#3-2021-0225) and registered at the Clinical Research Information Service (http://cris.nih.go.kr, KCT0006586) before patient enrolment. After obtaining informed consent, 110 patients scheduled to undergo thyroidectomy were recruited between September 2021 and June 2022. Female patients (aged $\geq$ 19 years) with American Society of Anesthesiologists (ASA) physical status 1-2 were eligible for inclusion. The exclusion criteria were emergency surgery, haemodynamic instability, systemic infection, neurological diseases including stroke, dementia, and epilepsy, difficulty in communication due to audio-visual restrictions, illiteracy, and foreign nationality.

The day before surgery, baseline QoR-15 was determined and evaluations were performed using several validated questionnaires assessing psychosocial factors, including the Big Five Inventory (BFI),[13] Hospital Anxiety Depression Scale (HADS),[14] and the pain catastrophising scale (PCS).[15] QoR-15 evaluates five dimensions of recovery: physical comfort, physical independence, emotional state, psychological support, and pain. Each item is rated on an 11-point scale according to the frequency of the item on the questionnaire (greater score at greater frequency for positive items and lower score at lesser frequency for negative items). The global score ranges from 0 (poorest QoR) to 150 (best QoR). The BFI is a 10-question measure of five personality domains: neuroticism, extraversion, openness, conscientiousness, and agreeableness. The score for each domain ranges from 2 to 10; the higher the score, the stronger the trait. The HADS is a 14-question instrument measuring anxiety and depression, with scores ranging from 0 (no symptoms) to 21 (severest symptoms) for each subscale. The PCS is a 13-question assessment of catastrophic thinking in response to pain with three subscales: rumination, magnification, and helplessness; the score ranges for the three subscales are 0–16, 0–12, and 0–24, respectively, yielding a total score ranging from 0 (no catastrophising) to 52 (severest catastrophising).

All patients underwent standardised surgical and anaesthetic management. Surgery was performed using either open or endoscopic/robotic procedures following the patient's preference and surgeon's discretion. Anaesthesia was induced with propofol, remifentanil, and rocuronium and maintained with sevoflurane and remifentanil infusion. At the end of the surgery, 1 g of acetaminophen and 0.3 mg of ramosetron were administered for analgesia and antiemetic prophylaxis, respectively. In the post-anaesthesia care unit (PACU), fentanyl (1 $\mu g\ kg^{-1}$) and metoclopramide (10 mg) were administered to relieve pain and nausea, respectively, if the numerical rating scale score exceeded 4. On postoperative day 1 (POD1), ibuprofen (300 mg) and ramosetron (0.1 mg) were administered orally to prevent pain and nausea. If the numerical rating scale score still exceeded 4, an additional dose of ibuprofen was administered. The patients were discharged from the hospital on POD1 or POD2 at the surgeon's discretion. QoR-15 was assessed on POD1 and POD2. For patients discharged on POD1, the POD2 assessment was performed via telephone. A trained research nurse who handed out all perioperative questionnaires was blinded to the EEG data and the scores of the questionnaire items.

We collected EEG data from 20 min preoperatively to 20 min postoperatively. The data were recorded using a SEDLine monitor (Masimo, Irvine, CA, USA) with a sampling rate of 178 Hz.[16] Patients were asked to close their eyes but remain awake during EEG recordings. As per our standards, none of the patients received preoperative anxiolytics. The recordings were performed in the preoperative patient holding area and PACU, respectively. After cleansing the skin with alcohol, a 4-channel sensor was attached to the corresponding location of the patient's forehead (10–20 international system: Fp1, Fp2, F7, and F8).[16] The ground channel (CB) and reference channel (CT) were placed near Fz. The recorded EEG data were processed using MATLAB R2022a (The MathWorks, Natick, MA, USA). First, gross artefacts related to patient movement and eye blinks were removed by visual inspection. Next, a bandpass filter with a low cut-off of 1 Hz and a high cut-off of 50 Hz was applied using the fieldtrip toolbox.[17] Data points exceeding an absolute amplitude of 100 μv were removed using automatic artefact rejection. Then, 2-s length of artefact-free epochs without overlapping were collected and assembled to yield 60-s length of artefact-free epochs from preoperative and postoperative periods of EEG data. Using the Chronux toolbox, a multi-taper spectral estimation method,[18] we obtained the absolute power of the alpha frequency band (8–13 Hz), which was then transformed into dB units. A 4-channel EEG topoplot was created using the EEGLAB toolbox.[19] Major quantitative analysis was performed using only the prefrontal electrodes Fp1 and Fp2. For the group-level comparisons of spectra, we computed the 95% confidence interval (CI) of the mean power difference between Fp1 and Fp2 using a bootstrap algorithm. FAA was defined using the following equation: FAA = 10·log 10 [mean power of Fp2 (right) lead] − 10·log10 [mean power of Fp1 (left) lead]. Patients with a negative FAA value were categorised into the left-sided frontal alpha asymmetry (LFAA) group, and those with a positive value constituted the right-sided frontal alpha asymmetry (RFAA) group.

The primary study endpoint was the evaluation of the relationship between FAA and postoperative QoR-15 scores. We compared the postoperative global QoR-15 scores on POD1 and POD2 between the preoperative LFAA and RFAA groups. Next, we classified the patients according to the tertile distribution of the global QoR-15 score on POD1 and compared the incidence of preoperative LFAA and psychological test results in relation to the tertiles. Predictors for the lowest tertile group, which was regarded as having poor QoR-15 scores, were also explored. We also evaluated features of postoperative changes in FAA and their associations with QoR-15 scores.

Statistical analyses

In a pilot study of 20 patients, the ratio of preoperative LFAA to RFAA was approximately 1:3. The difference in the global QoR-15 score on POD1 was 19, with a standard deviation of 25. To achieve 90% power at a significance level of 0.05, we needed a sample size of 100. Considering a dropout rate of 10%, we enrolled 110 patients.

Intention-to-treat analysis was performed for the full analysis set, including all participants who responded to the QoR-15 questionnaires postoperatively. Continuous data were presented as the mean (SD) or median (IQR) with comparisons made using the Student's t-test or Wilcoxon rank-sum test for two groups and one-way analysis of variance or the Kruskal–Wallis test for three groups, as appropriate, based on the normality of the distribution. Categorical data are presented as the number of patients (proportion) with comparisons using the chi-square test or Fisher's exact test, as appropriate. The correlation coefficient between the global QoR-15 scores and the values of FAA was assessed by Pearson's correlation analyses. Comparison of the QoR-15 score between the LFAA and RFAA groups was analysed using the Brunner and Langer method for repeated-measures data. Post-hoc analysis with Bonferroni correction was performed to adjust for multiple comparisons. The odds ratio and 95% confidence intervals investigating the predictability of FAA for poor QoR were assessed by logistic regression. The following parameters were evaluated in the univariate model: age, body mass index, type of surgery (open or endoscopic/robotic), duration of surgery, and other perioperative factors that showed a significant difference between the lowest tertile group of the QoR-15 score and the higher tertile groups. Only significant parameters were entered into the multivariate logistic regression model. All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was defined as a two-sided P value < 0.05, except for the existence of an interaction between group and time that was tested at a significance level of 0.15.[20,21]

Results

Among the 130 patients assessed for eligibility, patients with left-handedness (n = 11) and neurologic deficits or psychological diseases (n = 9) were excluded, and the remaining 110 patients who provided consent were enrolled (Supplementary Fig.S1).

The Pearson's correlation analysis showed that the FAA value has weak positive correlations with QoR-15 scores on POD1 and POD2 and a weak negative correlation with the % decrease in score from baseline to POD1 (Fig 1). The FAA value was not correlated with the baseline score and % decrease from baseline to POD2.

Patient characteristics and perioperative data according to the dominant side of preoperative FAA (n = 32 and 78 in the LFAA and RFAA groups, respectively) are shown in Table 1. The BFI-neuroticism, HADS-depression, and PCS-helplessness scores in the preoperative psychological assessment were significantly higher in the LFAA group than in the RFAA group.

A topoplot of representative patients in the LFAA (Fig 2a) and RFAA (Fig 2b) groups clearly indicates a difference in the power spectral density of frontal cortex alpha oscillations between the groups. The global QoR-15 scores were 122 (baseline), 52 (POD1), and 104 (POD2) in the LFAA group and 127 (baseline), 113 (POD1), and 123 (POD2) in the RFAA group. Group-level topoplots are shown in Supplementary Fig. S2.

Quantitative comparison of QoR-15 scores between the LFAA and RFAA groups showed a significant group-by-time interaction in the global score (Table 2). Post-hoc analysis revealed significantly lower score both on POD1 and POD2 in the LFAA group than in the RFAA group. Decreases in the scores from the baseline values were also significantly greater in the LFAA group than in the RFAA group both on POD1 and POD2. Supplementary Table S1 shows significant group-by-time interaction in the subdimensional scores of physical comfort, physical independence, and psychological support. Post-hoc analysis revealed significantly lower emotional status on POD1 and lower physical comfort, physical

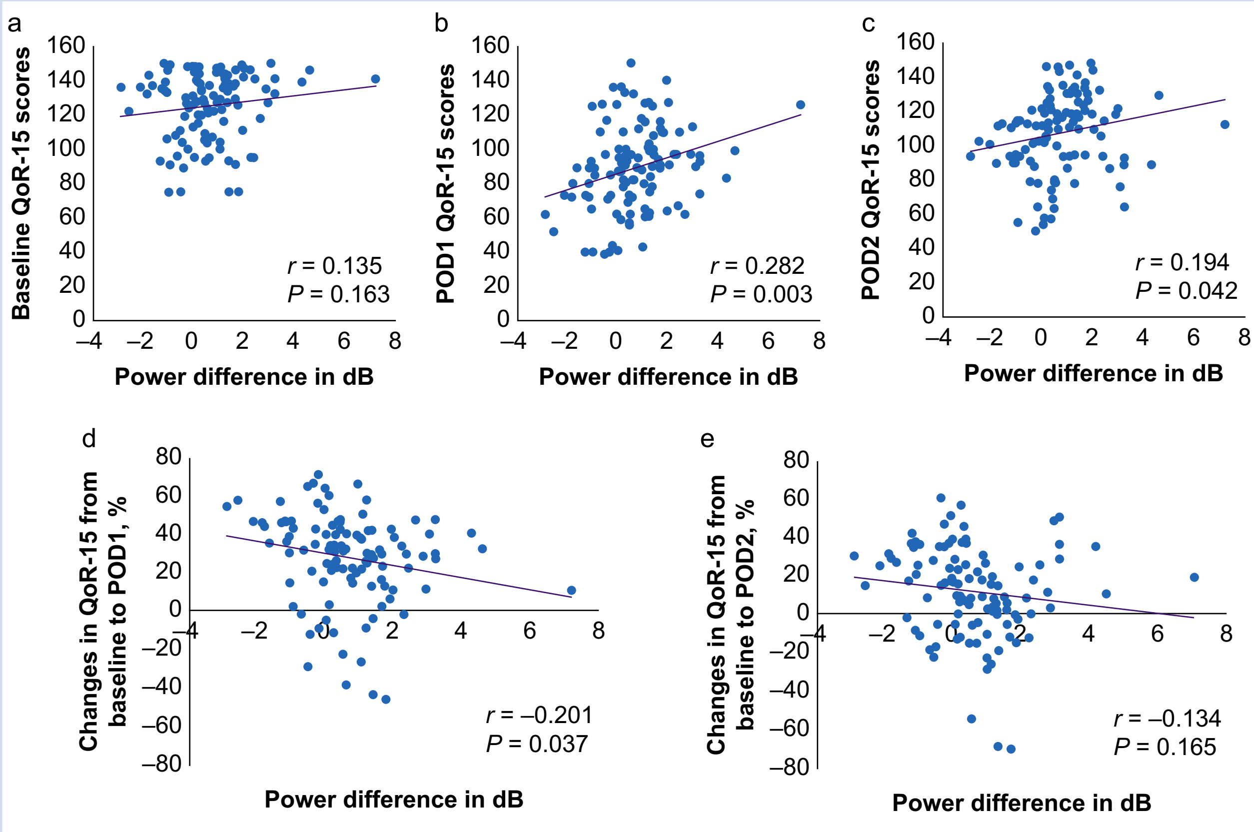

Fig 1. Scatterplots of the frontal alpha asymmetry value and global QoR-15 scores. γ indicates correlation coefficient of the FAA value with the (a) baseline score, (b) POD1 score, (c) POD2 score, (d) % Δ POD1, and (e) % Δ POD2, respectively. FAA is defined as 10·log 10 [mean power of Fp2 (right) lead] − 10·log10 [mean power of Fp1 (left) lead]. A lower FAA value, indicating an increase in relative left versus right frontal alpha power, reflects reduced relative left frontal activity. FAA, frontal alpha asymmetry; POD, postoperative day; QoR, quality of recovery; % Δ, percent decrease in the score from the baseline value.

independence, and emotional status on POD2 in the LFAA group than in the RFAA group.

The global QoR-15 scores on POD1 according to the tertile distribution were as follows: 62.5 (53–72 [39–78]), 90 (85–95 [80–97]), and 116 (109.5–127 [99–150]) in the first, second, and third tertiles, respectively (Supplementary Table S2). Comparisons of demographic and perioperative data among the tertile groups showed no difference. The proportion of patients who presented with LFAA preoperatively was 47%, 23%, and 18% in the first, second, and third tertile groups, respectively (P=0.013). The mean power spectra of left and right alpha oscillation according to the tertile groups indicates that the higher the relative right alpha power, the better the perioperative QoR-15 scores, and vice versa (Supplementary Fig. S3).

In comparisons between the lowest (first) tertile and the higher (second and third) tertiles, the ASA-PS class, BFI-neuroticism, HADS-anxiety, and baseline QoR-15 scores and preoperative LFAA showed significant differences (data not shown). Univariable analysis of the predictors for the lowest tertile revealed statistical significance with the ASA-PS class, baseline QoR-15 score, and LFAA. In the multivariable analysis of these variables, lower baseline QoR-15 score and LFAA remained independent risk factors (OR, 0.98; 95% CI, 0.95–1.0 and OR, 3.28; 95% CI, 1.31–8.24, respectively) (Table 3). When the FAA was analysed as a continuous variable in the logistic regression, lower baseline QoR-15 score and lower FAA value remained independent risk factors (OR, 0.98; 95% CI, 0.95–1.0 and OR, 0.65; 95% CI, 0.46–0.93, respectively) (Supplementary Table S3). Overall, LFAA was associated with a 3.3-fold increased risk for poor QoR on POD1, while a 1.0 dB increase in FAA value was associated with 35 % risk reduction.

Fig 3 shows the global QoR-15 scores according to the transition in the dominant side of FAA from the preoperative to postoperative period. In both preoperative LFAA and RFAA groups, comparisons between the postoperative LFAA vs. postoperative RFAA subgroups revealed significant group-by-time interactions, and the post-hoc analysis showed a greater decrease in the score on POD1 in the postoperative LFAA subgroup than in the RFAA subgroup. Subdimensional scores according to the perioperative FAA transition are depicted in Supplementary Fig. S4.

Discussion

We found significantly lower QoR-15 scores up to 2 days after thyroid surgery in female patients who presented with left-dominant frontal alpha power before surgery than in those

Table 1 Demographic and perioperative data in relation to preoperative frontal alpha asymmetry.

		LFAA (n = 32)	RFAA (n = 78)	P value
Demographic characteristics				
Age, yr		39.7 (8.2)	42.5 (11.6)	0.16
Height, cm		161.1 (5.6)	161.2 (6.0))	0.89
Weight, kg		60.90 (1.89)	61.64 (0.99)	0.70
ASA physical status (1/2)		6/28 (18.8/81.3 %)	27/51 (34.6/65.4 %)	0.099
Primary diagnosis (AH/cancer)		3/29 (9.4/90.6 %)	8/70 (10.3/89.7 %)	>0.99
Preoperative psychological assessment				
BFI	Extraversion	5 (4–6 [2–10])	5 (4–7 [2–9])	0.60
	Neuroticism	7.5 (5.3–9.0 [2–10])	6 (5–8 [2–10])	0.027
	Conscientiousness	8 (6.3–9.0 [1–10])	7 (6–1 [4–10])	0.16
	Agreeableness	12 (10–12 [7–15])	11 (10–12 [7–14])	0.72
	Openness	6 (5–10 [3–16])	7 (5–9 [3–12])	0.93
HADS	Anxiety	8.6 (2.9)	7.3 (3.1)	0.065
	Depression	5 (4–9 [1–15])	4.5 (2.3–7.0 [1–16])	0.045
PCS	Helplessness	3 (1–5 [0–11])	1 (0–3 [0–12])	0.010
	Magnification	3 (1–4 [0–9])	2 (0–3 [0–9])	0.15
	Rumination	4 (1–9 [0–14])	4 (2–7 [0–13])	0.87
	Total	8 (4.3–17.5 [0–30])	7 (3–12 [0–31])	0.14
Perioperative data				
Duration of surgery, min		52 (36.3–65.8 [18–140])	55 (42–70 [16-132])	0.38
Surgery type (Open/Endoscopic or Robotic)		26/6 (81.3/18.8 %)	55/23 (70.5/29.5 %)	0.25
Mean sevoflurane concentration, vol%		1.8 (1.6–1.9 [1.5–2.1])	1.7 (1.6–1.8 [1.2–2.1])	0.34
Total amount of remifentanilduring surgery, μg kg^{-1}		0.3 (0.3–0.4 [0.2–0.9])	0.3 (0.3–0.4 [0.2–0.7])	0.52
Mean PSI value		33.2 (4.2)	34.1 (5.2)	0.41
Patients requiring analgesics at PACU		11 (34.4 %)	18 (23.1 %)	0.22
Patients requiring antiemetics at PACU		0 (0 %)	2 (2.6 %)	0.36
Patients requiring analgesics at GW		13 (40.6 %)	27 (34.6 %)	0.55
Reoperation for bleeding		0 (0 %)	1 (1.3 %)	>0.99
Length of hospital stay after surgery, days		2 (2–2.8 [1–5])	2 (2–3 [1–5])	0.42

AH, adenomatous hyperplasia; ASA, American Society of Anesthesiologists; BFI, Big Five Inventory; GW, General Ward; HADS, Hospital Anxiety Depression Scale; PCS, Pain Catastrophising Scale; LFAA, left-sided frontal alpha asymmetry; PACU, post anaesthesia care unit; PSI, Patient Safety Index; RFAA, right-sided frontal alpha asymmetry; OPD, Outpatient Department. Values are the mean (SD), median (IQR [range]), or number (proportion).

showing dominance on the right side. The drop in the score from baseline to POD1 was quite large overall, but there was a significant difference according to the dominant side. Left dominance in the FAA could also independently predict poor QoR on POD1. The drop in the score from baseline to POD2 may indicate a different success level for restoration to the preoperative state according to the dominant side of FAA. All subdimensions of QoR-15 except for pain, including physical comfort and dependence, psychological support, and emotional status, were observed to be related to FAA.

Functional lateralisation of the frontal cortex has long been implicated in affective processing: positive affect is associated with greater relative left frontal activity, and negative affect is associated with greater relative right frontal activity.[22,23] A similar mechanism operates in stress responsivity; the right hemisphere initiates fight-or-flight responses to acute stress while the left hemisphere regulates the responses.[7,9] FAA is inversely correlated with the relative activation of the frontal areas responding.[9] Right dominance in FAA, which is indicative of relatively greater left frontal activation, is associated with greater emotional flexibility,[24] more efficient emotional regulation,[25] and superior resilience[9] when confronted with undesirable distress. In this context, the RFAA group in our study would represent patients with better capability to cope with postoperative stress than the LFAA group. The QoR-15 scores, which may indicate the levels of stress the individuals experienced after surgery and how well they overcame it, were significantly lower in the LFAA group, and the preoperative LFAA independently predicted the predefined poor QoR. Our result is consistent with previous psychiatric studies in which left dominance in FAA before stress induction was associated with greater cortisol secretion during stress and avoidance/withdrawal behaviour.[8,9]

The FAA measured during the resting state principally reflects affective traits, while that measured under an emotional challenge denotes state-dependent salience of affective processing.[26,27] Individual differences in FAA are more pronounced in the latter situation than in the former.[28] In our study, data for preoperative FAA levels were collected immediately before surgery. Patients awaiting surgery are under considerable stress because of the fear of surgery and worry about their safety, comfort, and families. Surgical oncology patients may experience additional psychological pressure due to concerns about incomplete cancer removal or recurrence, regardless of cancer type.[29] Therefore, we could assume that the dominance of FAA measured before surgery, which was indicative of state-dependent emotional processing, was

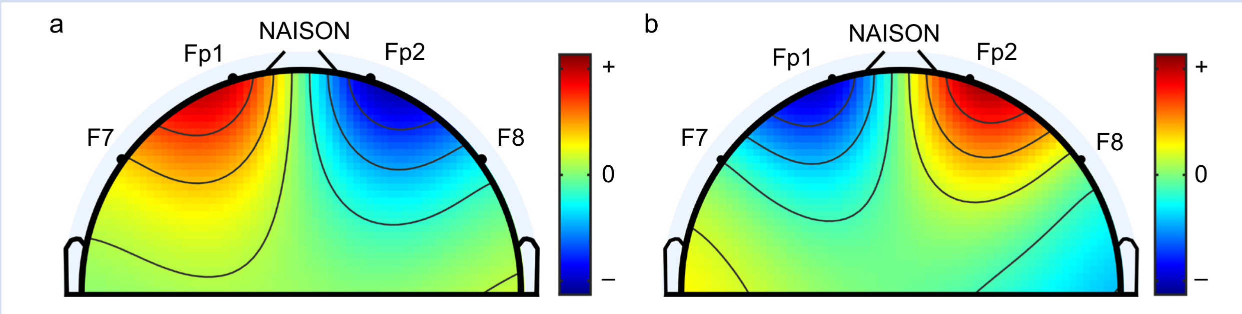

Fig 2. Topoplot for preoperative alpha band power (12 Hz) of representative patients (a, b) presenting with LFAA (a) and RFAA (b) preoperatively. Spectral density is higher in the Fp1 and F7 regions than in the Fp2 and F8 regions in the patient (a) and is higher in the Fp2 and F8 regions than in the Fp1 and F7 regions in the patient (b). Global QoR-15 score of the patient (a) decreased from 122 at baseline to 52 and 104 on postoperative day (POD)1 and POD2, while that of patient (b) was decreased from 127 at baseline to 113 and 123 on POD1 and POD2. LFAA, left-sided frontal alpha asymmetry; QoR, quality of recovery; RFAA, right-sided frontal alpha asymmetry.

Table 2 Global QoR-15 scores in relation to preoperative frontal alpha asymmetry

	LFAA (n = 32)	RFAA (n = 78)	Adjusted P value
Global QoR-15 score			0.11[a]
Baseline	128.5 (104.5–136.8 [75–150])	131.5 (118.5–141 [75–150])	0.78
POD1	73 (54.5–92 [39–136])	94.5 (81.5–110 [43–150])	0.006
POD2	97.5 (91–113 [51–123])	120 (98.5–132 [58–150])	<0.001
Decrease in global score from the baseline value			
Δ POD1	53.5 (21.3–67.8 [-30-105])	36.5 (18.3–51.3 [-37-89])	0.030
Percentage Δ POD1, %	43.5 (16.3–53.8 [-31-71])	29 (15.3–39.8 [-47-66])	0.014
Δ POD2	27.5 (10.3–47 [-25-79])	11.5 (-3.3-27.8 [-53-77])	0.038
Percentage Δ POD2, %	20.8 (9–31.8 [-27.5–60.8])	8.2 (-2.3-21.5 [-70.7–57])	0.039

Δ indicates QoR-15 score subtracted from the baseline QoR-15 score.
LFAA, left-sided frontal alpha asymmetry; POD, postoperative day; QoR, quality of recovery; RFAA, right-sided frontal alpha asymmetry. Values are median (IQR [range]).
[a] indicates P value for the group-by-time analysis.

Table 3 The predictive power of preoperative left-sided FAA for the lowest tertile of the global QoR-15 score on postoperative day 1.

	Univariable		Multivariable	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age	0.99 (0.95–1.03)	0.52		
Body mass index	0.96 (0.85–1.08)	0.47		
ASA physical status	2.87 (1.06–7.78)	0.038	2.54 (0.87–7.370)	0.087
BFI-neuroticism	1.24 (1.00–1.55)	0.053		
HADS-anxiety	1.13 (0.99–1.30)	0.076		
Baseline global QoR-15 score	0.98 (0.96–1.00)	0.022	0.98 (0.95–1.00)	0.034
Preoperative LFAA	3.52 (1.48–8.36)	0.004	3.28 (1.31–8.24)	0.011
Endoscopic/robotic surgery	1.11 (0.45–2.77)	0.82		
Duration of surgery	1.00 (0.99–1.02)	0.83		

ASA, American Society of Anesthesiologists; BFI, Big Five Inventory; CI, confidence interval; HADS, Hospital Anxiety Depression Scale; LFAA, left-sided frontal alpha asymmetry; QoR, quality of recovery.

able to discriminate the individual's capability to cope with the upcoming stress after surgery.

Nevertheless, innate positive or negative affective traits would have contributed to the QoR and FAA. We observed higher preoperative levels of depression and helplessness subscale scores of the PCS in the LFAA group than in the RFAA group. Moreover, a higher rank in neuroticism, which is related to anxiety, depression, and dysfunctional stress management, was also observed in the LFAA group. Although direct relationships between emotional and

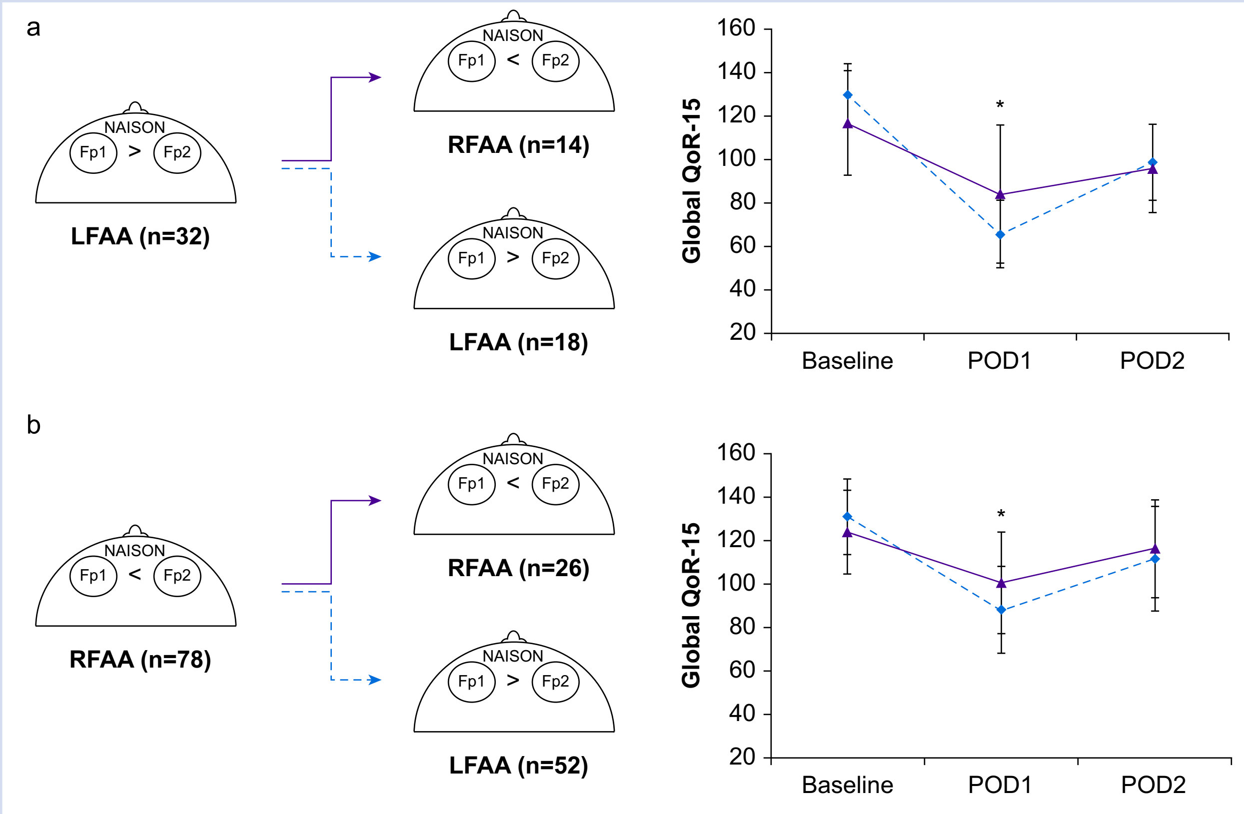

Fig 3. Global QoR-15 scores according to the changes in the dominant side of frontal alpha asymmetry from the preoperative to post-operative periods. In both preoperative LFAA (a) and RFAA (b) groups, the subgroup representing RFAA in the postoperative period (solid line) showed less decline in the score on POD1 than the subgroup representing LFAA (dashed line). * indicates P value <0.05 in the post-hoc analysis. LFAA, left-sided frontal alpha asymmetry; QoR, quality of recovery; RFAA, right-sided frontal alpha asymmetry.

personality traits and QoR scores did not exist, LFAA could have mediated and/or moderated the influence of negative traits on poor QoR.[30]

Associations of QoR-15 scores with postoperative LFAA measured in the PACU, when most patients were experiencing distress, were weaker than with the preoperative indices (data not shown). This might be an extension of previous psychiatric studies that administered aversive physical stress to healthy volunteers and demonstrated that LFAA presented before stress induction, not that presented during stress, was associated with the levels of stress hormones during stress.[10] In contrast, we found that the postoperative changes in the FAA of the dominant side had clinical relevance. In preoperative LFAA and RFAA groups, the subgroup representing RFAA in the PACU showed less decline in the score on POD1 than the subgroup representing LFAA. Based on a previous report on transient changes in FAA dominance to the left side induced by electroshocks during sleep in healthy volunteers,[10] we could assume that physically distressing states immediately after surgery tend to cause LFAA, which may or may not occur depending on how patients in the PACU perceive aversive stimulation. Serial measurements of FAA may provide a more detailed QoR prediction, which calls for further studies with larger sample sizes.

The preoperative FAA value, not only the LFAA, also independently predicted poor QoR as shown in Supplementary Table S3. Some researchers argue that FAA should be considered a continuous variable when evaluating its moderating role, while others consider left dominance itself as pathologically significant.[27] However, there was only a weak statistical correlation between the FAA value and postoperative QoR-15 score and area under the receiver operating characteristic curve of the FAA value to predict poor QoR was not meaningful enough (<0.7, data not shown), which might be attributable to the small proportion of left-sided FAA in our study participants. Indeed, the number of the participants who presented with LFAA (n=32) was much smaller than that of participants who presented with RFAA (n=78), which seem to be more common in the general population. This may be why the mean left frontal alpha power was not significantly higher than the right side in the poor QoR group as shown in Supplementary Fig. S3. Even though the proportion of LFAA was significantly higher in the poor QoR group (47%) than the higher QoR groups (approximately 20%), more than half of the group presented with RFAA, which could have resulted in comparable alpha power between the left and right sides in the poor QoR group. These findings underscore that FAA should be interpreted in terms of both the difference in values and dominant side, with a careful consideration of the psychiatric profile of the study cohort.

The limitations of this study are as follows: First, since the preoperative EEG data were collected while the patients were experiencing mental distress, as mentioned above, we were unable to perform separate analyses on the relationship between trait-related FAA and QoR, which may have provided more comprehensive information. A long-term cohort study with multi-disciplinary cooperation may be needed to obtain EEG data before diagnosis and surgical planning. Second, potential sex differences in stress coping and QoR[31,32] may not permit generalisation of the current results for the analysis of EEG features in male patients. Third, we used tertile classification for QoR-15 on POD1 to define a poor prognosis. Although quantile categorisation is a well-established method for outcome assessment, a poor or unfavourable QoR should be defined carefully according to different surgical cohorts before analysis. Fourth, our study participants included only a small percentage of elderly participants; 102 of 110 patients were below 60 years of age. This might partly explain why age was not a predictor for poor QoR. Lack of independent predictability of depression/anxiety scale, PCS score, and personality spectrum for poor QoR can be understood in the same context. Most of our study participants did not have serious mental problems. The influence of age and psychiatric illness should not be overlooked, and further investigations are needed in a cohort of a large spectrum of those factors. Fifth, regarding the 5 subdimensional QoR-15 scores, increase of type I error due to multiple comparisons cannot be fully excluded, and careful interpretation would be needed.

In summary, the present study demonstrated a close association between preoperative left-sided frontal alpha asymmetry and poor QoR after thyroidectomy in female patients. This is the first study to report the feasibility of frontal EEG measurements in predicting patient-centred outcomes following general anaesthesia and surgery. Further investigations are needed to reveal the optimal perioperative care strategies for ensuring better QoR according to the dominant side of the frontal alpha asymmetry.

Authors' contributions

Research design: YS.
Data acquisition: JYB, JSL, JWO, DWH, HJJ, SMK.
Data management: JSL, SMK.
Data analysis: JYB, JSL,YS.
Data interpretation: JYB, SMK, YS.
Article drafting: JYB, YS.
Article revision: JYB, YS.
Approval of the final manuscript: all authors.

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Declaration of interests

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.12.003.

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