ANESTHESIOLOGY

Preoperative Cognitive Abnormality, Intraoperative Electroencephalogram Suppression, and Postoperative Delirium

A Mediation Analysis

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative delirium is common in older surgical patients
- Intraoperative electroencephalogram suppression has been associated with postoperative delirium
- Patients with preoperative cognitive impairment have an increased risk of developing postoperative delirium

What This Article Tells Us That Is New

- The indirect effect of intraoperative electroencephalogram suppression on the development of postoperative delirium among patients with preexisting cognitive impairment is probably small but nonzero
- Approximately 28 cognitively impaired patients would need to be kept out of electroencephalogram suppression to avoid 1 case of postoperative delirium

ABSTRACT

Background: Postoperative delirium is a common complication that hinders recovery after surgery. Intraoperative electroencephalogram suppression has been linked to postoperative delirium, but it is unknown if this relationship is causal or if electroencephalogram suppression is merely a marker of underlying cognitive abnormalities. The hypothesis of this study was that intraoperative electroencephalogram suppression mediates a nonzero portion of the effect between preoperative abnormal cognition and postoperative delirium.

Methods: This is a prespecified secondary analysis of the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) randomized trial, which enrolled patients age 60 yr or older undergoing surgery with general anesthesia at a single academic medical center between January 2015 and May 2018. Patients were randomized to electroencephalogram-guided anesthesia or usual care. Preoperative abnormal cognition was defined as a composite of previous delirium, Short Blessed Test cognitive score greater than 4 points, or Eight Item Interview to Differentiate Aging and Dementia score greater than 1 point. Duration of intraoperative electroencephalogram suppression was defined as number of minutes with suppression ratio greater than 1%. Postoperative delirium was detected *via* Confusion Assessment Method or chart review on postoperative days 1 to 5.

Results: Among 1,113 patients, 430 patients showed evidence of preoperative abnormal cognition. These patients had an increased incidence of postoperative delirium (151 of 430 [35%] *vs.*123 of 683 [18%], $P < 0.001$). Of this 17.2% total effect size (99.5% CI, 9.3 to 25.1%), an absolute 2.4% (99.5% CI, 0.6 to 4.8%) was an indirect effect mediated by electroencephalogram suppression, while an absolute 14.8% (99.5% CI, 7.2 to 22.5%) was a direct effect of preoperative abnormal cognition. Randomization to electroencephalogram-guided anesthesia did not change the mediated effect size ($P = 0.078$ for moderation).

Conclusions: A small portion of the total effect of preoperative abnormal cognition on postoperative delirium was mediated by electroencephalogram suppression. Study precision was too low to determine if the intervention changed the mediated effect.

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Postoperative delirium is a common condition that not only causes distress for patients and caregivers during their hospital stay but also impacts their subsequent recovery. Approximately 15 to 25% of older adults who undergo elective major surgery have postoperative delirium, and the incidence is even higher after cardiac surgery or hip fracture repair surgery.[1] Patients who experience postoperative

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delirium require more days of mechanical ventilation and have longer stays in the intensive care unit and hospital.[2] After discharge, patients recovering from delirium require more assistance in performing activities of daily living.[3] They also exhibit sustained deficits in cognitive function that are more severe than those experienced by patients who recover without delirium.[3–5] Patients who experience delirium after surgery may also be more likely to die sooner than patients who do not experience delirium.[6]

In recent years, researchers have investigated associations between intraoperative electroencephalogram features and postoperative delirium. In two prospective observational cohort analyses, patients with longer cumulative duration of intraoperative electroencephalogram suppression were found to have an increased incidence of postoperative delirium.[7,8] This observation led to the hypothesis that titrating anesthesia to prevent or minimize electroencephalogram suppression would reduce the risk of postoperative delirium. Two randomized trials reporting reduced delirium after anesthesia guided by processed electroencephalogram monitors support this argument.[9,10] However, it is also plausible that electroencephalogram suppression occurs preferentially in patients whose brains are more susceptible to external stressors, such as patients with preoperative evidence of abnormal cognition. These patients may have an increased risk for postoperative delirium, regardless of anesthetic management. This theory is supported by a recent finding that patients who experienced electroencephalogram suppression with lower doses of volatile anesthetic agents were at increased risk for postoperative delirium.[11] To help distinguish between these two competing theories, the aim of this study was to quantify how much of the effect between preoperative abnormal cognition and postoperative delirium is mediated by intraoperative electroencephalogram suppression. The hypothesis was that electroencephalogram suppression would mediate a nonzero portion of the total effect.

Materials and Methods

This is a prespecified secondary analysis of the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) randomized clinical trial. In the ENGAGES trial, patients undergoing elective surgery were randomized to electroencephalogram-guided general anesthesia or to usual care (electroencephalogram-blinded general anesthesia).[12] The Human Research Protection Office at Washington University in St. Louis, St. Louis, Missouri, approved the ENGAGES trial. Anesthesiology clinicians caring for patients in the intervention group were instructed to titrate the volatile anesthetic agent to avoid electroencephalogram suppression. No significant difference in the incidence of postoperative delirium was observed between the two groups.[13] The ENGAGES trial's findings were reported according to the Consolidated Standards of Reporting Trials guidelines,[12] while this analysis is reported following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (checklist in Supplemental Digital Content 1, http://links.lww.com/ALN/C250).[14]

Patient Population

Patients age 60 yr or older undergoing surgery at a single academic medical center (Barnes-Jewish Hospital, St. Louis, Missouri) with general anesthesia and an expected hospital stay of at least 2 days were eligible for inclusion. Patients undergoing neurosurgical procedures, patients with preoperative ongoing delirium, patients with a history of intraoperative awareness, and patients expecting a second surgery within 5 days were excluded. Patients were enrolled from January 2015 to May 2018. All patients provided written, informed consent.

Data Collection and Intraoperative Management

The ENGAGES study protocol has been published.[12] Patients provided a detailed medical history, and a thorough preoperative physical examination was conducted. Research team members collected additional history elements, including history of delirium, falls in the previous 6 months, and limitations in hearing and vision. Participants also completed the Veteran's Rand 12-Item Health Survey,[15] Barthel index (activities of daily living),[16] Lawton's instrumental activities of daily living,[17] Short Blessed Test cognitive screen,[18] Eight Item Interview to Differentiate Aging and Dementia screen,[19] and the Personal Health Questionnaire depression scale.[20] Patients were defined as having evidence of abnormal cognition if they reported a history of delirium, scored greater than 4 points on the Short Blessed Test, or scored greater than 1 point on the Eight Item Interview to Differentiate Aging and Dementia screen. These thresholds are specified in the tests' scoring algorithms as separating normal from abnormal results.

All patients received general anesthesia with a volatile agent. Data from a frontal electroencephalogram channel were obtained in all patients, using a Bispectral Index Quatro sensor (Medtronic, Ireland). The suppression ratio, signal quality index, and Bispectral Index were captured at 1-min intervals using MetaVision software (iMDSoft, USA). Data points with a signal quality index 50% or less were excluded. Duration of electroencephalogram suppression was quantified as the cumulative number of minutes with suppression ratio greater than 1%. The end-tidal anesthetic concentration was also captured at 1-min intervals. Intraoperative medication documentation was retrieved from the electronic medical record.

Trained research team members screened patients for postoperative delirium once daily for 5 days using the Confusion Assessment Method[21] or the Confusion Assessment Method for the Intensive Care Unit (if intubated).[22] Research team members also identified delirium from inpatient records using the validated Chart Abstraction

for Delirium tool during the first 5 postoperative days.[23] Researchers assessing patients for delirium were blinded to randomization assignment. Patients were classified as having postoperative delirium if they screened positive at any time or if chart review was positive.

Statistical Analysis

A mediator is a variable that accounts for part of an observed relationship between two other variables.[24] We hypothesized that electroencephalogram suppression acts as a mediator in the relationship between preoperative abnormal cognition and postoperative delirium. Baron and Kenny described a three-step method to test for mediation, but this method requires either dichotomous variables or continuous variables with linear associations.[24] Because duration of electroencephalogram suppression followed a binomial distribution, we used the more general mediation formula described by Pearl.[25] This methodology allows for the use of generalized linear models with nonlinear link functions to describe the associations between variables.

Using Pearl's nomenclature, the total effect of preoperative abnormal cognition on postoperative delirium is the difference in the expected incidence of postoperative delirium between patients with and without abnormal cognition:

$$\text{Total Effect} = E(\text{Del} \mid \text{AbnCog}) - E(\text{Del} \mid \neg\text{AbnCog})$$

where Del is postoperative delirium, AbnCog is evidence of abnormal cognition, ¬ means "not," and $E()$ represents the expected value of the quantity in parenthesis. The total effect may be broken down into the indirect effect (the portion that is mediated) and the direct effect (the portion that is not mediated). The indirect effect is defined as the change in expected delirium incidence when preoperative cognition status is fixed, but electroencephalogram suppression changes as if preoperative cognition status had changed:

$$\text{Indirect Effect}_{\neg\text{AbnCog}} = E(\text{Del} \mid \neg\text{AbnCog}, E(\text{Supp} \mid \text{AbnCog})) - E(\text{Del} \mid \neg\text{AbnCog}, E(\text{Supp} \mid \neg\text{AbnCog}))$$

$$\text{Indirect Effect}_{\text{AbnCog}} = E(\text{Del} \mid \text{AbnCog}, E(\text{Supp} \mid \text{AbnCog})) - E(\text{Del} \mid \text{AbnCog}, E(\text{Supp} \mid \neg\text{AbnCog}))$$

where Supp is duration of electroencephalogram suppression. The natural direct effect is defined as the change in expected delirium incidence when the preoperative cognition status changes, but electroencephalogram suppression is artificially fixed:

$$\text{Direct Effect}_{\neg\text{AbnCog}} = E(\text{Del} \mid \text{AbnCog}, E(\text{Supp} \mid \neg\text{AbnCog})) - E(\text{Del} \mid \neg\text{AbnCog}, E(\text{Supp} \mid \neg\text{AbnCog}))$$

$$\text{Direct Effect}_{\text{AbnCog}} = E(\text{Del} \mid \text{AbnCog}, E(\text{Supp} \mid \text{AbnCog})) - E(\text{Del} \mid \neg\text{AbnCog}, E(\text{Supp} \mid \text{AbnCog}))$$

The relationships among these variables are summarized in figure 1.

All data analyses were performed using R.[26] Chi-square, Fisher exact, and Wilcoxon rank-sum tests were used to compare baseline characteristics of patients with and without evidence of preoperative abnormal cognition. We modeled duration of electroencephalogram suppression using a Poisson regression (log-linear model), with preoperative abnormal cognition as the independent variable and duration of anesthesia as an exposure. We modeled postoperative delirium using a logistic regression, with preoperative abnormal cognition and duration of electroencephalogram suppression as independent variables. The total, indirect, and direct effects were calculated using the "mediation" package.[27] Bootstrapping (10,000 iterations) was used to construct CIs around each effect size and around the coefficients of the Poisson regression. These effects were quantified in the full cohort and in each randomization group. The procedure was repeated after adjusting for age, sex, race, American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status greater

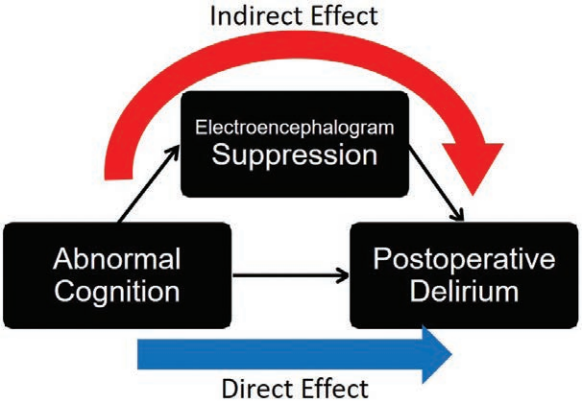

Fig. 1. Relationship among abnormal cognition, electroencephalogram suppression, and postoperative delirium. The direct effect represents the expected change in delirium if preoperative abnormal cognition changes, but electroencephalogram suppression remains artificially fixed. The indirect effect represents the expected change in delirium if preoperative abnormal cognition remains artificially fixed, but electroencephalogram suppression changes to the degree it would have changed if abnormal cognition were not fixed.

than III, smoking, number of comorbidities, and delirium risk associated with the patient's top three International Statistical Classification of Diseases and Related Health Problems procedure codes. (See Supplemental Digital Content 2, http://links.lww.com/ALN/C251, for detailed methods for deriving delirium risk from procedure codes.) In addition, mean end-tidal anesthetic concentration, total intraoperative opioid dose (morphine equivalents), and total intraoperative propofol dose were added to the model for duration of electroencephalogram suppression, while anesthesia length and units of packed erythrocytes given intraoperatively were added to the model for postoperative delirium. The impact of electroencephalogram-guided *versus* electroencephalogram-blinded anesthesia on the mediated effect size was quantified in a *post hoc* moderated mediation analysis. The interaction between preoperative abnormal cognition and duration of electroencephalogram suppression was also tested.

Three sensitivity analyses were performed to assess the degree to which choices made while designing the statistical methods impacted the findings. First, to determine whether use of Poisson regression rather than linear regression to predict duration of electroencephalogram suppression was necessary, the unadjusted mediation effect sizes were recalculated using a linear regression instead. When using the linear regression, we also calculated the mediation effect size described by Baron and Kenny, which is equal to the product of the coefficient for preoperative abnormal cognition in the linear regression times the coefficient for duration of electroencephalogram suppression in the logistic regression.[24] Second, to determine whether the metric chosen to quantify electroencephalogram suppression changed the findings, electroencephalogram suppression was quantified as the total number of seconds of suppression (rather than minutes with suppression ratio greater than 1%). This was achieved by treating the suppression ratio as the fraction of the preceding minute with isoelectric electroencephalogram (suppression ratio equals 1% corresponding to 0.01 min of suppression) and summing over the case. Third, to determine whether the decision to use electroencephalogram suppression as the mediator rather than other electroencephalogram markers impacted the findings, the analysis was repeated using duration of Bispectral Index less than 40 rather than duration of electroencephalogram suppression. Because there were minimal missing data, each analysis used complete cases only. To reduce the likelihood of reporting false negative new discoveries, P values less than 0.005 were considered statistically significant, and P values between 0.005 and 0.05 were considered as providing suggestive evidence.[28] All hypothesis tests were two-tailed.

Power Calculation

Because this was a secondary analysis of data collected for the ENGAGES trial, the sample size was fixed at 1,113 patients. Monte Carlo simulation was performed using R package MonteCarlo, creating simulated cohorts by resampling observed combinations of preoperative abnormal cognition and electroencephalogram suppression from the ENGAGES population. Various indirect effect sizes were tested while keeping the total effect size of abnormal cognition on postoperative delirium fixed at the value observed in ENGAGES. With $\alpha = 0.005$, this study had 80% power to detect an absolute mediated effect size of 1.2% (equal to 7% of the total effect).

Results

The analysis included 1,113 patients, of whom 430 (39%) showed evidence of preoperative abnormal cognition (fig. 2). They included 145 patients with a history of delirium, 218 patients with Short Blessed Test score greater than 4, and 189 patients with Eight Item Interview to Differentiate Aging and Dementia screen score greater than 1. Patients with abnormal cognition had more comorbid conditions, reported higher numbers of recent falls, and experienced greater degrees of vision impairment (table 1). Specific comorbid conditions are shown in Supplemental Digital Content 3 (http://links.lww.com/ALN/C252). Patients with abnormal cognition reported lower quality of life and performed more poorly on activities of daily living, timed up-and-go, and grip strength (table 2). Intraoperatively, these patients received comparable age-adjusted concentrations of volatile anesthetic (table 3).

Postoperative delirium occurred in 274 of the 1,113 patients (25%). Patients with preoperative abnormal cognition had a greater incidence of postoperative delirium compared to other patients (151 of 430 [35%] *vs.* 123 of 683 [18%], $P < 0.001$). Thus, the total effect of preoperative abnormal cognition on postoperative delirium was 17.2% (99.5% CI, 9.3 to 25.1%). Patients with preoperative abnormal cognition also spent a greater number of minutes in electroencephalogram suppression intraoperatively compared to patients without abnormal cognition (median [interquartile range] 13 [2 to 53] *vs.* 7 [1 to 28], $P < 0.001$). In a logistic regression, associations with postoperative delirium existed for preoperative abnormal cognition (odds ratio 2.21 [99.5% CI, 1.46 to 3.33]) and duration of electroencephalogram suppression (odds ratio 1.04 [99.5% CI, 1.03 to 1.06 per 5 min]). When an interaction term between abnormal cognition and duration of electroencephalogram suppression was added to the model, the interaction was not significant (Supplemental Digital Content 4, http://links.lww.com/ALN/C253). In a Poisson regression, preoperative abnormal cognition predicted greater duration of electroencephalogram suppression (coefficient 0.43 [99.5% CI, 0.14 to 0.72]). Of the 17.2% total effect size, an absolute 14.8% (99.5% CI, 7.2 to 22.5%) represented a direct effect of abnormal cognition, while an absolute 2.4% (99.5% CI, 0.6 to 4.8%) represented the indirect effect mediated by electroencephalogram suppression.

The prevalence of preoperative abnormal cognition was 222 of 558 (40%) in the electroencephalogram-blinded group and 208 of 555 (37%) in the electroencephalogram-guided group. The overall incidence of delirium was not significantly different ($P = 0.170$) between the

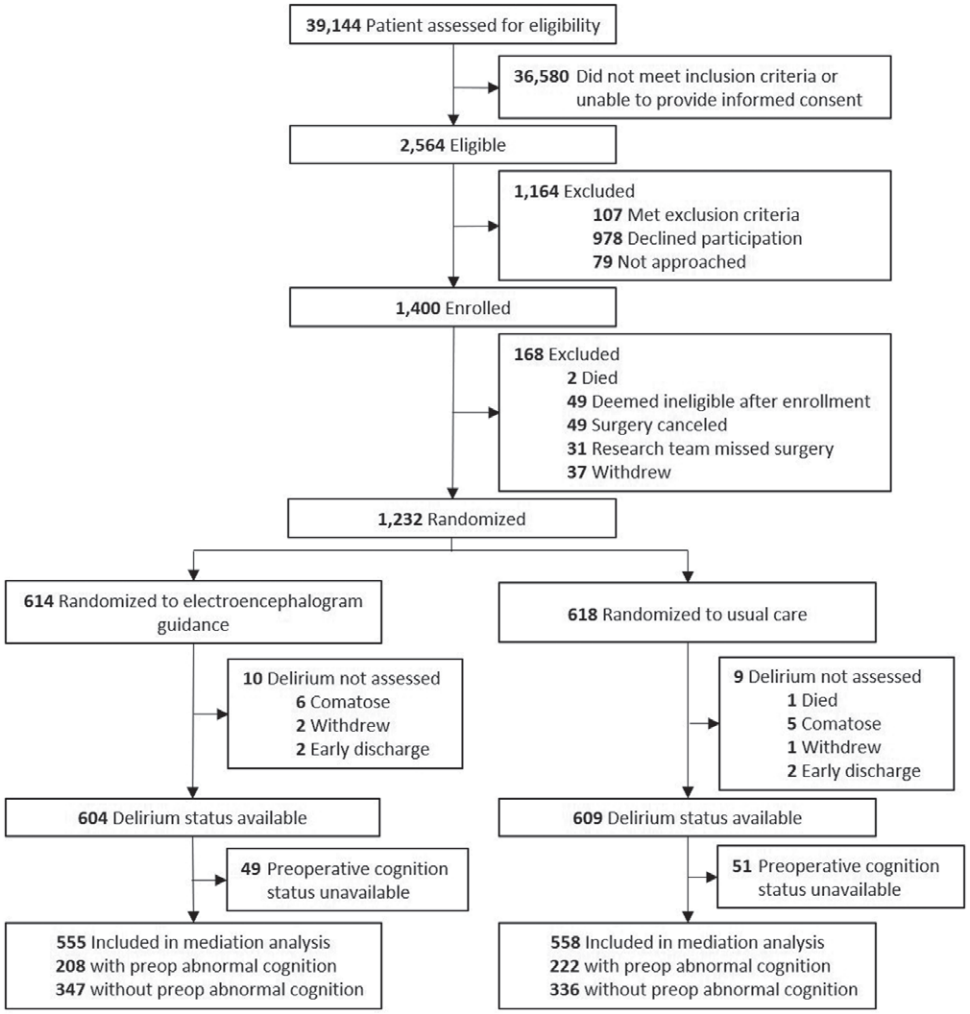

Fig. 2. Flow diagram. The number of patients included at each stage of the analysis is shown.

electroencephalogram-blinded group (127 of 558, [23%]) and the electroencephalogram-guided group (147 of 555, [26%]). Duration of electroencephalogram suppression was shorter in the electroencephalogram-guided group (median 8 [interquartile range, 1 to 22] min) than in the electroencephalogram-blinded group (median 12 [interquartile range, 1 to 57] min, $P < 0.001$). Figure 3 shows the indirect (mediated) and direct effect sizes in each randomization group. The indirect (mediated) effect size was statistically significant in the electroencephalogram-blinded group (absolute 3.7% [99.5% CI, 0.9 to 7.5%]) but not in the electroencephalogram-guided group (1.0% [99.5% CI, –1.2 to 4.8%). However, the difference in indirect effects between groups was not statistically significant in a *post hoc* moderated mediation analysis (difference 3.2% [99.5% CI, –2.1 to 8.4%, $P = 0.078$). The indirect effect size in the electroencephalogram-blinded group indicates that the number-needed-to-treat for an intervention eliminating all electroencephalogram suppression to prevent 1 case of delirium among patients with preoperative abnormal cognition would be 28 (99.5% CI, 14 to 107). Based on the difference in indirect effect sizes between the two groups, the number-needed-to-treat for applying electroencephalogram-guided anesthesia in the way it was employed in the real-world pragmatic ENGAGES trial (achieving partial but not complete elimination of electroencephalogram suppression) among patients with preoperative abnormal cognition would be 32 (99.5% CI, 12 to infinity).

The sensitivity analyses using linear regression rather than Poisson regression and using seconds of electroencephalogram suppression rather than minutes of suppression ratio greater than 1% yielded results similar to the primary analysis (table 4). When using duration of Bispectral Index less than 40 rather than duration of electroencephalogram suppression, the mediated effect size was no longer significantly greater than 0 (table 4). Figure 4 shows the

Table 1. Baseline Characteristics of Patients with and without Preoperative Abnormal Cognition*

Feature	With Abnormal Cognition (N = 430)	Without Abnormal Cognition (N = 683)	*P* Value
Age	70 [65–76]	69 [65–75]	0.029†
Sex			0.442
Male	242 (56%)	367 (54%)	
Female	188 (44%)	316 (46%)	
Race			0.407
White	383 (89%)	620 (91%)	
Black	45 (10%)	55 (8%)	
Other	2 (< 1%)	4 (< 1%)	
Not reported	3 (< 1%)	4 (< 1%)	
American Society of Anesthesiologists Physical Status			0.012‡
I	1 (< 1%)	5 (< 1%)	
II	50 (12%)	117 (17%)	
III	210 (49%)	342 (50%)	
IV	169 (39%)	218 (32%)	
Number of comorbid conditions	4 [2–6]	3 [1–4]	< 0.001†
Living alone	113 (26%)	147 (22%)	0.080
Number of falls in last 6 months			< 0.001
0	296 (69%)	567 (83%)	
1	79 (18%)	77 (11%)	
2	27 (6%)	19 (3%)	
3	11 (3%)	9 (1%)	
4 or more	17 (4%)	11 (2%)	
Limited vision			0.001‡
Mild	40 (9%)	49 (7%)	
Moderate	20 (5%)	18 (3%)	
Severe	6 (1%)	0 (0%)	
Limited hearing			0.256‡
Mild	44 (10%)	52 (8%)	
Moderate	19 (4%)	23 (3%)	
Severe	5 (1%)	4 (1%)	
Ever smoked	269 (63%)	387 (57%)	0.051
Drinks per week			0.038
< 1	341 (79%)	509 (75%)	
1 or 2	23 (5%)	59 (9%)	
3 or 4	27 (6%)	29 (4%)	
5–10	22 (5%)	51 (7%)	
11–15	10 (2%)	21 (3%)	
> 15	7 (2%)	20 (3%)	

Data are presented as No. (percentage) or median [interquartile range].

*Preoperative abnormal cognition is defined as history of delirium, abnormal Short Blessed Test cognitive score (>4 points), or abnormal Eight Item Interview to Differentiate Aging and Dementia score (>1 point). †These *P* values refer to Wilcoxon rank sum test. ‡These *P* values refer to Fisher exact test. Unmarked *P* values refer to chi-square test.

proportion of the total effect mediated by electroencephalogram suppression (indirect effect divided by total effect) in each of these sensitivity analyses. Full model coefficients are shown in Supplemental Digital Content 4 (http://links.lww.com/ALN/C253). The Baron–Kenny mediated effect size was 0.12 (99.5% CI, 0.03 to 0.22) in the overall cohort, 0.20 (99.5% CI, 0.03 to 0.37) in the electroencephalogram-blinded group, and 0.05 (99.5% CI, –0.08 to 0.18) in the electroencephalogram-guided group.

Discussion

In this secondary analysis of a clinical trial, patients with preoperative evidence of abnormal cognition had a 17.2% (99.5% CI, 9.3 to 25.1%) absolute increase in the incidence of postoperative delirium compared with other patients, of which an absolute increase of 2.4% (99.5% CI, 0.6 to 4.8%) was mediated by intraoperative electroencephalogram suppression. The mediated effect size was not significantly different between the electroencephalogram-blinded and electroencephalogram-guided groups (absolute difference 3.2% [99.5% CI, –2.1 to 8.4%]).

These results suggest that patients with a history of delirium or with abnormal scores on dementia screening tests have an increased risk for postoperative delirium primarily as a direct result of their underlying liability, not because their brains are more likely to experience electroencephalogram suppression intraoperatively. In other words, most of the risk associated with the patient's preexisting cognitive abnormality will remain unchanged regardless of how much electroencephalogram suppression they experience.

Table 2. Performance on Baseline Assessments of Patients with and without Preoperative Abnormal Cognition*

Assessment	With Abnormal Cognition (N = 430)	Without Abnormal Cognition (N = 683)	*P* Value†
Timed Up-and-Go (s) (lower is better)	11.9 [10.1–14.7]	10.4 [9.1–12.1]	< 0.001
Dominant Hand Grip Strength (kg) (higher is better)	23 [18–31]	26 [18–36]	0.005
VR-12 Physical Summary Score (0–100; higher is better)	34 [26–44]	40 [31–49]	< 0.001
VR-12 Mental Summary Score (0–100; higher is better)	55 [44–61]	58 [51–62]	< 0.001
Barthel Index (0–100; higher is better)	100 [95–100]	100 [100–100]	< 0.001
AD8 Dementia Screen (0–8; lower is better)	1 [0–2]	0 [0–0]	—‡
Short Blessed Test (0–15; lower is better)	5 [0–8]	0 [0–2]	—‡
PHQ8 Depression Screen (0–21; lower is better)	4 [2–7]	2 [0–5]	< 0.001
Lawton Instrumental Activities of Daily Living (0–8; higher is better)	7 [6–7]	7 [7–7]	< 0.001

Data are presented as median [interquartile range].

*Preoperative abnormal cognition is defined as history of delirium, abnormal Short Blessed Test cognitive score (>4 points), or abnormal Eight Item Interview to Differentiate Aging and Dementia score (>1 point). †All *P* values refer to Wilcoxon rank sum test. ‡No *P* values presented for AD8 and Short Blessed Test because these tests were part of the definition of vulnerable brain.

AD8, Eight Item Interview to Differentiate Aging and Dementia; PHQ8, Personal Health Questionnaire;

VR-12, Veteran's RAND 12-Item Health Survey.

Table 3. Intraoperative Management of Patients with and without Preoperative Abnormal Cognition*

Feature	With Abnormal Cognition (N = 430)	Without Abnormal Cognition (N = 683)	*P* Value
Anesthesia duration (min)	325 [244–399]	310 [234–397]	0.050
Age-adjusted mean end-tidal anesthetic concentration (minimum alveolar concentration units)	0.89 [0.80–0.99]	0.90 [0.81–0.98]	0.413
Total opioid dose (morphine equivalents in mg)	50 [30–85]	43 [29–75]	0.011
Total propofol dose (mg)	160 [120–230]	160 [121–208]	0.577
Midazolam use (yes)	204 (47%)	373 (55%)	0.023†
Total packed erythrocytes transfused (units)	0 [0–1]	0 [0–0]	0.011
Electroencephalogram suppression (min)	13 [2–53]	7 [1–28]	< 0.001

Data are presented as No. (percentage) or median [interquartile range].

*Preoperative abnormal cognition is defined as history of delirium, abnormal Short Blessed Test cognitive score (>4 points), or abnormal Eight Item Interview to Differentiate Aging and Dementia score (>1 point). †This *P* value refers to chi-square test. All unmarked *P* values refer to Wilcoxon rank-sum test.

Nonetheless, the results do not rule out a small causal effect of electroencephalogram suppression on postoperative delirium. Although the indirect effect of preoperative abnormal cognition on delirium mediated by electroencephalogram suppression was small, it was nonzero. These findings suggest that an idealized intervention that eliminates all electroencephalogram suppression among patients with preoperative abnormal cognition would need to be applied to 28 patients (99.5% CI, 14 to 107) to prevent 1 case of delirium. A real-world intervention, like the one tested in this study setting, can reduce the amount of electroencephalogram suppression but cannot eliminate it completely. This is why the point estimate on the number-needed-to-treat for the electroencephalogram-guidance intervention (32) is greater than the point estimate for the idealized intervention described earlier in this paragraph. The residual electroencephalogram suppression that could not be prevented through electroencephalogram-guided titration of anesthesia may behave differently than the electroencephalogram suppression that was successfully eliminated; our analysis does not permit further clarification of this question. Furthermore, these calculations only account for the indirect effect of preoperative abnormal cognition on postoperative delirium mediated by electroencephalogram suppression; there is likely also an independent effect of electroencephalogram suppression that is unrelated to preoperative cognition.

The results of this study are consistent with previous studies reporting risk factors for postoperative delirium. History of delirium and preoperative cognitive impairment are both well-established risk factors for delirium.[29–32] The modest association between intraoperative electroencephalogram suppression and postoperative delirium is of comparable size (4% increase in the odds of postoperative delirium for every 5 min of electroencephalogram suppression) to the effect previously reported in a different cohort.[9] The current results are also consistent with the recently published finding that patients who experience electroencephalogram suppression at lower concentrations of volatile anesthetic have a higher

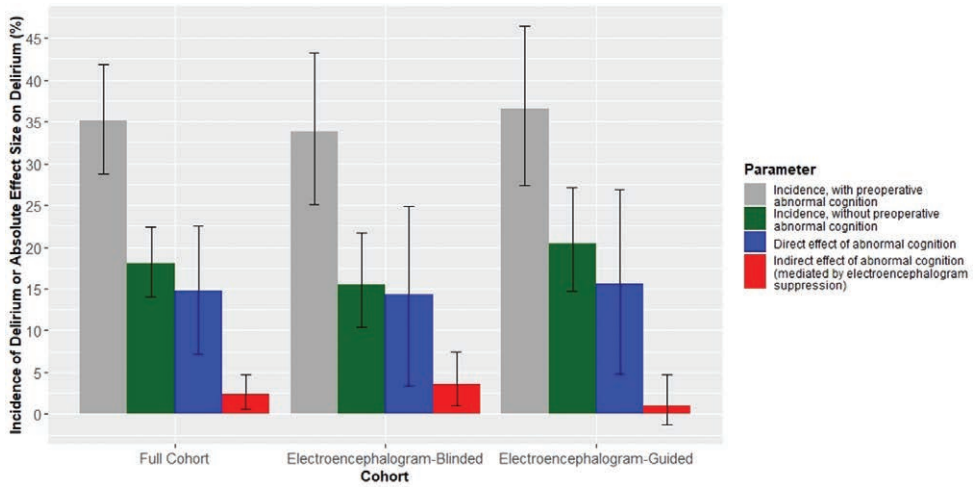

Fig. 3. Contributions to delirium incidence in unadjusted analysis. Within each cohort, the incidence of delirium among patients with preoperative abnormal cognition (*gray bar*) should be equal to the sum of the incidence without preoperative abnormal cognition (*green bar*), the absolute incidence increase associated with the direct effect of preoperative abnormal cognition (*blue bar*), and the absolute incidence increase associated with the indirect effect of abnormal cognition mediated by electroencephalogram suppression (*red bar*). *Error bars* represent 99.5% CIs around incidence rates (*gray and green*) or 99.5% CIs around effect sizes (*blue and red*).

Table 4. Effect Sizes in Primary Analysis and Sensitivity Analyses

Model	Delirium Incidence with Preoperative Abnormal Cognition	Delirium Incidence without Preoperative Abnormal Cognition	Total Effect (99.5% CI)	Indirect Effect (99.5% CI)	Direct Effect (99.5% CI)
Primary analysis					
Unadjusted	151/430 (35%)	123/683 (18%)	17.2% (9.3 to 25.1%)	2.4% (0.6 to 4.8%)	14.8% (7.2 to 22.5%)
Adjusted	136/375 (36%)	108/586 (18%)	13.3% (5.6 to 21.4%)	1.2% (0.2 to 3.1%)	12.1% (4.2 to 20.0%)
Sensitivity analyses					
Linear regression	151/430 (35%)	123/683 (18%)	16.8% (9.0 to 24.6%)	2.3% (0.6 to 4.5%)	14.6% (6.6 to 22.2%)
Seconds of suppression, unadjusted	145/411 (35%)	116/658 (18%)	18.3% (9.9 to 26.6%)	2.3% (0.6 to 5.3%)	16.0% (7.9 to 23.9%)
Seconds of suppression, adjusted	130/361 (36%)	102/570 (18%)	13.4% (5.3 to 21.4%)	1.3% (0.1 to 3.1%)	12.1% (4.0 to 20.0%)
Bispectral Index < 40, unadjusted	151/430 (35%)	123/683 (18%)	16.9% (9.2 to 24.7%)	0.4% (–0.6 to 1.8%)	16.5% (8.6 to 24.4%)
Bispectral Index < 40, adjusted	136/375 (36%)	108/586 (18%)	13.3% (5.5 to 21.2%)	0.4% (–0.2 to 1.5%)	12.9% (5.0 to 20.8%)

incidence of postoperative delirium.[11] Patients in the preoperative abnormal cognition group had a longer duration of electroencephalogram suppression than patients without abnormal cognition, despite both groups receiving similar concentrations of volatile anesthetic (table 3). This suggests these two studies may have focused on comparable groups of patients, even though they were defined in different ways.

The study has several strengths. A large cohort of patients was enrolled, and patients were assessed for delirium by trained personnel using rigorous validated methods. Investigators performing delirium assessments were blinded to randomization assignments. The statistical methods used to quantify the mediation effect size are well-established. The amount of missing data was low. The results were stable in sensitivity analyses employing alternative analytic methods and different mediator variable definitions, suggesting that the results are robust to "investigator degrees of freedom." These factors increase the internal validity of the results. Anesthesiology clinicians of all levels of experience cared for the patients in this trial, potentially increasing the external validity of the findings.

This study also has limitations that should be noted. The findings of this single-center trial may not be generalizable to other centers, especially if frequent conversations about depth-of-anesthesia at this institution have altered treatment patterns in the usual-care group. Delirium was detected using daily Confusion Assessment Method and chart review, which may have underdetected delirium (especially its hypokinetic form) compared to twice-daily Confusion Assessment Method. However, the observed incidence of delirium was higher than in similar previous studies,[33,34] suggesting that underdetection was unlikely to be a large issue. The results may depend upon the specific definition used to define

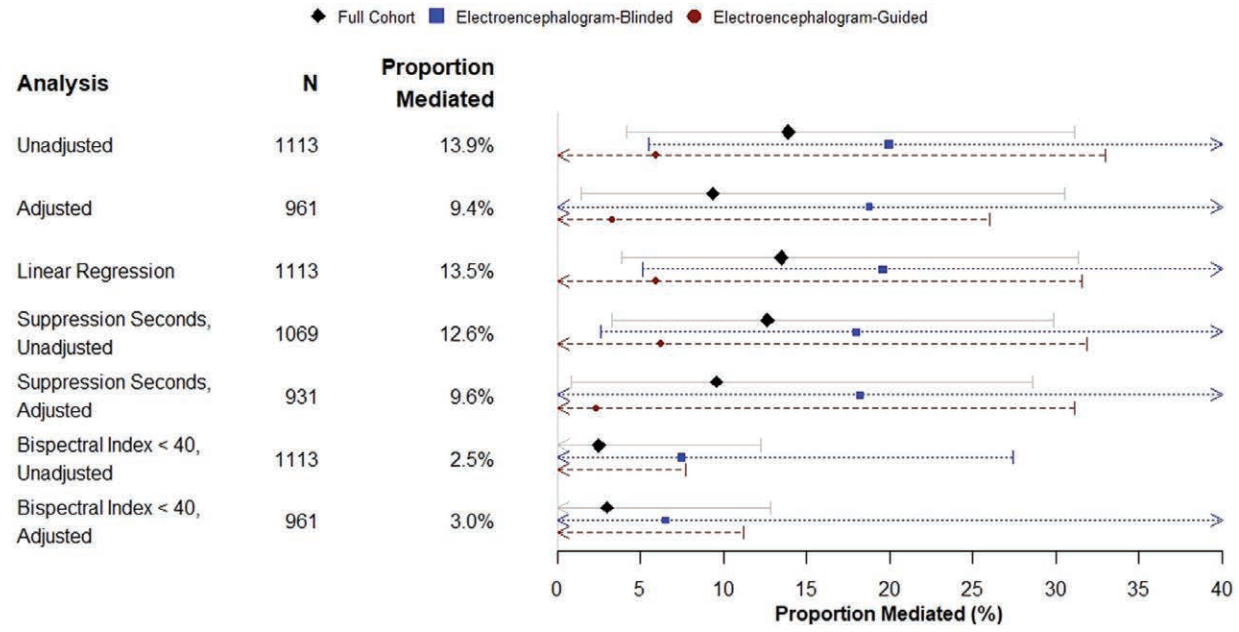

Fig. 4. Sensitivity analyses of mediation effect. Percentage of the total effect of preoperative abnormal cognition on postoperative delirium that is mediated by intraoperative electroencephalogram suppression. (Equal to indirect effect size divided by total effect size.)

preoperative abnormal cognition. However, the correlation of the current definition with a previous definition of "brain vulnerability" (more electroencephalogram suppression despite similar concentrations of volatile anesthetic) suggests that it may have been a reasonable choice. Another limitation is the nesting of this analysis within a clinical trial where the intervention was essentially to manipulate the mediator variable that was of interest to us. It is possible that actively avoiding electroencephalogram suppression changed the relationships between electroencephalogram suppression and other variables in our models. However, because the size of the effect of electroencephalogram suppression on postoperative delirium was similar in this study to our previous observational study, this is less likely. Finally, use of a mediation analysis to draw conclusions about causal effects requires assumptions regarding the lack of residual confounding or other bias threats. No method to test these assumptions is available, so readers should be cautious about inferring causality based on these results.

In conclusion, a small proportion of the elevated risk of postoperative delirium associated with preoperative cognitive abnormality is mediated by intraoperative electroencephalogram suppression. Future large trials are needed to clarify whether avoidance of electroencephalogram suppression has a small, but perhaps important, benefit in relation to postoperative delirium.

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Competing Interests

The authors declare no competing interests.

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