A Prospective Study of Age-dependent Changes in Propofol-induced Electroencephalogram Oscillations in Children

Johanna M. Lee, A.B., Oluwaseun Akeju, M.D., M.M.Sc., Kristina Terzakis, Kara J. Pavone, B.S., Hao Deng, M.B.B.S., M.P.H., Timothy T. Houle, Ph.D., Paul G. Firth, M.B., Ch.B., Erik S. Shank, M.D., Emery N. Brown, M.D., Ph.D., Patrick L. Purdon, Ph.D.

ABSTRACT

Background: In adults, frontal electroencephalogram patterns observed during propofol-induced unconsciousness consist of slow oscillations (0.1 to 1 Hz) and coherent alpha oscillations (8 to 13 Hz). Given that the nervous system undergoes significant changes during development, anesthesia-induced electroencephalogram oscillations in children may differ from those observed in adults. Therefore, we investigated age-related changes in frontal electroencephalogram power spectra and coherence during propofol-induced unconsciousness.

Methods: We analyzed electroencephalogram data recorded during propofol-induced unconsciousness in patients between 0 and 21 yr of age (n = 97), using multitaper spectral and coherence methods. We characterized power and coherence as a function of age using multiple linear regression analysis and within four age groups: 4 months to 1 yr old (n = 4), greater than 1 to 7 yr old (n = 16), greater than 7 to 14 yr old (n = 30), and greater than 14 to 21 yr old (n = 47).

Results: Total electroencephalogram power (0.1 to 40 Hz) peaked at approximately 8 yr old and subsequently declined with increasing age. For patients greater than 1 yr old, the propofol-induced electroencephalogram structure was qualitatively similar regardless of age, featuring slow and coherent alpha oscillations. For patients under 1 yr of age, frontal alpha oscillations were not coherent.

Conclusions: Neurodevelopmental processes that occur throughout childhood, including thalamocortical development, may underlie age-dependent changes in electroencephalogram power and coherence during anesthesia. These age-dependent anesthesia-induced electroencephalogram oscillations suggest a more principled approach to monitoring brain states in pediatric patients. **(Anesthesiology 2017; 127:293-306)**

In the United States, approximately 6 million children[1–3] are placed under general anesthesia or sedation for surgical and nonsurgical procedures each year. Although general anesthesia and sedation are considered safe, animal studies suggest exposure to anesthetic drugs at a young age could have long-term neurodevelopmental effects.[1,4,5] How this applies to human children receiving general anesthesia is an area of ongoing investigation.[6,7] Although limited retrospective studies suggest a link between anesthetic exposure in early development and later neurocognitive deficits,[1,4,5] recent large-scale clinical trials have found that short sevoflurane exposures are not associated with changes in performance on pediatric neurocognitive assessments.[8,9] However, it remains unclear whether repeated or prolonged exposures could have adverse effects on the developing brain. Typically, anesthetic drugs are dosed using population-based pharmacologic models that account for a patient's age, weight, and other variables.[10] However, individual patients may respond differently to anesthetic drugs. In adults, the anesthetic concentrations required to induce unconsciousness can vary by as much as a factor of 2 above or below suggested doses.[11] If anesthetic drugs are underdosed, intraoperative awareness can occur.[12,13] On

What We Already Know about This Topic

- General anesthesia induces highly structured brain oscillations that have been well characterized in adults but not children
- The nervous system undergoes significant changes from birth to adulthood, including thalamocortical development, myelination, and pruning

What This Article Tells Us That Is New

- In 97 patients 0-21 yr old, propofol-induced electroencephalogram oscillations were qualitatively similar among patients 1 yr through adulthood (slow and coherent alpha oscillations), but not for children less than 1 yr (noncoherent alpha oscillations)
- Such age-dependent changes in electroencephalogram oscillations likely reflect critical neurodevelopmental changes and have implications for brain monitoring in children

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Submitted for publication February 19, 2016. Accepted for publication May 2, 2017. Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts (J.M.L., O.A., K.T., K.J.P., H.D., T.T.H., P.G.F., E.S.S., E.N.B., P.L.P.); Harvard Medical School, Boston, Massachusetts (J.M.L., O.A., P.G.F., E.S.S., E.N.B., P.L.P.); Harvard-Massachusetts Institute of Technology Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts (J.M.L., E.N.B.); Department of Brain and Cognitive Science, Massachusetts Institute of Technology, Cambridge, Massachusetts (E.N.B.); and Institute for Medical Engineering and Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts (E.N.B.).

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the other hand, there is growing evidence that exposure to anesthetic drugs in excess of what is required to maintain general anesthesia could have detrimental effects: children who receive greater than 4% sevoflurane can show epileptiform activity,[14,15] and adults who experience burst suppression, a state of anesthesia-induced coma beyond what is required for unconsciousness, are at greater risk of postoperative delirium and cognitive deficits.[16,17] Consequently, it remains important to consider how to manage the level of anesthetic exposure when surgery under general anesthesia is required and cannot be postponed.

One approach for managing anesthetic exposure in children would be to adjust anesthetic dosing using electroencephalogram-based brain monitoring.[18] Studies in adults have shown that general anesthetics induce structured electroencephalogram oscillations that reflect activity in specific neural circuits.[19–22] Given that the nervous system undergoes significant changes from birth to adulthood,[23] it is not surprising that anesthesia-induced electroencephalogram oscillations in children differ significantly from those in adults,[24–28] and that current depth-of-anesthesia monitors developed for adults are inaccurate when applied to children.[18,24–29] By understanding how the effects of general anesthesia change during development, we may be able to develop more effective ways of tracking and establishing appropriate brain states in pediatric patients and, in doing so, enhance anesthetic safety.

Frontal electroencephalogram patterns observed in adults during propofol-induced unconsciousness consist of large amplitude slow oscillations (0.1 to 1 Hz) and coherent alpha oscillations (8 to 13 Hz).[21,22,30,31] We recently reported that sevoflurane-induced electroencephalogram oscillations vary with age in children.[18] Age-related changes in propofol-induced electroencephalogram oscillations in children have not been studied. We hypothesized that electroencephalogram dynamics during propofol-induced unconsciousness in children would vary with age in a manner similar to sevoflurane. We therefore performed a prospective observational study to characterize and compare age-dependent propofol electroencephalogram dynamics.

Materials and Methods

Patient Selection and Data Collection

This prospective observational study was approved by the Human Research Committee at Massachusetts General Hospital, Boston, Massachusetts. We collected a total of 155 cases from individuals between 0 and 21 yr of age. Of these, we identified 150 cases in which propofol was administered as the sole primary anesthetic. We excluded patients who had neurologic or psychiatric abnormalities, including autism, attention-deficit/hyperactivity disorder, seizures, and other congenital or psychiatric conditions (n = 32). We also excluded cases with electroencephalogram artifacts and burst suppression (n = 11), cases too short to identify a stable epoch without other drugs administered (n = 4), and subjects who received the potentially confounding adjunct drugs midazolam or scopolamine (n = 6). We ultimately identified a total of 97 cases that contained a 2-min epoch of stable propofol infusion with no other anesthetic drugs given for at least 5 min before the epoch. Figure 1 summarizes patient selection, with inclusion and exclusion criteria. We analyzed patient characteristics for each age group, including age, gestational age, sex, weight, procedure type, and length of procedure. We also tested whether propofol infusion rates were significantly different between age groups, using a Kruskal–Wallis test by rank.

We recorded four-channel frontal electroencephalogram data using the SEDLine brain function monitor (Masimo Corporation, USA). We selected time windows for analysis from the recorded electroencephalograms using information from the electronic anesthesia record (Metavision, USA). The concentrations of drugs administered to patients were manually recorded in the electronic anesthesia record by the anesthesia providers. For each patient, we identified a 2-min epoch with a stable propofol infusion rate. For patients induced with inhaled anesthesia (sevoflurane and/or nitrous oxide), this 2-min period occurred at least 5 min after cessation of the inhaled anesthetic. Two of the authors (J.M.L., K.T.) visually inspected all electroencephalogram data for each patient and manually identified epochs that were free of noise, artifacts, or segments of burst suppression for analysis.

Spectral Analysis

For each patient, we computed the power spectrum and visualized the spectrogram using the multitaper spectral analysis methods implemented in the Chronux toolbox in MATLAB (Mathworks, USA).[32] The parameters used for the multitaper spectral analysis were: sampling frequency Fs = 250 Hz, window length T = 2 s with no overlap, time-bandwidth product TW = 3, and number of tapers K = 5. To calculate estimates of power spectra, we used an electroencephalogram derivation equally weighting the signals from the channels Fp1, Fp2, F7, and F8. Median power was calculated from the electroencephalogram spectrum of each patient in the slow (0.1 to 1 Hz) and alpha (8 to 13 Hz) bands, in addition to total power (0.1 to 40 Hz). We modeled the total power and power in the slow and alpha bands as polynomial functions of age, using forward stepwise multiple linear regression analysis to select the polynomial order.

Fentanyl can induce electroencephalogram slow oscillations at high doses.[33] We therefore sought to analyze potential confounds related to fentanyl administration. To quantify potential interactions between fentanyl and age, we calculated the correlation between age polynomial terms (*i.e.*, age, age^2) and fentanyl dose (μg/kg). To quantify the potential influence of fentanyl administration on slow

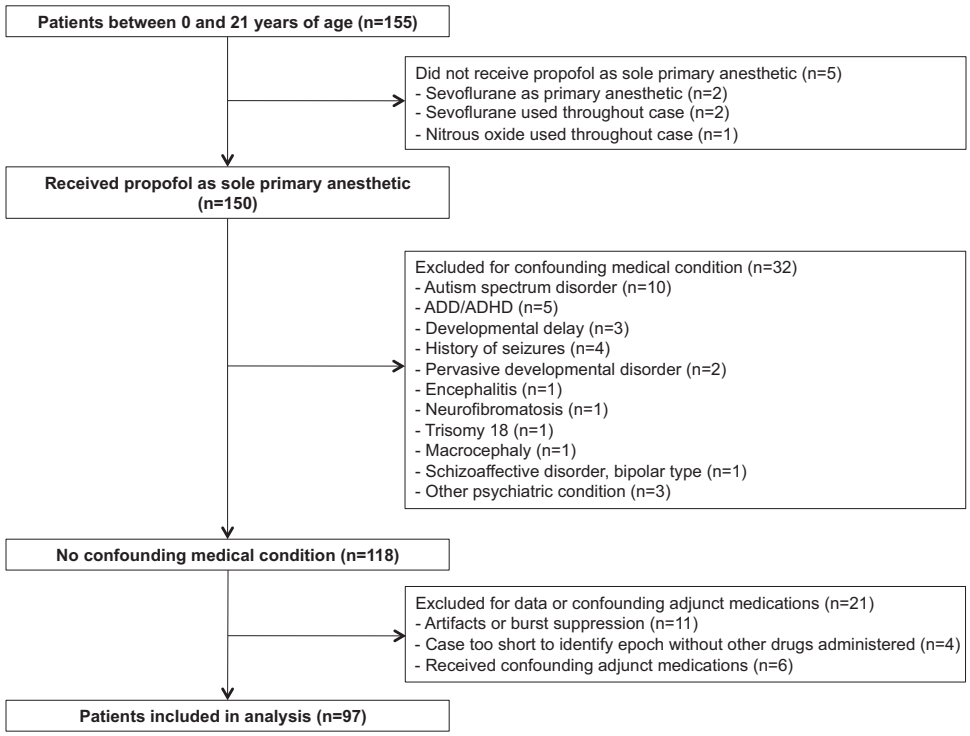

Fig. 1. Patient selection: inclusion and exclusion criteria. We collected 155 cases from individuals between 0 and 21 yr of age. Of these, we identified 150 cases in which propofol was administered as the sole primary anesthetic during maintenance of anesthesia. We excluded patients who had confounding medical conditions, including autism, attention-deficit/hyperactivity disorder (ADD/ADHD), history of seizures, and other congenital or psychiatric conditions (n = 32). Finally, we also reviewed cases for electroencephalogram artifacts, burst suppression, or other confounding adjunct drugs administered, making it difficult to identify a clean 2-min segment of time during maintenance (n = 21). We ultimately identified a total of 97 cases that contained a 2-min epoch of stable propofol infusion with no other anesthetic drugs given for at least 5 min preceding the epoch.

oscillation power, we performed a regression analysis featuring the age polynomial terms and fentanyl dose. We used the statistical software R to perform these analyses.

In addition, we estimated group-level spectra and spectrograms from the selected epochs by taking the median across all patients within each of the following age groups: 4 months to 1 yr old (n = 4), greater than 1 to 7 yr old (n = 16), greater than 7 to 14 yr old (n = 30), and greater than 14 to 21 yr old (n = 47). We also computed an age-varying spectrogram using overlapping moving windows (0.5 yr) spanning a ±2 yr age range in patients ranging from 1 to 21 yr.

Coherence Analysis

The coherence $C_{xy}(f)$ function between two signals x and y is defined as

$$C_{xy}(f) = \frac{|S_{xy}(f)|}{\sqrt{S_{xx}(f)S_{yy}(f)}}$$

where $S_{xy}(f)$ is the cross-spectrum between the signals $x(t)$ and $y(t)$, $S_{xx}(f)$ is the power spectrum of the signal $x(t)$, and $S_{yy}(f)$ is the power spectrum of the signal $y(t)$.[32] For each patient, we computed the coherence between two bipolar frontal channels, F7 – Fp1 (left) and F8 – Fp2 (right), using the multitaper methods implemented in the Chronux toolbox in MATLAB.[32] The parameters used for the multitaper coherence analysis were: sampling frequency Fs = 250 Hz, window length T = 2 s with no overlap, time-bandwidth product TW = 3, and number of tapers K = 5. Median coherence was calculated from the electroencephalogram of each patient, within the frequency ranges defined above. We modeled frontal coherence in the slow, theta, and alpha bands as polynomial functions of age and used forward stepwise multiple linear regression analysis to select the polynomial order. We then estimated group-level coherence and coherograms for the selected epochs by taking the median across all patients within each of the age groups specified above. We also computed an age-varying coherogram using overlapping moving windows (0.5 yr) spanning a ±2 yr age range in patients ranging from 1 to 21 yr.

Statistical Analysis

We used frequency-domain bootstrap methods to determine the CIs for the spectral and coherence estimates and for differences in power and coherence between groups. We calculated 95% CIs for each spectral and coherence estimate, as well as for differences between power spectra or coherences, using a bootstrap procedure. Briefly, bootstrap

samples (n = 5,000) for the median spectrum, median coherence, and differences in spectrum or coherence were drawn from each group. Bootstrap CIs were calculated using the percentile method.[34] To take into account the spectral resolution of the power spectra estimates, for frequencies f greater than 2 W, power or coherence between two groups was considered to have a statistically significant difference only if the significance threshold (95% CI did not contain 0) was met for consecutive frequencies throughout a frequency interval greater than or equal to the spectral resolution 2 W. For frequencies $0 \leq f \leq 2W$, differences in spectral estimates were considered significant only if the significance threshold was met throughout a consecutive frequency range from 0 to a maximum of (f, W) less than or equal to 2 W.[29,35]

We also used the bootstrap to compare the age dependence of different electroencephalogram features, such as alpha and slow power. Briefly, bootstrap samples for each regression model were constructed by adding normally distributed errors to the fitted regression curve. The variance of the normally distributed bootstrap errors was set equal to the residual variance of the original regression analysis. The regression relationship was then reestimated for each bootstrap sample to construct the 95% CI for the regression curve. CIs for differences in the regression curves were estimated by taking the difference in regression curves from randomly drawn bootstrap samples from each group being compared. Power or coherence between two groups was considered to have a statistically significant difference if the bootstrap 95% CI of the difference did not include 0. All bootstrap analyses were computed using MATLAB.

Results

Analysis of Patient Characteristics

Table 1 summarizes the characteristics of patients included in the study, and table 2 summarizes the propofol infusion rates and fentanyl doses administered before the chosen epoch. Propofol infusion rates were not significantly different between age groups (Kruskal–Wallis test by rank, $P = 0.21$).

Power Spectra Analysis

For patients greater than 1 yr old, the electroencephalogram spectra show a structure that is qualitatively similar regardless of age, featuring slow and alpha oscillations (fig. 2). Total electroencephalogram power (0.1 to 40 Hz) peaked at approximately 8 yr old and subsequently declined with increasing age

Table 1. Characteristics of Patients Included in Analysis (n = 97)

	4 mo to 1 yr (n = 4)	>1–7 yr (n = 16)	>7–14 yr (n = 30)	>14–21 yr (n = 47)
Age (yr), median (range)	0.6 (0.3–0.9)	4.5 (1.4–6.9)	11 (7.3–13.9)	17.3 (14–20.7)
Gestational age at birth (weeks), median (range)*	39 (35–40) (n = 4)	40 (36–40) (n = 12)	40 (36–40) (n = 12)	40 (36–40) (n = 17)
Sex (male), n (%)	2 (50)	11 (68.8)	17 (56.7)	26 (55.3)
Weight (kg), median (range)	5.5 (5–8)	15 (9–28)	37 (21–80)	63 (35–106)
Procedure type, n (%)				
EGD		11 (68.8)	23 (76.7)	22 (46.8)
EGD + colonoscopy	1 (25)	3 (18.8)	7 (23.3)	23 (48.9)
EGD + sigmoidoscopy	2 (50)			
Colonoscopy				2 (4.3)
Sigmoidoscopy		1 (.06)		
MRI brain and lumbar puncture	1 (25)			
Right inguinal hernia repair		1 (.06)		
Length of procedure (min), median (range)	12 (7–74)	9.5 (5–43)	14.5 (5–129)	20 (5–107)

We report the characteristics of subjects included in the analysis for each age group.

*Gestational age was included for subjects who had this information documented in their medical records. For the purposes of this paper, a "full-term" birth as documented in the medical records was equated with 40 weeks gestational age at birth.

EGD = esophagogastroduodenoscopy; MRI = magnetic resonance imaging.

Table 2. Medications Administered

	4 mo to 1 yr (n = 4)	>1–7 yr (n = 16)	>7–14 yr (n = 30)	>14–21 yr (n = 47)
Propofol infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$), median (range)*	250 (200–300)	250 (200–333)	250 (250–444)	250 (120–300)
Fentanyl (μg/kg), median (range)	1.13 (1–2) (n = 3)	0.98 (0.59–1.33) (n = 14)	0.79 (0.61–2.27) (n = 19)	0.83 (0.35–3.03) (n = 40)

We report the weight-adjusted propofol infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$) and fentanyl dose (μg/kg).

*The propofol infusion rates were not significantly different (Kruskal–Wallis test by rank, $P = 0.21$).

(fig. 2I). Multiple linear regression analysis showed a significant model fit for total electroencephalogram power (fig. 2I).

We compared the median spectra of the following age groups: 4 months to 1 yr old, greater than 1 to 7 yr old, greater than 7 to 14 yr old, and greater than 14 to 21 yr old (fig. 3). We found that a distinct increase in power in the alpha oscillation frequency range was not apparent until approximately 1 yr of age (fig. 3). Instead, there appeared to be an increase in spectral power over a broader frequency range (fig. 3, A–E). For patients greater than 1 yr old, the spectra and spectrograms showed electroencephalogram features that were qualitatively similar with distinct peaks in the slow and alpha oscillation frequency ranges (fig. 3, B–D and F–H). Statistically significant differences in power between age groups are reported in table 3.

Coherence Analysis

We found age-related variation in the electroencephalogram coherence and coherograms during propofol-induced unconsciousness (fig. 4). In patients 1 to 21 yr old, we observed coherent frontal alpha oscillations (fig. 4, B–D and F–H), which were not seen in patients less than 1 yr old (fig. 4, A and E). We also observed that slow coherence increased with age, particularly in the adolescent years (fig. 4, C, D, G, and H). For patients greater than 1 yr old, the coherence and coherograms showed electroencephalogram features that were qualitatively similar, with prominent peaks in the alpha oscillation frequency range (fig. 4, B–D and F–H). Statistically significant differences in power between age groups are reported in table 3.

Slow and Alpha Oscillations

To further explore the age-related variations in frontal power and coherence, we investigated age-related changes in the slow and alpha oscillations, which are prominent during propofol-induced unconsciousness. We compared regression models characterizing slow and alpha oscillation power across age (fig. 5). Frontal slow oscillation power peaked at approximately 11.6 yr of age (95% CI, 10.7 to 12.5 yr; fig. 5), whereas frontal alpha oscillation power peaked at approximately 7.3 yr of age (95% CI, 6.5 to 8.2 yr; fig. 5). The difference between these peak ages was statistically significant (95% CI, 3.0 to 5.5 yr). Alpha oscillation power was greater than slow power from 3.6 to 5.3 yr, whereas slow oscillation power was greater than alpha power from 10.5 to 20.3 yr of age (95% CI, bootstrap analysis).

We found no evidence of age dependence in fentanyl administration: the correlation coefficient between age and fentanyl dose was −0.029, and the correlation coefficient between age^2 and fentanyl dose was 0.011. These correlation coefficients were not statistically significant. When fentanyl dose was added as a regressor to the model for slow oscillation power, we found that fentanyl dose did not have a significant association with slow oscillation power (coefficient = −1.08112, 95% CI = [−2.28, 0.11], P = 0.08; equivalent to ~1 dB power). This suggests that fentanyl dose did not have a significant effect on slow oscillation power in this study.

We also compared regression models characterizing slow and alpha coherence across age (fig. 6). Slow coherence appeared to increase linearly between 1 and 21 yr of age (fig. 6A), whereas alpha coherence peaked at 8.9 yr of age (95% CI, 7.4 to 12.2 yr; fig. 6B). Alpha coherence was significantly greater than slow coherence for ages 2.6 to 14 yr (95% CI, bootstrap analysis; fig. 6C).

Infants under 2 Yr of Age

Because we observed qualitatively significant changes between the 4 month to 1 yr and 1 yr to 7 yr age groups, we decided to examine this transition in more detail by comparing patients between 4 months and 1 yr old and patients between 1 and 2 yr old (fig. 7). For patients less than 2 yr of age, we consistently observed slow (0.1 to 1 Hz) oscillations in all subjects (figs. 7A and 2, A and E). However, the power spectrum in subjects less than 1 yr old illustrates the relative absence of well-defined alpha (8 to 13 Hz) oscillations, instead showing oscillations over a broader and faster frequency range, spanning approximately 12 to 25 Hz. Quantitatively, electroencephalogram power is significantly greater in the 1 to 2 yr age group relative to the 4 month to 1 yr age group for the following frequency ranges: 0 to 15.14 Hz and 20.51 to 33.69 Hz (95% CI, bootstrap analysis; fig. 7A).

We also observed that although frontal alpha power seemed to appear at about 5 months of age (results not shown),[36] frontal alpha coherence was not apparent until between 1 and 2 yr of age (fig. 7B). Frontal coherence is significantly greater in the 1- to 2-yr age group relative to the 4-month to 1-yr age group over a frequency range of 6.35 to 11.72 Hz (95% CI, bootstrap analysis; fig. 7B).

Discussion

In this study, we found age-related changes in the electroencephalogram power spectra and coherence during propofol-induced unconsciousness in pediatric patients, summarized with an age-varying spectrogram and coherogram from 1 to 21 yr of age in figure 8. The increase in electroencephalogram power over the first several years of life, followed by a decline in the adolescent years, is generally consistent with previous pediatric electroencephalogram studies during wakefulness,[37,38] sleep,[39,40] and sevoflurane anesthesia.[18,28,41] These age-related changes in the electroencephalogram could reflect underlying neurodevelopmental processes that occur over childhood and adolescence, including synaptogenesis, neural pruning, and the maturation of neural circuits.[18,23,42–45] Early postnatal brain development is characterized by marked myelination and synaptogenesis, with synaptic density peaking around 6 to 10 yr of age.[23,44–46] After this process, the brain undergoes neural pruning and synaptic elimination to strengthen the newly formed neural circuits and reduce the

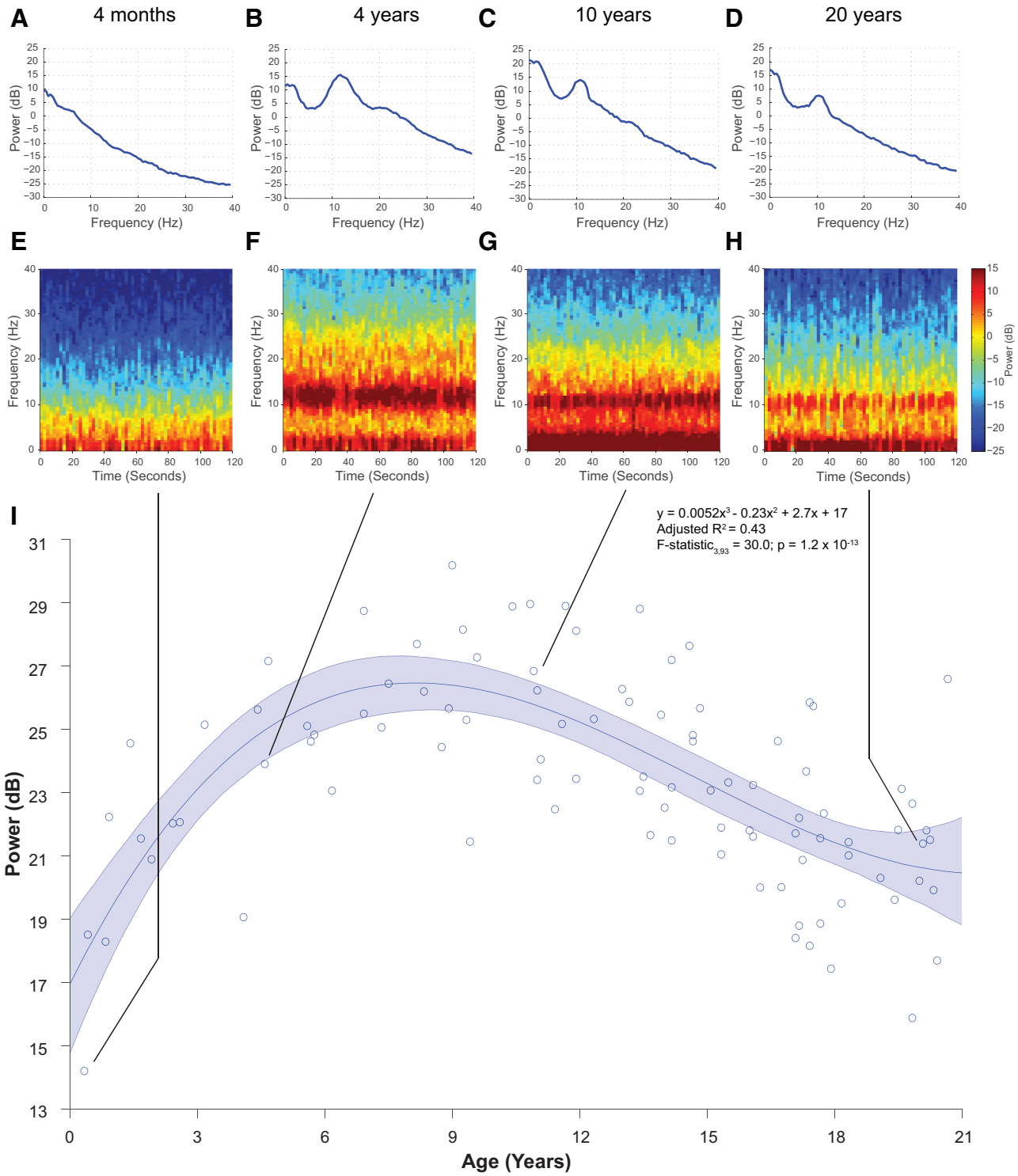

Fig. 2. Age-related variation in spectra, spectrograms, and total electroencephalogram power from 0 to 21 yr old. (*A–D*) Representative frontal electroencephalogram median spectra in selected patients aged 4 months, 4 yr, 10 yr, and 20 yr show that slow (0.1 to 1 Hz) oscillations are present at all ages during propofol general anesthesia maintenance. Alpha (8 to 13 Hz) oscillations are observed in patients after 1 yr of age. (*E–H*) Corresponding spectrograms in selected patients during propofol general anesthesia maintenance show that slow (0.1 to 1 Hz) oscillations are present in all patients and that alpha (8 to 13 Hz) oscillations are observed in patients greater than 1 yr of age. (*I*) Total electroencephalogram power (0.1 to 40 Hz) for each subject, plotted as a function of age (shown in *circles*). The *central blue line* represents a multiple linear regression (third-degree polynomial) describing the relationship between total electroencephalogram power and age. The *shaded bounds* represent the 95% CI for this regression model. The regression equation, F statistic, and *P* value are displayed. The adjusted $R^2 = 0.43$ for the model. Total electroencephalogram power increased with increasing age, peaking at approximately 8 yr of age and then declining and plateauing during the adolescent years.

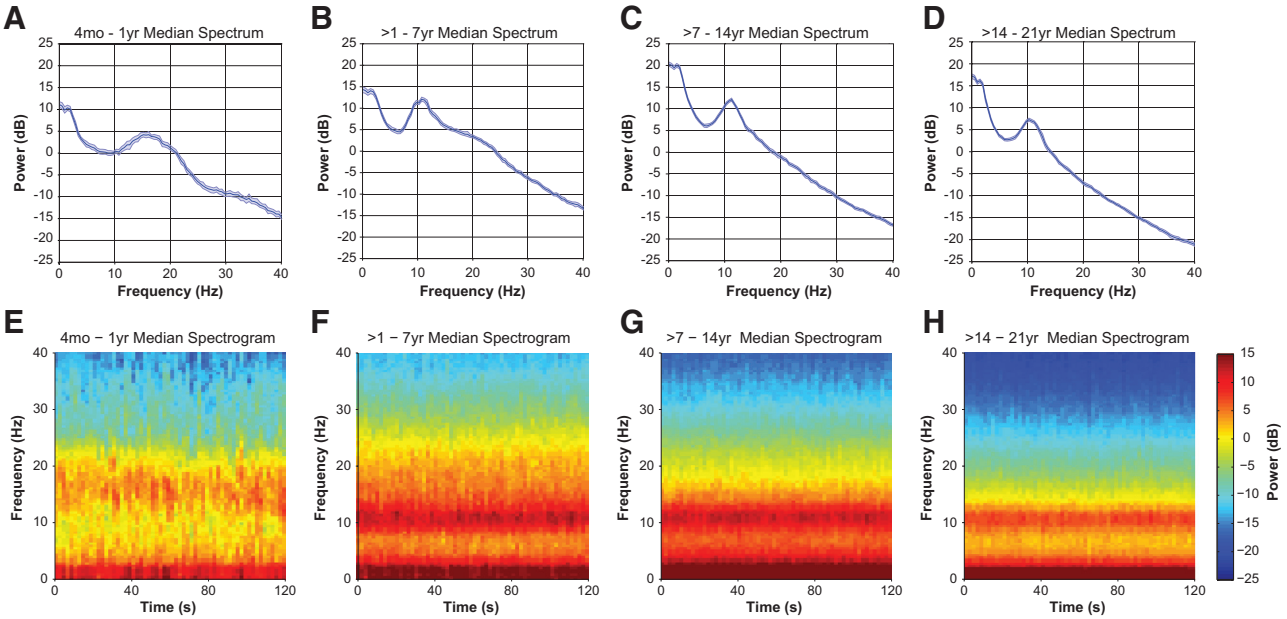

Fig. 3. Median spectra and spectrograms in age groups. (*A*, *E*) 4 months to 1 yr. The median power spectrum and spectrogram show prominent power in the slow frequency band (0.1 to 1 Hz) and a broad secondary peak in power between 10 and 25 Hz. (*B*, *F*) Greater than 1 to 7 yr. The median power spectrum and spectrogram show prominent power in the slow (0.1 to 1 Hz) and alpha (8 to 13 Hz) frequency bands. (*C*, *G*) Greater than 7 to 14 yr. The median power spectrum and spectrogram show prominent power in the slow and alpha frequency bands. (*D*, *H*) Greater than 14 to 21 yr. The median power spectrum and spectrogram show prominent power in the slow and alpha frequency bands. Statistically significant differences between age groups can be found in table 3.

Table 3. Results of Statistical Analysis: Comparison between Age Groups

	Power Spectra	Coherence
4 mo to 1 yr *vs*. 1–7 yr	1–7 yr > 4 mo to 1 yr, 0–39.55 Hz	1–7 yr > 4 mo to 1 yr, 6.35–13.18 Hz
1–7 yr *vs*. 7–14 yr	7–14 yr > 1–7 yr, 0–7.81 Hz; 1–7 yr > 7–14 yr, 13.18–39.55 Hz	7–14 yr > 1–7 yr, 0–8.30 Hz, 11.23–22.95 Hz, 32.23–38.09 Hz
7–14 yr *vs*. 14–21 yr	7–14 yr > 14–21 yr, 0–39.55 Hz	14–21 yr > 7–14 yr, 0–2.93 Hz

Bootstrap analysis (95% CI) was used to compare the power spectra and coherence between age groups. This table reports the frequencies for which there was a statistically significant difference in power or coherence between age groups, as well as which age group had greater power or coherence.

number of synapses.[44–46] The time frame of these neurodevelopmental processes is generally consistent with the age-dependent changes in total electroencephalogram power we observed in this study, suggesting that these changes may reflect the normal developmental processes of synaptogenesis and neural pruning. In addition, propofol-induced slow and alpha oscillations showed different age-dependent time courses between 1 and 21 yr, suggesting that the neural circuits supporting these specific oscillations might develop at different rates. Because propofol exerts its actions primarily *via* inhibitory γ-aminobutyric acid receptor type A receptors, we hypothesize that these age-dependent changes in the structure of the propofol-induced electroencephalogram oscillations could reflect the development of γ-aminobutyric acid–mediated (GABAergic) inhibitory interneurons in the cerebral cortex and in connected structures such as the thalamus.

We observed striking changes in the structure of the electroencephalogram during propofol-induced unconsciousness over the first year of life. In infants (less than 1 yr old), the propofol-induced electroencephalogram consisted mainly of slow oscillations. Consistent with previous studies of infants receiving general anesthesia,[18,36] we saw that alpha–beta oscillations began to appear at approximately 5 months of age but did not become coherent until approximately 1 yr of age. Electroencephalogram studies in adults have shown that coherent frontal alpha waves are a hallmark of the propofol-induced unconscious state.[21] Computational modeling studies suggest that thalamocortical connections are required to produce coherent propofol-induced alpha oscillations.[20] Moreover, recent invasive neurophysiologic studies in rodents show that propofol-induced frontal alpha oscillations involve both thalamus and cortex.[47] Thus, it is likely that the development of frontal alpha coherence under propofol reflects underlying development within thalamocortical circuits. This interpretation is consistent with recent functional imaging studies in humans showing that frontal

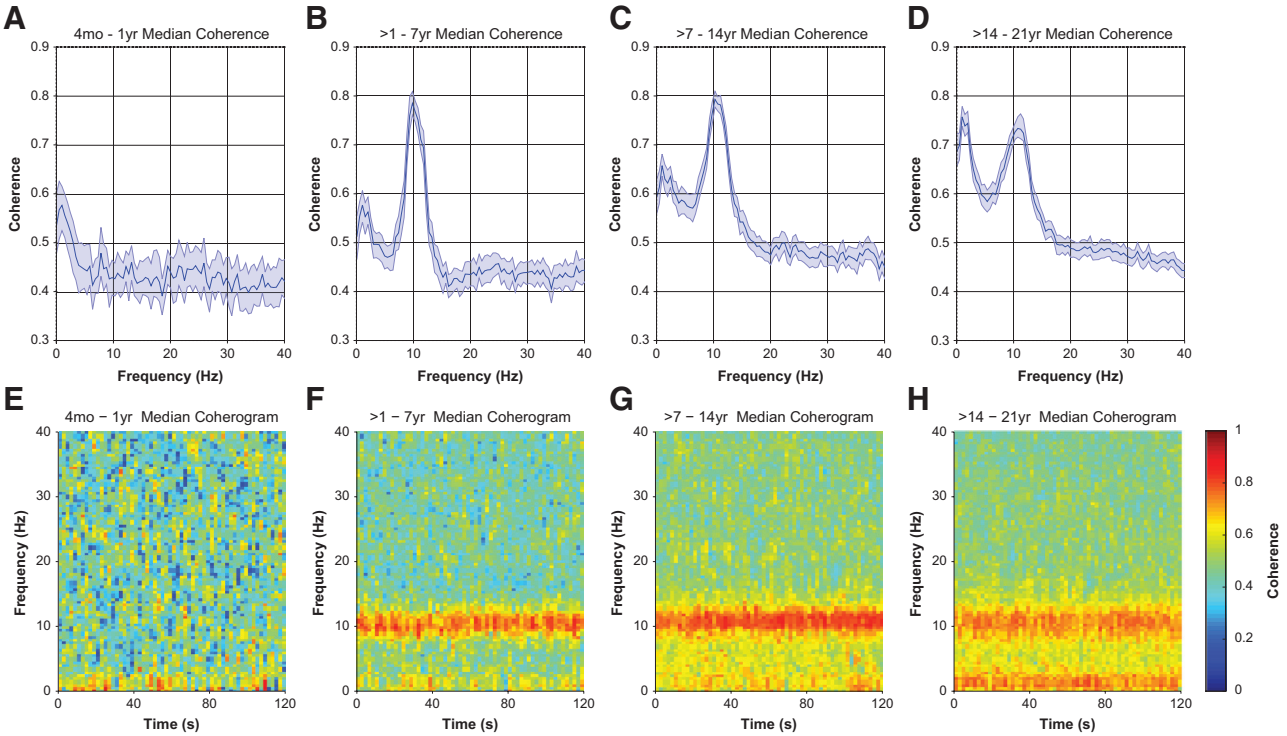

Fig. 4. Median coherence and coherograms in age groups. (*A*, *E*) 4 months to 1 yr. The median coherence and coherogram show faint slow (0.1 to 1 Hz) coherence, but no significant frontal coherence is observed overall. (*B*, *F*) Greater than 1 to 7 yr. The median coherence and coherogram exhibit some slow coherence and significant alpha (8 to 13 Hz) coherence. (*C*, *G*) Greater than 7 to 14 yr. The median coherence and coherogram show a relative increase in slow coherence, and prominent alpha coherence. (*D*, *H*) Greater than 14 to 21 yr. The median coherence and coherogram show a significant increase in slow coherence and a relative decrease in alpha coherence. Statistically significant differences between age groups can be found in table 3.

thalamocortical functional connectivity does not develop until 1 yr of age.[48] Maturation of GABAergic interneurons within the cerebral cortex and the thalamic reticular nucleus could play a role in mediating this thalamocortical functional connectivity,[49,50] as could development of diffusely projecting calbindin-positive thalamocortical matrix cells thought to mediate coherent thalamocortical spindle oscillations during sleep.[51,52] Computational modeling studies also suggest that cortical circuits containing both excitatory and inhibitory neurons in the absence of thalamic connections can generate propofol-induced alpha–beta oscillations.[53] We hypothesize that the development of incoherent propofol-induced alpha–beta oscillations in the 4- to 6-month time frame could reflect the development of inhibitory GABAergic transmission, possibly influenced by age-related changes in the expression levels of cation-chloride cotransporters NKCC1 and KCC2,[54] within the cerebral cortex or thalamocortical circuit. Overall, these significant differences in brain dynamics and development in infants compared to older children suggest that, with further research, the clinical definitions and endpoints for sedation and general anesthesia could ultimately be refined or redesigned in a manner to reflect the unique features of infant brain development.

The age-dependent changes in the propofol-induced electroencephalogram we report here are consistent with our previous study of pediatric patients between 0 and 28 yr of age during sevoflurane general anesthesia.[18] General anesthesia maintained with propofol or sevoflurane are both associated with large slow and coherent frontal alpha oscillations.[30] Accordingly, we saw that propofol and sevoflurane both showed qualitatively similar age-dependent changes in these oscillations. Sevoflurane induces a theta oscillation not seen under propofol,[30] whose power and coherence also vary with age. The differences in the age-varying oscillatory structure in propofol- and sevoflurane-induced electroencephalograms could reflect differences in the circuit- and receptor-level effects of these drugs. Although propofol and sevoflurane both act at γ-aminobutyric acid receptor type A receptors, sevoflurane also acts at a number of other receptors including *N*-methyl-D-aspartate, serotonin, and two-pore potassium channels.[30] Because some neural circuits may be influenced differently depending on the molecular receptors or channels being affected, further characterization of the age-related differences in the electroencephalogram under propofol, sevoflurane, and other anesthetic drugs could inform our understanding of development within different receptor-dependent circuits.

We found that the structure of propofol-induced electroencephalogram oscillations were qualitatively similar for patients from 1 yr of age through adulthood, featuring slow and coherent alpha oscillations. Quantitatively, total

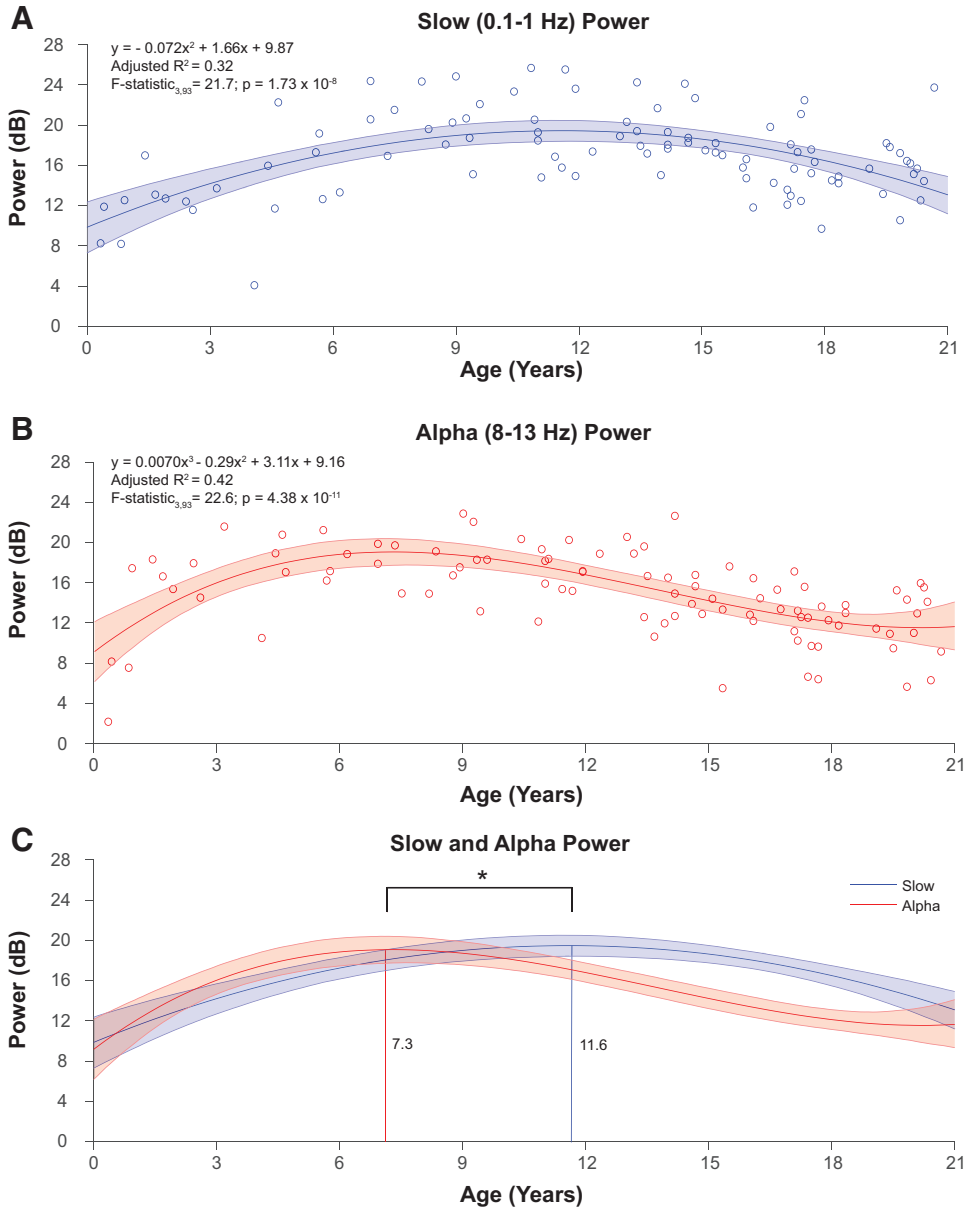

Fig. 5. Age-related changes in slow and alpha electroencephalogram power. (*A*) A multiple linear regression model was used to describe the relationship between frontal slow (0.1 to 1 Hz) power and age (*blue*). (*B*) A multiple linear regression model was used to describe the relationship between frontal alpha (8 to 13 Hz) power and age (*red*). The *shaded bounds* represent the 95% CI for these regression models. (*C*) Frontal slow power peaks at approximately 11.6 yr of age, and alpha power peaks at approximately 7.3 yr of age. The difference between these peak ages is statistically significant (95% CI, 3.0 to 5.5 yr). Slow oscillation power was greater than alpha power from 3.6 to 5.3 yr, whereas alpha oscillation power was greater than slow power from 10.5 to 20.3 yr of age (95% CI, bootstrap analysis).

electroencephalogram power in the pediatric population increased and peaked at approximately 8 yr old and then declined with increasing age. In general, children tended to have greater power than adults in the beta- and gamma-band oscillations (13 to 40 Hz), which are often associated with lighter levels of anesthesia and with muscle activity indicative of emerging consciousness.[21,55–57] Commonly used depth-of-anesthesia monitors use power in different electroencephalogram bands to compute an index between 0 and 100 to indicate level of consciousness. These monitors typically interpret power at higher frequencies to indicate lighter levels of anesthesia or increased levels of awareness.[55–58] If applied to children, these monitors would therefore tend to misinterpret the increased high frequency power to suggest that patients are not adequately anesthetized, which in turn could lead clinicians to administer higher levels of anesthetic than actually needed to maintain unconsciousness during general anesthesia. An alternative to using depth-of-anesthesia indices is to use the unprocessed electroencephalogram and spectrogram to monitor brain states during general anesthesia and

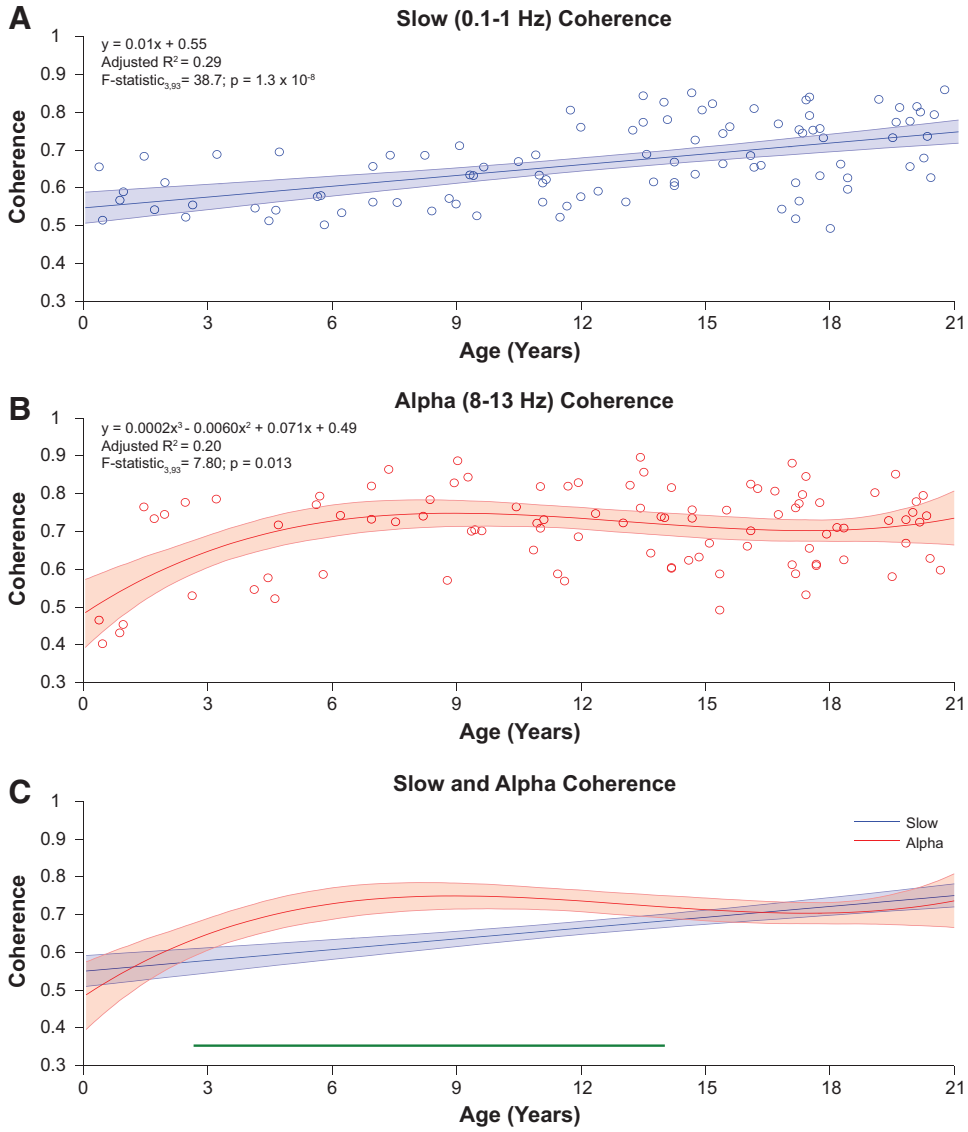

Fig. 6. Age-related changes in slow and alpha coherence. (*A*) A multiple linear regression model was used to describe the relationship between frontal slow (0.1 to 1 Hz) coherence and age (*blue*). Slow coherence appeared to increase linearly between 1 and 21 yr of age. (*B*) A multiple linear regression model was used to describe the relationship between frontal alpha (8 to 13 Hz) coherence and age (*red*). Alpha coherence peaked at 8.9 yr of age (95% CI, 7.4 to 12.2 yr). The *shaded bounds* represent the 95% CI for these regression models. (*C*) Alpha oscillation power was greater than slow power from 2.6 to 14 yr of age (95% CI, bootstrap analysis). The *horizontal green line* represents the ages for which there is a statistically significant difference between slow and alpha coherence.

sedation.[22,55] Given the qualitative similarity in the structure of propofol-induced electroencephalogram oscillations in children and adults, our results suggest that this approach to monitoring brain states could be fully applicable to children greater than 1 yr of age. Children less than 1 yr of age show different anesthesia-induced electroencephalogram signatures, and further investigation will be required to establish principled monitoring approaches in these very young patients.[18,36]

A limitation of this study is that there were relatively few patients under the age of 1 yr that were included in this analysis (n = 4). As such, it is possible that the magnitude of the difference we observe between 4-month- to 1-yr-old children and 1- to 2-yr-old children may not be representative of the larger population. However, the absence of coherent alpha oscillations in infants, followed by the appearance of coherent alpha oscillations after 1 yr of age that we observed, is consistent with previous studies of the electroencephalogram under sevoflurane in children.[18,36] Another limitation of this observational study is that the anesthetic management of patients was not controlled or standardized. As such, it is possible that differences in the anesthetic management of these patients may have influenced the observed differences in electroencephalogram. However, this seems unlikely due to the minimal variation in clinical procedures and propofol

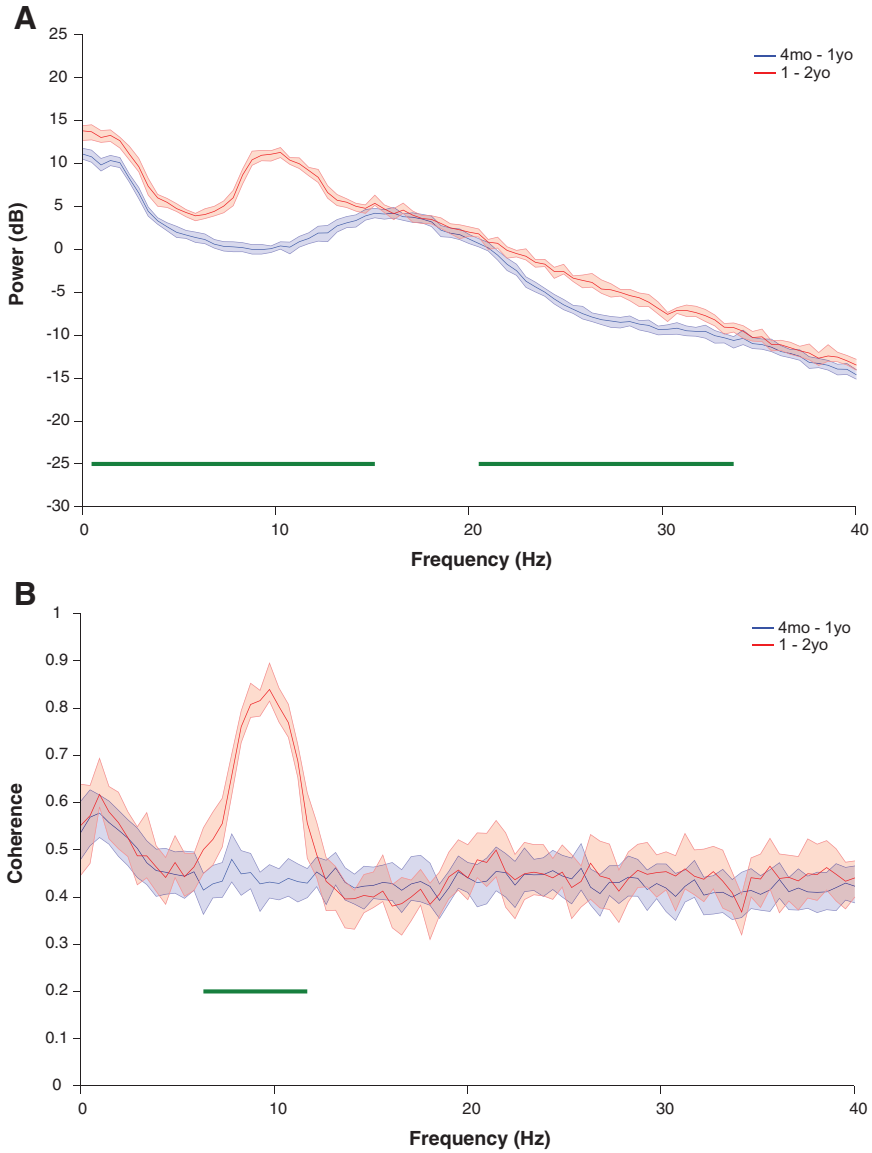

Fig. 7. Frontal electroencephalogram power and coherence in infants under 2 yr of age. (*A*) Median power spectra for two groups of subjects are shown: subjects between 4 months and 1 yr of age (n = 4; *blue*) and subjects between 1 and 2 yr of age (n = 3; *red*). The *shaded bounds* represent the 95% CI for these power spectra. The spectra show that slow (0.1 to 1 Hz) oscillations are consistently observed in all subjects. However, the power spectrum in subjects less than 2 yr old shows the relative absence of well-defined alpha (8 to 13 Hz) oscillations, instead showing a higher frequency broad increase in electroencephalogram power for 12 to 25 Hz oscillations. Electroencephalogram power is significantly greater in the 1- to 2-yr age group relative to the 4-month to 1-yr age group for the following frequency ranges: 0 to 15.14 Hz and 20.51 to 33.69 Hz (95% CI, bootstrap analysis). *Horizontal green lines* represent the frequency ranges for which there is a significant difference. (*B*) Median coherence in patients less than 2 yr old shows the absence of alpha (8 to 13 Hz) oscillation coherence in subjects between 4 months and 1 yr of age, with alpha oscillation coherence becoming apparent in subjects between 1 and 2 yr of age. Frontal coherence is significantly greater in the 1- to 2-yr-old age group relative to the 4-month to 1-yr-old age group for the 6.35 to 11.72 Hz frequency range (95% CI, bootstrap analysis). The *horizontal green line* represents the frequency ranges for which there is a significant difference.

infusion rates across the patients studied. In particular, most of our data came from patients receiving propofol for esophagogastroduodenoscopy and/or colonoscopy who underwent relatively similar levels of procedural stimulation. Thus, in comparison with a more general pediatric surgical population, the patients we studied experienced highly consistent rates and patterns of propofol administration, fewer adjunct medications, without use of neuromuscular blocking agents, all of which improve the quality and consistency of the electroencephalogram data we analyzed.

Moreover, it seems unlikely that small variations in clinical management, pharmacokinetics, and/or pharmacodynamics could account for the magnitude of the electroencephalogram changes observed in our data, which show

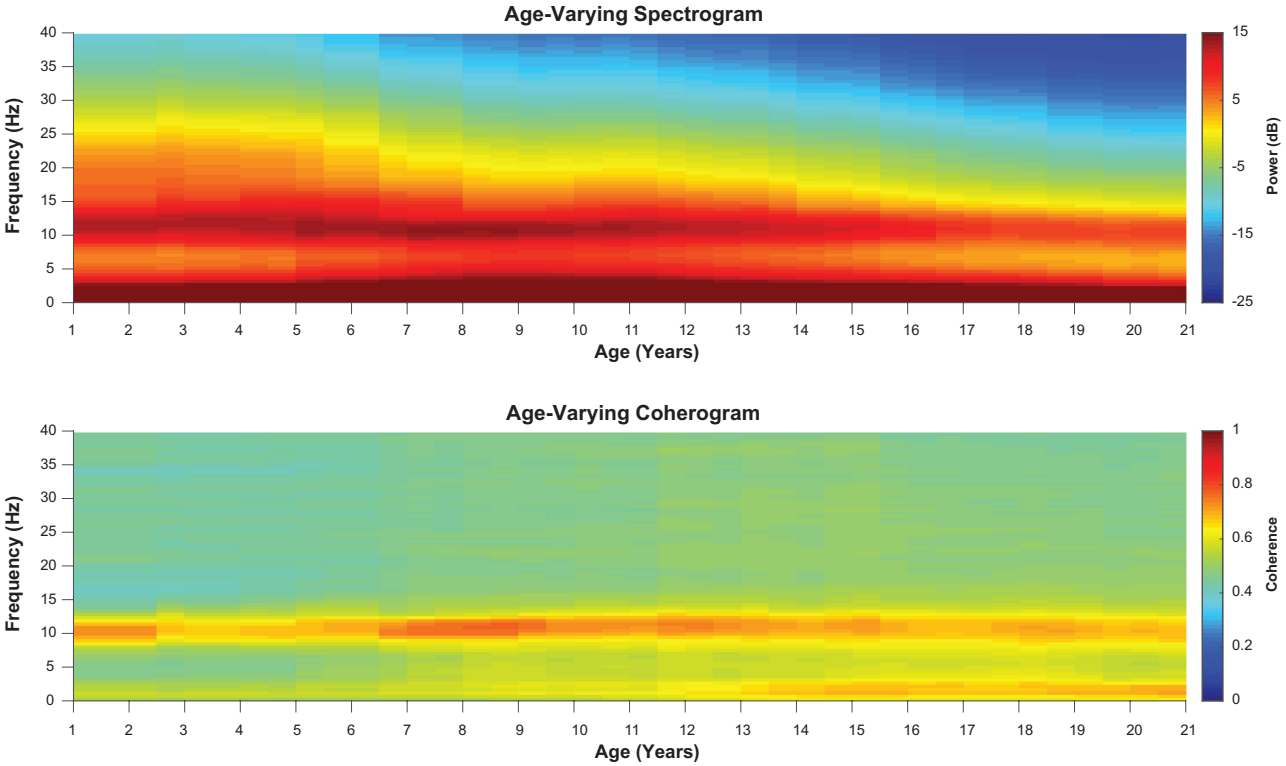

Fig. 8. Age-varying spectrogram and coherogram during propofol general anesthesia. (*Top*) An age-varying spectrogram for patients 1 to 21 yr old shows that the frontal electroencephalogram structure during propofol-induced unconsciousness appears to be qualitatively consistent across age and is comprised of slow (0.1 to 1 Hz) oscillations and alpha (8 to 13 Hz) oscillations. At the same time, the power of these oscillations changes as a function of age. Specifically, we observed age-dependent changes in the spectrogram, with high frequency power declining with increasing age and alpha oscillation power significantly decreasing by approximately 16 yr of age. (*Bottom*) An age-varying coherogram for patients 1 to 21 yr old consistently shows prominent alpha oscillation coherence. In addition, slow oscillation coherence appears to increase with age, particularly after about 11 yr of age.

differences in slow and alpha power, respectively, spanning ~10 dB across the age range studied, equivalent to a ~3-fold difference in the size of these oscillations. Similarly, such clinical or pharmacologic variations are unlikely to explain the absence of alpha-band coherence in infants, because this is a prominent feature of propofol-induced unconsciousness in adults. Nonetheless, future studies that carefully characterize age-dependent dose–response relationships in the electroencephalogram alongside structured assessments of level of consciousness are clearly warranted. Overall, the large number of patients studied (n = 97) within this cross-sectional analysis and the largely consistent trend in electroencephalogram power and coherence over age suggest that the age-related electroencephalogram changes we observed during propofol-induced unconsciousness reflect neurophysiologic changes that occur during development.

In summary, the age-related changes in electroencephalogram power and coherence that we report here provide a strong argument for a more specific and principled approach to monitoring brain states in pediatric patients. Further investigation may help establish the precise correspondence between the structure of electroencephalogram oscillations and neurologic development, as well as facilitate the development of specific pediatric recommendations for anesthesia. We expect that such an approach will improve anesthetic monitoring and inform personalized anesthetic care for children.[59] Future research could lead in a number of interesting directions. First, the electroencephalogram measures developed through our studies could be tested in clinical studies to determine whether the use of these measures leads to better patient outcomes than standard approaches that do not use the electroencephalogram. Second, we could use an animal model of the developing brain to investigate in greater detail the neuronal mechanisms of the anesthesia-related phenomena observed throughout early postnatal neurodevelopment. Ultimately, we believe that the proposed studies will provide a strong foundation to better understand and improve anesthetic care and monitoring in the pediatric population.

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Competing Interests

Drs. Akeju, Brown, and Purdon have submitted patent applications describing the use of electroencephalogram measures described in this article for monitoring sedation and general anesthesia. Some of these patents have been licensed to Masimo Corporation, Irvine, California, by Massachusetts General Hospital, Boston, Massachusetts. Drs. Akeju, Brown, and Purdon are due to receive institutionally distributed royalties under this licensing agreement. Drs. Purdon and Brown had consulting agreements with Masimo Corporation in 2014 and 2015. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Purdon: 149 13th Street, Room 4012, Charlestown, Massachusetts 02129. patrickp@nmr.mgh.harvard.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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