ANESTHESIOLOGY

Electroencephalographic Biomarkers, Cerebral Oximetry, and Postoperative Cognitive Function in Adult Noncardiac Surgical Patients: A Prospective Cohort Study

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ANESTHESIOLOGY 2023; 139:568–79

ABSTRACT

Background: Perioperative neurocognitive disorders are a major public health issue, although there are no validated neurophysiologic biomarkers that predict cognitive function after surgery. This study tested the hypothesis that preoperative posterior electroencephalographic alpha power, alpha frontal-parietal connectivity, and cerebral oximetry would each correlate with postoperative neurocognitive function.

Methods: This was a single-center, prospective, observational study of adult (older than 18 yr) male and female noncardiac surgery patients. Whole-scalp, 16-channel electroencephalography and cerebral oximetry were recorded in the preoperative, intraoperative, and immediate postoperative settings. The primary outcome was the mean postoperative T-score of three National Institutes of Health Toolbox Cognition tests—Flanker Inhibitory Control and Attention, List Sorting Working Memory, and Pattern Comparison Processing Speed. These tests were obtained at preoperative baseline and on the first two postoperative mornings. The lowest average score from the first two postoperative days was used for the primary analysis. Delirium was a secondary outcome (*via* 3-min Confusion Assessment Method) measured in the postanesthesia care unit and twice daily for the first 3 postoperative days. Last, patient-reported outcomes related to cognition and overall well-being were collected 3 months postdischarge.

Results: Sixty-four participants were recruited with a median (interquartile range) age of 59 (48 to 66) yr. After adjustment for baseline cognitive function scores, no significant partial correlation (ρ) was detected between postoperative cognition scores and preoperative relative posterior alpha power (%; $\rho = -0.03$, $P = 0.854$), alpha frontal-parietal connectivity (*via* weight phase lag index; $\rho = -0.10$, $P = 0.570$, respectively), or preoperative cerebral oximetry (%; $\rho = 0.21$, $P = 0.246$). Only intraoperative frontal-parietal theta connectivity was associated with postoperative delirium ($F[1,6,291] = 4.53$, $P = 0.034$). No electroencephalographic or oximetry biomarkers were associated with cognitive or functional outcomes 3 months postdischarge.

Conclusions: Preoperative posterior alpha power, frontal-parietal connectivity, and cerebral oximetry were not associated with cognitive function after noncardiac surgery.

(ANESTHESIOLOGY 2023; 139:568–79)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Impaired perioperative cognitive function may be caused by diminished cortical information processing, which may manifest as disruptions in frontal-parietal alpha connectivity and intraoperative electroencephalogram suppression
- Diminished cerebral oxygenation may also be associated with impaired perioperative cognitive function

What This Article Tells Us That Is New

- Neither preoperative relative alpha power nor preoperative fronto-parietal functional connectivity was associated with decline in cognition in the early postoperative period
- Similarly, no significant correlation was found between preoperative cerebral oximetry and postoperative cognitive function
- Only intraoperative fronto-parietal theta connectivity was associated with postoperative delirium

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 557. This article has a related Infographic on p. A18. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version. Preliminary data for this article were presented at the Foundation for Anesthesia Education and Research 2018 Medical Student and Resident Scholar Research Symposium in San Francisco, California, October 15, 2018.

Submitted for publication November 11, 2022. Accepted for publication June 12, 2023. Published online first on June 26, 2023.

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 Anesthesiology 2023; 139:568–79. DOI: 10.1097/ALN.0000000000004664

Perioperative neurocognitive disorders represent a major public health issue, as nearly 20 million adults 65 yr of age and older undergo surgery annually in the United States,[1] and associated complications threaten postoperative recovery. Postoperative delirium, for example, is associated with increased mortality,[2] cognitive and functional decline,[3,4] and prolonged hospitalization.[5] In fact, the American Society of Anesthesiologists (ASA; Schaumburg, Illinois) is currently pursuing a Brain Health Initiative, which highlights the programmatic need to optimize postoperative neurocognitive recovery.[6] While prediction models have been published for postoperative delirium based on demographics and comorbidities, predictive capabilities tend to be low,[7] and the neurobiological processes that underlie perioperative neurocognitive function remain incompletely understood. Consequently, there are no standards for perioperative brain monitoring, despite the frequency and severity of brain-related perioperative complications.

Candidate biomarkers have emerged that may track with perioperative neurocognitive function. For example, posterior electroencephalographic alpha power after general anesthesia in human volunteers correlates with cognitive performance testing.[8] Functional connectivity between the frontal and parietal cortices supports cognitive processing,[9] and perioperative disruptions in frontal-parietal alpha connectivity are associated with early postoperative delirium.[10,11] Intraoperatively, electroencephalogram suppression and shifts to slow-wave connectivity states are also associated with delirium and older age, respectively.[12,13] These phenomena are postulated to reflect breakdown in structural and functional integrity required to support cortical information processing. As such, altered cortical oscillatory patterns, particularly in the alpha and theta bands, may be scientifically informative and clinically useful for tracking altered perioperative brain states.

Perioperative cerebral oximetry may also be predictive of postoperative cognitive function. Cerebrovascular disease, and attendant impairment with cerebral oxygenation, could contribute to perioperative neurocognitive dysfunction *via* ischemic and hypoxic injury.[14] Prevention of cerebral desaturations may prevent postoperative delirium in high-risk settings.[15] Monitoring cerebrovascular function might thus serve as a useful complementary strategy to electroencephalographic monitoring for comprehensively assessing neurocognitive function in surgical patients.

The objective of this study was to simultaneously test candidate neurophysiologic and cerebrovascular biomarkers in relation to postoperative neurocognitive outcomes. Specifically, this study tested the primary hypothesis that preoperative, resting-state posterior alpha power, alpha frontal-parietal connectivity, and cerebral oximetry would correlate with postoperative neurocognitive function. The approach to testing this hypothesis was to perform a single-center, prospective, observational cohort study with whole-scalp electroencephalography and cerebral oximetry monitoring in the perioperative period while assessing postoperative neurocognitive outcomes. This design allowed for simultaneous analysis of electroencephalography and cerebral oximetry.

Materials and Methods

This was a single-center, prospective, observational study conducted at Michigan Medicine (Ann Arbor, Michigan). The study was approved by the University of Michigan Medical School (Ann Arbor, Michigan) Institutional Review Board (3/6/2018, HUM00139555), and written informed consent was obtained from all participants before enrollment. Patients were recruited from April 2018 to March 2020. This investigation satisfies the Strengthening the Reporting of Observational Studies in Epidemiology criteria for observational studies (Supplemental Digital Content 1, https://links.lww.com/ALN/D178).[16]

Study Participants

Adult surgical patients (18 yr or older, men and women) requiring general anesthesia for noncardiac, nonintracranial, nonmajor vascular surgery (*i.e.*, major defined as operating above the inguinal ligament) with anticipated hospital length of stay at least 72 h were recruited. Patients meeting any of the following criteria were excluded: urgent or emergent surgery, surgery involving the head and neck, patients with previous intracranial surgery (which can confound neurophysiologic signals), patients known to have difficulty with intubation (*i.e.*, "difficult airway"), non–English-speaking, any cognitive impairment precluding the capacity for informed consent, severe auditory or visual impairment, or enrolled in a conflicting research study.

Perioperative and anesthetic management was left to the discretion of clinical care teams. All participants ultimately received isoflurane as the maintenance anesthetic, with one participant also receiving a concurrent propofol infusion and one receiving nitrous oxide in addition to isoflurane. Anesthetic depth was titrated based on age-adjusted minimum alveolar concentration, as is the practice at our institution.

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Outcomes

The primary outcome was the postoperative National Institutes of Health Cognition Toolbox score,[17] defined as the average fully corrected T-score from the Flanker Inhibitory Control and Attention Test, List Sorting Working Memory Test, and Pattern Comparison Processing Speed Test. Collectively, these tests assess executive function, attention, working memory, and processing speed, which are cognitive domains affected by delirium.[18,19] Fully corrected T-scores were used across all analyses, as these scores correct for age, sex, race, ethnicity, and level of education.[20] Given the fluctuating nature of delirium and cognitive impairment, the goal was to capture the lowest score in the early postoperative setting, as low scores may reflect presence of delirium or subsyndromal delirium. Thus, the lowest average score, taken from the first two postoperative days, was used for the primary analysis.

Delirium was the secondary outcome, which was assessed using the Confusion Assessment Method (3-min diagnostic version).[21] Delirium assessors were trained in Confusion Assessment Method assessment *via* previously described methods,[22] with any new team members required to achieve identical Confusion Assessment Method scoring agreement with fully trained assessors for two delirious and nondelirious patients before independent Confusion Assessment Method administration. Delirium was assessed both in the postanesthesia care unit and twice daily for the first 3 postoperative days. Of note, delirium screening took place before National Institutes of Health Cognition Toolbox tests to ensure that participants were awake and alert enough to engage in further testing.

Last, exploratory outcomes were collected at 3 months after discharge. A mailed survey was sent to all participants to determine physical and mental well-being (20-Item Short Form Survey[23,24]) along with subjectively reported, perceived cognitive abilities (Patient-Reported Outcomes Measurement Information System–Cognitive Function–Short Form 4a tests).

Exposure Variables: Electroencephalography and Cerebral Oximetry

The exposure variables of interest included specific electroencephalographic and cerebral oximetry measures. A 16-channel, whole-scalp electroencephalogram system (CGX, Inc., USA) was used for obtaining neurophysiologic data, and spectral and connectivity data were generated using previously described methods (see Supplemental Digital Content 2, https://links.lww.com/ALN/D179, for full acquisition and analytical methodology).[25] Given the presence of cerebral oximetry electrodes, prefrontal electroencephalographic channels were not available; F_5, F_z, and F_6 frontal channels (10–20 montage system) were the most anterior channels used in the study. The primary electroencephalographic measures were relative posterior alpha power (parietal channels P_5, P_z, and P_6) and frontal-parietal connectivity, as posterior alpha (8 to 13 Hz) power (decibels) correlates with postanesthetic functional brain network recovery,[8] and frontal-parietal connectivity is implicated with cognitive processing and delirium risk.[9,10] Given that pre- and postoperative differences in oscillatory and connectivity measures may hold clinical significance,[26] and early reductions in posterior alpha power may reflect cognitive impairment,[8] differences between baseline and postanesthesia care unit (PACU) values were also tested. Additionally, dynamic shifts in intraoperative cortical connectivity were analyzed (*via* previously described methods; Supplemental Digital Content 2, https://links.lww.com/ALN/D179),[25] as intraoperative shifts to frontal-parietal theta connectivity correlate with age,[13] and older age is predictive of postoperative delirium.[27] Intraoperative frontal-parietal theta connectivity state occurrence rate was thus also calculated. Connectivity state occurrence rate was defined as the proportion of time (%) spent in a given connectivity state during the anesthetic maintenance phase (see Supplemental Digital Content 2, https://links.lww.com/ALN/D179, for complete details and calculations).

Cerebral oximetry was monitored using the INVOS 5100C monitor (Medtronic, USA). Forehead sensors were placed in the preoperative holding room, and baseline values were obtained with patients breathing room air and before premedication. Intraoperatively, a cerebral desaturation event was defined as a 3-min drop in oximetry values to either less than 50% (absolute) or 20% or greater from baseline,[28] and area under the curve (min-%) below desaturation thresholds were calculated.

Statistical Analysis

For the primary analysis plan, partial correlation coefficients were calculated while controlling for the fully corrected baseline mean score of all three National Institutes of Health Toolbox tests. Partial correlation was then calculated between six measures of interest (preoperative relative posterior alpha power; preoperative minus PACU relative posterior alpha power; preoperative frontal-parietal connectivity; preoperative minus PACU frontal-parietal connectivity; intraoperative theta connectivity state occurrence rate; and average preoperative cerebral oximetry values) and the lowest composite postoperative cognitive function score within the first 2 postoperative days. For patients with only one score available between the first 2 postoperative days, the available score was chosen for analysis.

As a supplemental analysis, generalized estimating equations were used to test associations between exposure variables above and all available composite National Institutes of Health Toolbox Cognition scores across all time points (*i.e.*, baseline, postoperative day 1, and postoperative day 2). This generalized estimating equation approach is useful with population-averaged estimates even with the possibility of skewed distributions and

misspecification of correlation structures.[29] Fully corrected T-scores were used for analysis, which account for age, educational attainment, sex, race, and ethnicity, with a normative population mean score of 50 and SD of 10.[20] Three different models were then used to construct a final optimal model by incorporating clinical and neurophysiologic predictor variables. The first model contained the ASA Physical Classification Score along with time (*i.e.*, day of cognition testing). A second model was then constructed that included variables from the first model plus subjective pain scores (10-cm visual analog scale) and daily cumulative opioid consumption until the time point measured (given associations among pain, opioid use, and cognition[30]). Last, a final model was constructed by incorporating variables from the first two models, history of depression (given the relatively high prevalence in this study and relationship to delirium[31]), and each of the six candidate neurophysiologic measures described above *via* forward selection. Variables that did not contribute to the model were deleted. A repeated-measures ANOVA was used to test for a statistically significant association between the exposure variables above and postoperative delirium. The Tukey Studentized Range Test was used to control the Type I experiment-wise error rate.

Based on *a priori* power calculations, a cohort sample size of 34 patients would achieve 80% power to detect a correlation of 0.65 (null hypothesis correlation 0.15) using a two-sided hypothesis with a significance level of 0.0083 (corrected for six comparisons). For nonparametric data, power calculations for Spearman rank order correlation reveal a required sample size of 48 for achieving 80% power to detect a correlation of 0.5 using two-sided hypothesis testing with a significance level of 0.0083 (family-wise error adjusted for six comparisons). Power analysis was conducted using Power Analysis and Sample Size Software (2018; NCSS, L.L.C., USA, https://ncss.com/software/pass). Given the high likelihood of attrition and artifact present with electroencephalographic and oximetry data, the target enrollment was 65 participants for this study.

Results

In total, 64 patients were enrolled in the study. Three were withdrawn before surgery, and two were withdrawn due to the COVID-19 pandemic (*i.e.*, suspension of clinical research activities), leaving 59 participants eligible for analysis (Supplemental Digital Content 3, Figure S1, https://links.lww.com/ALN/D180). Cohort demographics are presented in table 1. For the study cohort, baseline attention scores were nearly one SD below the U.S. adult population mean (adjusted for age, sex, race, ethnicity, and level of education); working memory and processing speed scores were close to the adjusted U.S. population mean (table 1). Attrition with cognitive function testing was due to participant refusal, nausea, pain, and other reasons, as outlined in Supplemental Digital Content 3 (Table S1, https://links.lww.com/ALN/D180).

Table 1. Participant Characteristics

	Surgical Patients (n = 64)
Age, yr, median (interquartile range)	59 (48–66)
Men, No. (%)	36 (56)
Women, No. (%)	28 (44)
Race, No. (%)	
White	58 (91)
Black	4 (6)
Asian	2 (3)
Ethnicity, No. (%)	
Non-Hispanic	62 (97)
Hispanic	2 (3)
Education, college or higher, No. (%)	23 (38)
ASA Physical Classification Score, median (interquartile range)	3 (2–3)
Type of surgery, No. (%)	
Colorectal	17 (27)
Gastrointestinal	18 (28)
Pancreatic	7 (11)
Hepatobiliary	
Urology	22 (34)
Comorbidities, No. (%)	
Atrial fibrillation	16 (25)
Chronic kidney disease	11 (17)
Chronic obstructive pulmonary disease	7 (11)
Congestive heart failure	2 (3)
Coronary artery disease	6 (9)
Depression	19 (30)
Diabetes mellitus	11 (17)
Hypertension	31 (48)
Malignancy	40 (63)
Obstructive sleep apnea	19 (30)
Stroke	1 (2)
Transient ischemic attack	2 (3)
Fully corrected T-scores, National Institutes of Health Toolbox, baseline, mean ± SD	
Flanker Inhibitory Control and Attention	42 ± 11
List Sorting Working Memory	51 ± 11
Pattern Comparison Processing Speed	48 ± 14

Demographic data presented for the entire initial cohort (n = 64). Fully corrected T-scores correct for age, educational attainment, sex, race, and ethnicity. The normative population mean score is 50 with a SD of 10 (see Methods section for additional explanation and references).

ASA, American Society of Anesthesiologists.

Electroencephalographic Spectral and Connectivity Analysis

Spectral and connectivity data are presented for all participants in figure 1. Spectrograms reveal a predominance of frontal alpha, theta, and delta oscillatory power (fig. 1A). Connectivity data demonstrate coherent frontal-parietal alpha connectivity at baseline, alpha- and theta-dominant frontal-parietal connectivity intraoperatively, and reduced frontal-parietal alpha connectivity during PACU recovery (fig. 1B).

Dynamic connectivity states were then identified *via* principal component analysis and k-means clustering as described in the Methods section and Supplemental Digital

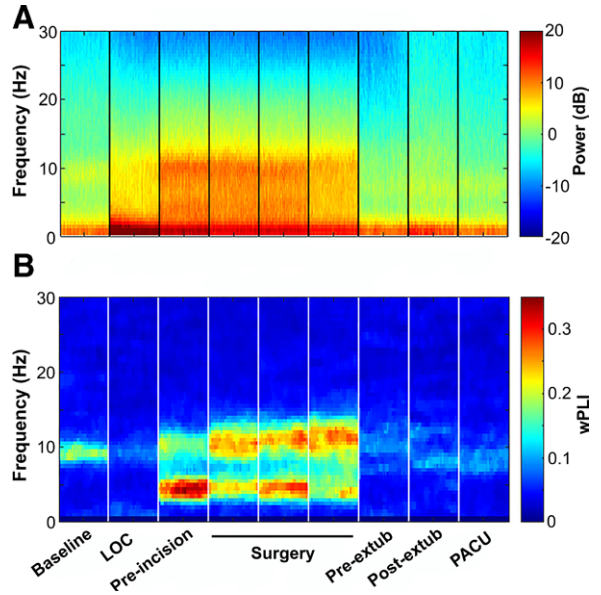

Fig. 1. Electroencephalographic data derived from n = 52 participants (electroencephalographic data were not collected from 7 participants), with median average data presented across time epochs. (*A*) Spectrogram presented across various perioperative time periods. The surgery and general anesthesia time points demonstrate increased alpha, theta, and delta power compared to pre- and postoperative periods. (*B*) Frontal-parietal connectivity (weighted phase lag index [wPLI], n) presented across each perioperative time period. As described in the main texted, wPLI is a surrogate marker of functional connectivity, and increased frontal-parietal alpha connectivity is present during preoperative baseline and immediately decreases after anesthetic induction. Frontal-parietal alpha and theta connectivity then increase during surgery and general anesthesia. Alpha connectivity is then reduced in the postextubation and postanesthesia care unit (PACU) settings. dB, decibels; extub, extubation; LOC, loss of consciousness.

Content 2 (https://links.lww.com/ALN/D179). For the solution with three clusters using the first two principal components, the stability index was 0.15 (±0.08) with the 1-Hamming distance of 0.90 (±0.05), suggesting that 90% of the data are allocated to the same clusters through different clustering solutions, and clustering is 90% consistent among subjects. Three connectivity state clusters were identified: alpha frontal-parietal dominance (State 1), theta-dominant frontal-parietal connectivity (State 2), and suppression of both alpha and theta connectivity (State 3; fig. 2A). State transitions were low, as it was more likely to remain within a given connectivity state rather than transition to a separate state (fig. 3B, *top*). However, when transitions occurred, shifts between alpha and theta frontal-parietal connectivity states were more common (fig. 2B, *bottom*). Descriptive statistics for these electroencephalographic measures are presented in Supplemental Digital Content 3 (Table S2, https://links.lww.com/ALN/D180).

Cerebral Oximetry

The median (interquartile range) preoperative cerebral oximetry (%) value across the cohort was 66 (62 to 70) % (n = 58; baseline data not obtained for one participant). Two participants experienced desaturation events less than 50% (mean area under the curve, 239 min-% and 2,689 min-%, respectively). The first participant experienced delirium in the PACU but no delirium during the remainder of hospital admission. The other participant experienced no delirium during admission. National Institutes of Health Toolbox scores for these participants are available in Supplemental Digital Content 3 (Table S3, https://links.lww.com/ALN/D180). Only one participant experienced a desaturation event 20% or more below baseline (mean area under the curve, 149 min-%), and this patient did not experience any episode of postoperative delirium (no National Institutes of Health Cognition Toolbox scores were available for this participant).

Neurocognitive Outcomes

National Institutes of Health Cognition Toolbox scores are reported in figure 3A. Attention scores (mean ± SD) were significantly reduced from baseline (42 ± 11) on the first postoperative day (37 ± 8; $P < 0.0001$). Working memory scores were also reduced from baseline (52 ± 11) on the first postoperative day (48 ± 11; $P = 0.010$). Scores then returned to baseline levels by postoperative day 2 (fig. 3A).

There was no significant association between any of the cerebral physiologic measures and cognitive function scores across the entire study period (table 2; unadjusted results available in Supplemental Digital Content 3, Table S4, https://links.lww.com/ALN/D180). The intraoperative frontal-parietal theta connectivity occurrence rate (%) was positively associated with postoperative delirium ($F[1,6,291] = 4.53$, $P = 0.034$); otherwise, no other measures were statistically associated with delirium (table 3). Additional *post hoc*, exploratory analyses are presented in Supplemental Digital Content 3 (Tables S5 and S6, https://links.lww.com/ALN/D180). These hypothesis-generating analyses test the relationship between spectral edge frequency and intraoperative alpha power with neurocognitive outcomes based on previous associations with delirium.[32,33]

Exploratory Analysis: 3-Month Survey

There were no significant correlations between any of the electroencephalographic measures, or cerebral oximetry, and 3-month cognitive or general health outcomes (Supplemental Digital Content 3, Table S7, https://links.lww.com/ALN/D180). The largest correlation magnitude was observed with intraoperative frontal-parietal theta connectivity and the Patient-Reported Outcomes

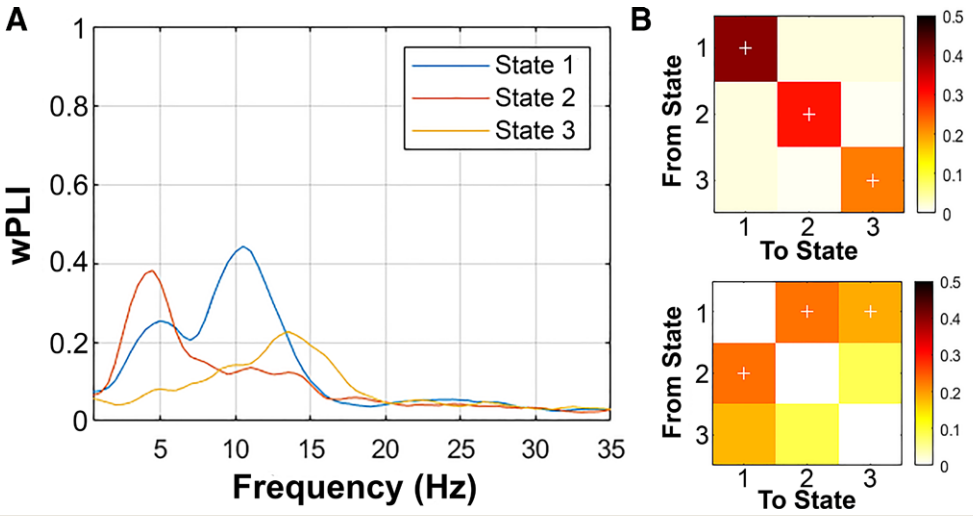

Fig. 2. Dynamic cortical connectivity data presented (n = 49 participants with available, artifact-free data) during the anesthetic maintenance period. (*A*) Frontal-parietal connectivity states are characterized by alpha predominance (State 1), theta predominance (State 2), and suppression of both alpha and theta connectivity (State 3). (*B*) Transition probabilities between connectivity states are presented. The *top* represents all possibilities, including connectivity states remaining within their current state *versus* transitioning to a different state. Each connectivity state was more likely to remain within its state (indicated by the + sign, false-discovery rate adjusted $P < 0.05$) rather than transition to a different connectivity state. The *bottom* only includes shifts to different connectivity states. When shifts between connectivity states occurred, the most likely transition was between State 1 (alpha frontal-parietal connectivity) and State 2 (theta frontal-parietal connectivity). wPLI, weighted phase lag index.

Measurement Information System-based Cognitive Function Abilities 4a test, but this correlation was not statistically significant ($\rho = -0.387$, $P = 0.062$, uncorrected).

Post Hoc Analysis: Cognitive Domains Affected by Delirium

A *post hoc* analysis was conducted to determine how delirium affected cognitive performance across different domains tested—attention and inhibitory control, working memory, and processing speed—based on National Institutes of Health Cognition Toolbox fully corrected T-scores. Overall, working memory and processing speed were significantly reduced in patients who screened positive for delirium compared to nondelirium encounters (fig. 3B).

Discussion

Preoperative posterior alpha power, frontal-parietal connectivity, and cerebral oximetry measures were not associated with postoperative cognitive function, as assessed *via* National Institutes of Health Cognition Toolbox tests. Intraoperative propensity for global theta connectivity was associated with postoperative delirium. None of these cerebral physiologic measures correlated with self-reported cognitive or general health outcomes 3 months after surgery. Overall, these results suggest that a brief snapshot of highly variable dynamic measures (*e.g.*, cortical connectivity) is not strongly predictive of cognitive or health outcomes after surgery.

Spectral Dynamics, Cortical Connectivity, and Neurocognitive Function

No association was observed with perioperative alpha power and postoperative cognitive outcomes after adjustment for relevant confounders. The cognitive functions tested in this study—attention, working memory, and processing speed—involve neural activity across multiple frequency bands.[34] For example, attentional network activities are reflected by distinct oscillatory patterns from theta through high-frequency gamma activity.[34] Likewise, broadband activity contributes to cognitive processing speed,[35] and working memory is supported by a complex interplay involving frontal theta and parietal alpha rhythms.[36] Spectral edge frequency, which reflects cortical activity across multiple bands, may thus be a more appropriate electroencephalographic biomarker for detecting neurocognitive deficits (Supplemental Digital Content 3, Table S6, https://links.lww.com/ALN/D180).[32,33] Neurocognitive disorders (*e.g.*, Alzheimer's disease and related dementias) manifest as macroscale, global changes involving multiple neuroanatomical regions,[37] rather than the posterior parietal region, which was the primary focus of this study. As such, it is perhaps not surprising that transient perioperative cortical oscillations, restricted to specific frequency bands and anatomical regions, were not associated with postoperative neurocognitive function in this study.

Similar to perioperative posterior alpha power, frontal-parietal alpha connectivity was not associated

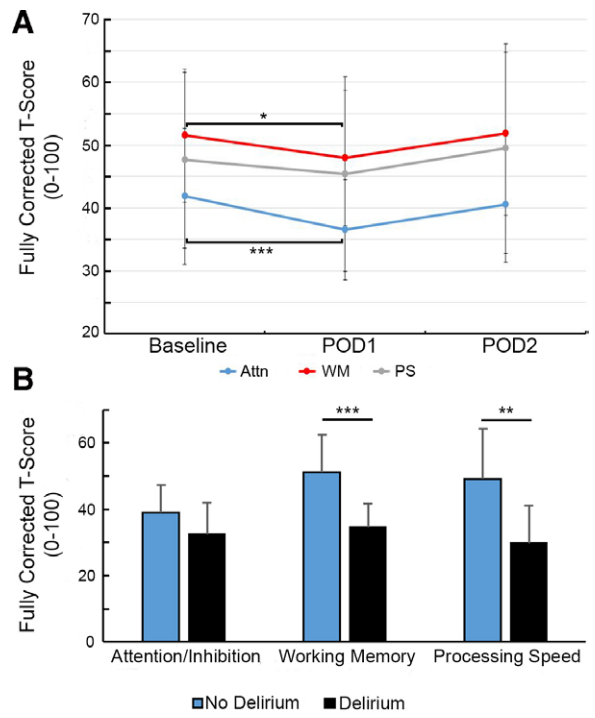

Fig. 3. (*A*) Temporal trends in cognitive function from baseline through postoperative day (POD) 2. Attention (Attn) scores are derived from the Flanker Inhibitory Control and Attention Test (n = 58, baseline; n = 40, POD 1; n = 32, POD 2), working memory (WM) scores are from the List Sorting Working Memory Test (n = 58, baseline; n = 40, POD 1; n = 32, POD 2), and processing speed (PS) is from the Pattern Comparison Processing Speed Test (n = 56, baseline; n = 40, POD 1; n = 31, POD 2). Attention and WM scores were significantly reduced on POD 1 compared to baseline, as assessed *via* generalized estimating equations. There were no statistically significant differences detected between cognitive function scores on POD 2 compared to baseline. (*B*) Postoperative scores from all available delirium encounters (n = 7) were compared to nondelirium encounters (n = 65). During delirium, WM and PS scores were significantly reduced compared to nondelirium encounters. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ *via* independent *t* tests. *Error bars* reflect SD in both panels.

with postoperative cognitive function scores. In a previous study of healthy volunteers undergoing general anesthesia, cortical connectivity—measured *via* phase lag index, the same connectivity measure used in this study—did not distinguish between different stages of postanesthetic neurocognitive recovery.[8] Connectivity measures such as phase lag index are limited in their ability to capture the spatiotemporal coordination of neural activity that subserves cognitive function. More sophisticated neurophysiologic methods that capture the global repertoire of brain states and dynamic coordination of neural processes may thus be required to identify the cortical dynamics underlying perioperative cognitive function. Indeed, Alzheimer's disease and related dementias reflect macroscale disruptions in oscillatory synchrony across multiple frequency bands and anatomical regions, including the prefrontal cortex and temporal lobe.[38–40] Future electroencephalographic strategies for identifying perioperative neurocognitive disorders and function may thus benefit from incorporating approaches that involve multiple frequency bands, anatomical regions, and analytical techniques.

Intraoperative Neurophysiology and Cerebral Oximetry

In this study, shifts to intraoperative theta connectivity were associated with postoperative delirium. Frontal-parietal theta connectivity during surgical anesthesia correlates with older age, which is a consistent predictor of delirium.[13,27] Theta connectivity states also occurred in lieu of frontal alpha connectivity states, which is relevant given that intraoperative frontal alpha oscillations correlate with preoperative cognitive function.[41] As such, the presence of frontal-parietal theta connectivity and the simultaneous absence of frontal alpha oscillations might reflect an aging, vulnerable brain prone to development of postoperative delirium. Indeed, cognitive decline is associated with increased theta activity, which may be reflective of cerebral hypoperfusion and regional atrophy.[42] Intraoperative shifts toward theta activity, along with electroencephalogram suppression,[43] may thus represent a neurophysiologic phenotype reflective of neurocognitive vulnerability. However, delirium was a secondary outcome, and intraoperative theta connectivity was not associated with cognitive function scores postoperatively. The current findings are thus hypothesis-generating, and the relationship between theta connectivity states and perioperative cognitive function thus warrants additional testing.

Intraoperative cerebral desaturation was uncommon in this study, as only 3 of 59 (5%) of participants met prespecified criteria for a desaturation event. Moreover, these three participants experienced fairly unremarkable postoperative courses, other than one participant experiencing PACU delirium. Intraoperative cerebral oximetry monitoring may be more useful in relatively high-risk populations, such as cardiac surgery patients and those with pre-existing cerebrovascular disease, as desaturation events are more common with these patients.[44,45]

Cognitive Domains Affected by Delirium

Impaired working memory and processing speed were observed during episodes of delirium. These findings align with basic science models of postoperative cognitive dysfunction, which demonstrate working memory impairment in mice with pre-existing neurodegeneration.[46] Likewise, a cohort study of cardiac surgery patients revealed that preoperative working memory scores, based on the Mini

Table 2. Perioperative Neurophysiologic Associations with Postoperative National Institutes of Health Toolbox Scores

Preoperative Neurophysiologic Measure	Partial Spearman Correlation (ρ)	*P* Value	Adjusted Estimate (β)	95% CI	*P* Value
Baseline relative parietal alpha (%)	–0.03	0.854	–0.04	–0.15 to 0.08	0.552
Baseline-PACU parietal alpha (%)	–0.19	0.309	–0.12	–0.26 to 0.02	0.102
Baseline frontal-parietal alpha weighted phase lag index (n)	–0.10	0.570	–3.43	–20.02 to 13.17	0.686
Baseline-PACU frontal-parietal alpha weighted phase lag index (n)	–0.19	0.305	–3.69	–16.65 to 9.27	0.577
Intraoperative theta frontal-parietal weighted phase lag index occurrence rate (%)	–0.25	0.171	–1.40	–11.05 to 8.25	0.776
Average baseline cerebral oximetry (%)	0.21	0.246	0.16	–0.04 to 0.36	0.107

Partial correlation coefficients and sequential generalized estimating equation model estimates presented. Partial correlation analysis controls for the fully corrected baseline mean score of all three National Institutes of Health Toolbox tests, and generalized estimating equation models are adjusted for American Society of Anesthesiologists Physical Classification Score, depression, subjective pain during cognitive assessment (*via* visual analog scale), and cumulative daily opioid consumption leading up to assessment. Fully corrected T-scores were included, which account for age, sex, race, ethnicity, and level of education. Data were available for n = 33 participants for the partial correlation analysis and n = 58 participants with 130 observations for the generalized estimating equations.

PACU, postanesthesia care unit.

Table 3. Perioperative Neurophysiologic Associations with Delirium

Preoperative Neurophysiologic Measure	Participants	Repeated Measures	Degrees of Freedom	F Statistics	*P* Value
Baseline relative parietal alpha (%)	47	288	(1,6,281)	0.18	0.674
Baseline-PACU parietal alpha (%)	38	236	(1,6,229)	0.01	0.913
Baseline frontal-parietal alpha weighted phase lag index	47	288	(1,6,281)	0.27	0.606
Baseline-PACU frontal-parietal alpha weighted phase lag index	40	246	(1,6,239)	0.02	0.887
Intraoperative theta frontal-parietal weighted phase lag index occurrence rate (%)	49	298	(1,6,291)	4.53	0.034
Average baseline cerebral oximetry (%)	56	334	(1,6,327)	0.85	0.358

Delirium was assessed *via* the 3-min Confusion Assessment Method at preoperative baseline, in the postanesthesia care unit (PACU), and twice daily during the first 3 postoperative days. A repeated-measures ANOVA was used to determine associations between neurophysiologic variables listed and delirium presence during this time period. Tukey Studentized Range Test was used to control the Type I experiment-wise error rate. As displayed in the table, theta connectivity occurrence rate was significantly higher in patients experiencing postoperative delirium compared to those not experiencing any delirium (mean %, 47% *vs.* 31%, respectively; dF[1,6,291], F value, 4.53; $P = 0.034$). Data were available from n = 38 to n = 56 participants across ANOVA analyses as displayed in the table.

Mental Status Exam, were independently associated with delirium risk.[47] Processing speed is associated with white matter integrity,[48] and reduced white matter integrity has been observed with delirium.[49] Identifying specific cognitive domains affected by delirium is important, as even subsyndromal states of delirium are associated with increased mortality.[50] Working memory and processing speed may thus serve as target cognitive domains for future diagnostic evaluations and therapeutic interventions.

Methodologic Strengths and Limitations

Important study strengths are worth highlighting. A whole-scalp electroencephalography system was used, which enabled analysis of global neurophysiologic measures, such as frontal-parietal connectivity. Dynamic connectivity changes were also analyzed across all three phases of the perioperative period, allowing for a more comprehensive assessment of the dynamic, temporal connectivity changes that occur and their relationship to postoperative neurocognitive recovery. The intra- and perioperative oscillatory and connectivity patterns identified aligned with previous whole-scalp electroencephalographic findings (*e.g.*, preoperative frontal-parietal alpha connectivity, intraoperative frontal-parietal alpha and theta connectivity, *etc.*).[25] This suggests reliability of electroencephalographic measures obtained, given the reproducibility of previous neurophysiologic findings.[25] Electroencephalography and cerebral oximetry data were also simultaneously collected in the same participants, allowing for direct comparisons. Importantly, the analysis included adjustments for relevant clinical confounders, including ASA Physical Classification Score, subjective pain scores, and daily cumulative opioid consumption that preceded the cognitive testing session, as comorbidities, pain, and opioids all impact cognition.[30] Moreover, the fully corrected National Institutes of Health Toolbox scores account for age, sex, race, ethnicity, and level of education. Collectively, the adjusted analyses thus account for several important confounders that may impact cognitive function. The National Institutes of Health

Toolbox Cognition Battery also offers validated tests that are standardized to the U.S. population, with demographically corrected normative values. This battery allowed for direct assessment of cognitive domains affected by delirium with validated, standardized tests designed to analyze cognitive changes with aging.

Key limitations also warrant consideration. First, attrition was present with cognitive function testing, as participants reported testing difficulty because of postoperative nausea, pain, and overall discomfort (Supplemental Digital Content 3, Table S1, https://links.lww.com/ALN/D180). Nonetheless, regression estimates between variables are not substantially affected with longitudinal data, particularly when estimates are not dependent on baseline variables.[51] As such, imputation analysis was deferred. As an additional limitation, study inclusion criteria allowed for patients 18 yr or older. This design allowed for comparison of electroencephalographic biomarkers and cerebral oximetry across a broad age range, such that results could be compared between relatively young, healthy participants and older patients who are more prone to neurocognitive disorders. Nonetheless, this methodologic approach may have limited the ability to detect neurophysiologic signatures in older patients who may have clinical (or subclinical) features of neurocognitive impairment. Missing data were present with electroencephalography and cerebral oximetry as well, largely due to inadequate time for preoperative data collection or artifactual interference. Prefrontal electroencephalographic channels were not included given the presence of cerebral oximetry electrodes. Prefrontal neurophysiologic analysis was thus not possible for the current study. Nonetheless, the focus on posterior alpha rhythms was relevant given the previous associations with parietal alpha power and cognitive recovery after general anesthesia.[8] Finally, the sample size of the study was limited, as power analysis was based on moderate-to-strong correlation strengths. This is because the correlation strength of these physiologic measures with cognitive outcomes should ideally exceed the predictive value of clinical, non-neurobiological measures in order to be clinically useful. The final sample size available for analysis (n = 59) is ultimately similar to previous studies of perioperative neurophysiologic and neurocognitive function.[10,11,41,52]

In summary, brief, preoperative resting-state alpha power and connectivity were not associated with postoperative cognitive outcomes, nor was baseline cerebral oximetry. Propensity for intraoperative theta connectivity states may reflect neurocognitive vulnerability, although additional, confirmatory studies are required.

Acknowledgments

The authors would like to acknowledge the Michigan Medicine Department of Anesthesiology (Ann Arbor, Michigan) for support of study operations.

Research Support

Supported by the National Institutes of Health (Bethesda, Maryland; grant No. K23GM126317; Dr. Vlisides) and the Foundation for Anesthesia Education and Research (Schaumburg, Illinois; Drs. Vlisides and Maywood). Funding was also provided by departmental and institutional resources.

Competing Interests

Dr. Vlisides and A. M. McKinney receive support from Blue Cross Blue Shield of Michigan (Detroit, Michigan) for quality improvement initiatives related to delirium. The other authors declare no competing interests.

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Supplemental Digital Content 2: Expanded Electroencephaolgram Methods, https://links.lww.com/ALN/D179
Supplemental Digital Content 3: Additional Data and Analyses, https://links.lww.com/ALN/D180

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