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Effects of Sevoflurane and Propofol on Frontal Electroencephalogram Power and Coherence

Oluwaseun Akeju, M.D., M.M.Sc.^{1,3}, M. Brandon Westover, M.D., Ph.D.^{2,4}, Kara J. Pavone, B.S.¹, Aaron L. Sampson, B.S.¹, Katharine E. Hartnack, B.S.¹, Emery N. Brown, M.D., Ph.D.^{1,3,4,5,6}, and Patrick L. Purdon, Ph.D.^{1,3,4}

¹Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts

²Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts

³Harvard Medical School, Boston, Massachusetts

⁴Department of Brain and Cognitive Science, Massachusetts Institute of Technology, Cambridge, Massachusetts

⁵Harvard-Massachusetts Institute of Technology Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts

⁶Institute for Medical Engineering and Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts

Abstract

Background—The neural mechanisms of anesthetic vapors have not been studied in depth. However, modeling and experimental studies on the intravenous anesthetic propofol indicate that potentiation of γ -Aminobutyric acid receptors leads to a state of thalamocortical synchrony, observed as coherent frontal alpha oscillations, associated with unconsciousness. Sevoflurane, an ether derivative, also potentiates γ -Aminobutyric acid receptors. However, in humans, sevoflurane-induced coherent frontal alpha oscillations have not been well detailed.

Methods—To study the electroencephalogram dynamics induced by sevoflurane, we identified age and gender matched patients in which sevoflurane ($n = 30$) or propofol ($n = 30$) were used as the sole agent for maintenance of general anesthesia during routine surgery. We compared the electroencephalogram signatures of sevoflurane to propofol using time-varying spectral and coherence methods.

Results—Sevoflurane general anesthesia is characterized by alpha oscillations with maximum power and coherence at ~ 10 Hz, (mean \pm std; peak power, $4.3\text{dB} \pm 3.5$; peak coherence, 0.73 ± 0.1). These alpha oscillations are similar to those observed during propofol general anesthesia, which also has maximum power and coherence at ~ 10 Hz (peak power, $2.1\text{dB} \pm 4.3$; peak coherence, 0.71 ± 0.1). However, sevoflurane also exhibited a distinct theta coherence signature

(peak frequency, $4.9\text{Hz} \pm 0.6$; peak coherence, 0.58 ± 0.1). Slow oscillations were observed in both cases, with no significant difference in power or coherence.

Conclusion—Our results indicate that sevoflurane, like propofol, induces coherent frontal alpha oscillations and slow oscillations in humans to sustain the anesthesia-induced unconscious state. These results suggest a shared molecular and systems-level mechanism for the unconscious state induced by these drugs.

Introduction

Sevoflurane is an anesthetic agent with a rapid induction, emergence and recovery profile.¹ Evidence suggests that sevoflurane, similar to other ether derivatives in clinical use, exerts its physiological and behavioral effects by binding at multiple targets in the brain and spinal cord.² Action at these targets includes potentiation of γ -Aminobutyric acid (GABA_A), glycine and two-pore potassium channels; and inhibition of voltage gated potassium, N-methyl-D-aspartate, muscarinic and nicotinic acetylcholine, serotonin, and α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid channels.^{2–5} Despite detailed characterizations of the molecular and cellular pharmacology of anesthetics, the neural circuit-level mechanisms of general anesthesia-induced unconsciousness are still being actively investigated.^{3,4} Extensive work has helped propose neural circuit mechanisms to the electroencephalogram patterns of propofol (2,6-di-isopropylphenol).^{6–12} Clinically, we have observed that sevoflurane induces stereotypical changes in the electroencephalogram that appear grossly similar to propofol (fig. 1A–C). Hence, comparing the electroencephalogram dynamics induced by sevoflurane to propofol may provide insights into the neural circuit mechanism through which sevoflurane and other ether derivatives induce unconsciousness.

Propofol primarily acts at GABA_A receptors throughout the brain and spinal cord to enhance inhibition.^{3–5,13,14} It also potentiates glycine receptors, and provides inhibition to voltage gated potassium, acetylcholine, α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic and kainate channels amongst others.^{3–5} Unconsciousness under propofol is characterized in the electroencephalogram by alpha (8–12 Hz) oscillations that are coherent across the frontal cortex, delta (1–4 Hz) oscillations, and high amplitude incoherent slow (0.1–1 Hz) oscillations.^{7,9,11,13,15–17} Intracortical recordings during propofol-induced unconsciousness suggest that local and long range cortical communication are impeded by spatially incoherent slow oscillations that exhibit phase-limited spiking.¹⁵

Analysis of the scalp electroencephalogram, a readily accessible measure of the average activity in large populations of cortical neurons, has established that propofol induces synchronous frontal alpha oscillations.^{7,9–11} Biophysical modeling provides further evidence that propofol induces coherent alpha activity by increasing GABA_A conductance and decay time.^{6,12} This increase in GABA_A conductance facilitates involvement of the thalamus in a highly coherent thalamocortical alpha oscillation loop.^{6,12} This pathologically coherent frontal alpha oscillation pattern reduces the dimensionality of the thalamocortical network, reducing the ability of the thalamus to project and coordinate exogenous inputs to the neocortex.^{12–14}

Coherent alpha oscillations have also been identified in animal studies of the inhaled anesthetics during unconsciousness.^{18–20} However, human studies examining this inhaled anesthesia-induced electroencephalogram dynamics are limited. Given that both sevoflurane and propofol are known to act at GABA_A receptors,^{3–5,13,14} it is possible that comparing the electroencephalogram patterns elicited by sevoflurane to those elicited by propofol can provide insights into the neural circuit mechanisms of sevoflurane. Given a similar GABAergic mechanism of action, we hypothesized that the spectral and coherence features of sevoflurane general anesthesia would be similar to propofol general anesthesia. That is, at surgical anesthetic depth, there would be a predominance of large amplitude slow, delta, and coherent alpha oscillations.

To explore these hypotheses, we performed an observational study to record intraoperative frontal electroencephalogram in 30 patients undergoing general anesthesia with sevoflurane or propofol as the primary maintenance agent. We compared electroencephalogram dynamics during sevoflurane and propofol general anesthesia using time varying spectral and coherence methods.

Materials and Methods

Patient Selection and Data Collection

Following a protocol approved by the Partners Human Research Committee, we reviewed our database of anesthesia and electroencephalogram recordings and identified age and gender matched patients in which sevoflurane (n = 30) or propofol (n = 30) were used as the sole hypnotic agent for maintenance of general anesthesia during routine surgery. Table 1 summarizes the patient characteristics while table 2 summarizes the end tidal sevoflurane vapor concentration and propofol infusion rates used during the maintenance phases of the electroencephalogram epochs selected. Table 3 provides additional information on coadministered medications.

Frontal electroencephalogram data were recorded using the Sedline brain function monitor (Masimo Corporation, Irvine CA). The electroencephalogram data were recorded with a pre-amplifier bandwidth of 0.5 to 92 Hz, sampling rate of 250Hz, with 16-bit, 29 nV resolution. The standard Sedline Sedtrace electrode array records from electrodes located approximately at positions Fp1, Fp2, F7, and F8, with ground electrode at Fpz, and reference electrode approximately 1 cm above Fpz. Electrode impedance was less than 5k Ω in each channel. An investigator experienced in reading the electroencephalogram (O.A.) visually inspected the data from each patient and selected electroencephalogram data free of noise and artifacts for analysis.

Electroencephalogram data segments were selected using information from the electronic anesthesia record. For each patient, 5-min electroencephalogram segments representing the maintenance phase of general anesthesia during surgery were carefully selected. The data was selected from a time period after the initial induction bolus of an intravenous hypnotic and while the maintenance agent was stable. These data have not been reported upon in previous publications.

Spectral Analysis

The power spectral density, also referred to as the power spectrum or spectrum, quantifies the frequency distribution of energy or power within a signal. For example, figures 1A–B show representative electroencephalogram spectrograms under general anesthesia maintained with sevoflurane and propofol. In these spectrograms, frequencies are arranged along the y-axis, and time is along the x-axis, and power is indicated by color on a decibel (dB) scale. Figures 1C–D show selected 10-second epochs of raw electroencephalogram signals from time-points encompassed in figures 1A–B. Figures 1E–L show the 0.1–1 Hz, 1–4 Hz, 4–8 Hz and 8–14 Hz bandpass filtered electroencephalogram signals from figures 1C–D. We computed spectrograms using the multitaper method, implemented in the Chronux toolbox.²¹ We computed group-level spectrograms by taking the median across all patients. We also calculated the spectrum for the selected electroencephalogram epochs. The resulting power spectra were then averaged for all epochs, and 95% confidence intervals were computed via multitaper-based jackknife techniques.²¹ The spectral analysis parameters were: window length $T = 2$ s with 0 s overlap, time-bandwidth product $TW = 3$, number of tapers $K = 5$, and spectral resolution of 3 Hz. We estimated the peak power, and its frequency, of the frontal alpha oscillation for each individual subject. We then averaged across subjects to obtain the group-level peak power and frequency for these oscillations.

Coherence Analysis

The coherence quantifies the degree of correlation between two signals at a given frequency. It is equivalent to a correlation coefficient indexed by frequency: a coherence of 1 indicates that two signals are perfectly correlated at that frequency, while a coherence of 0 indicates that the two signals are uncorrelated at that frequency. 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 $y(t)$. Similar to the spectrum and spectrogram, the coherence can be estimated as time-varying quantity called the coherogram. To obtain estimates of coherence, we computed coherograms between two frontal electroencephalogram electrodes F7 and F8 (fig. 2A) using the multitaper method, implemented in the Chronux toolbox.²¹ To illustrate how the coherogram quantifies relationships between signals, and how this is distinct from the spectrogram, we devised a simulated data example. Figure 2B shows time domain traces from three simulated oscillatory signals, two of which are highly correlated (signal A and signal B), and one which is uncorrelated with the other two (signal C). Figures 2C–E show the spectrograms for these signals. Figures 2F–G show the coherograms for signal pairs A–B and B–C. All three signals have identical spectrograms, by construction, but the coherence between the signals is very different, reflecting the presence or absence of the visible correlation evident in the time domain traces. The coherogram also indicates the frequencies over which two signals are correlated. In the example in figure 2F, signals A and B are correlated at

frequencies below approximately 20 Hz. This example shows how the coherogram characterizes the correlation between two signals as a function of frequency. The coherence can be interpreted similarly.

We computed group-level coherograms by taking the median across patients. We also calculated coherence for the selected electroencephalogram epochs. The resulting coherence estimates were averaged for all epochs, and 95% confidence intervals were computed via multitaper-based jackknife techniques.^{21,22} The coherence analysis parameters were: window length $T = 2$ s with 0 s overlap, time-bandwidth product $TW = 3$, number of tapers $K = 5$, and spectral resolution of $2W = 3$ Hz. We estimated the peak coherence, and its frequency, of the frontal alpha oscillation for each individual subject. We then averaged across subjects to obtain the group-level peak coherence and frequency for these oscillations.

Statistical Analysis

To compare spectral and coherence estimates between groups, we used jackknife-based methods, the two-group test for spectra, and the two-group test for coherence, as implemented in the Chronux toolbox routine.²² This method accounts for the underlying spectral resolution of the spectral and coherence estimates, and considers differences to be significant only if they are present for contiguous frequencies over a frequency band wider than the spectral resolution $2W$. Specifically, for frequencies $f > 2W$, the null hypothesis was rejected only if the test statistic exceeded the significance threshold over a contiguous frequency range $2W$. For frequencies $0 \leq f \leq 2W$, to account for the properties of multitaper spectral estimates at frequencies close to zero, the null hypothesis was rejected only if the test statistic exceeded the significance threshold over a contiguous frequency range from 0 to $\max(f, W) - 2W$. We selected a significance threshold of $p < 0.001$ for comparisons between the two groups.

Results

Sevoflurane versus Propofol Power Spectra Analysis

We observed similarities and differences in the spectrograms of the sevoflurane and propofol general anesthesia groups (fig. 3A–B). Both spectrograms were similarly characterized by large alpha band power. However, sevoflurane elicited higher power across the theta (4–8 Hz) and beta (12–25 Hz) frequency ranges (fig. 3A–B). Sevoflurane general anesthesia electroencephalogram power exhibited an alpha oscillation peak (mean \pm std; peak frequency, $9.2\text{ Hz} \pm 0.84$; peak power, $4.3\text{ dB} \pm 3.5$) that was only slightly different from the propofol general anesthesia alpha oscillation peak (peak frequency, $10.3\text{ Hz} \pm 1.1$; peak power, $2.1\text{ dB} \pm 4.3$). We next compared the electroencephalogram spectrum between these two groups and found significant differences in power across most frequencies between 0.4 and 40 Hz. Sevoflurane exhibited increased electroencephalogram power across a range of frequencies except at slow oscillations (<0.4 Hz) and the propofol alpha oscillation peak (fig. 3C; 0.4–11.2 Hz, 14.7–40 Hz; $P < 0.001$, two-group test for spectra). As illustrated in figure 3C, compared to propofol-induced unconsciousness, sevoflurane-induced

unconsciousness was characterized by larger theta and beta oscillation power, and similar slow and alpha oscillation power.

Sevoflurane vs. Propofol Coherence Analysis

We also observed similarities and differences in coherograms of the sevoflurane and propofol general anesthesia groups (fig. 4A–B). Both coherograms were similarly characterized by alpha band coherence, and the absence of slow oscillation coherence. However, the sevoflurane group coherogram also showed a coherence peak within the theta frequency range that was not evident in the propofol general anesthesia group (fig. 3A–B; peak frequency, $4.9\text{Hz} \pm 0.6$; peak coherence, 0.58 ± 0.1). Sevoflurane general anesthesia electroencephalogram coherence exhibited an alpha oscillation peak (peak frequency, $9.8\text{Hz} \pm 0.91$; peak coherence, 0.73 ± 0.1) that was very similar to propofol general anesthesia alpha oscillation peak (peak frequency, $10.2\text{Hz} \pm 1.3$; peak coherence, $0.71\text{dB} \pm 0.1$). We next compared the electroencephalogram coherence between these two groups. We found that the sevoflurane and propofol coherence were qualitatively similar, showing a strong alpha peak, and lower slow oscillation peak. Sevoflurane exhibited increased electroencephalogram coherence across a range of theta and alpha frequencies (fig. 3C; $3.41\text{--}10.7\text{Hz}$; two-group test for coherence, $P < 0.001$) while propofol exhibited increased electroencephalogram coherence across a slightly different range of alpha and beta frequencies (fig. 3C; $11.7\text{--}19.5\text{Hz}$; two-group test for coherence, $P < 0.001$). As illustrated in figure 4C, sevoflurane and propofol general anesthesia were characterized by coherent frontal alpha oscillations with very similar peak frequencies and coherence values. However, sevoflurane also exhibited a coherent theta oscillation peak.

Discussion

Sevoflurane- and propofol-induced electroencephalogram signatures appear grossly similar. However, our analysis identifies a distinct difference in theta coherence that may be further studied to provide insights into the neural circuit mechanisms of sevoflurane. We briefly summarize our findings as follows: (i) Similar to propofol-induced frontal alpha oscillations, sevoflurane is characterized by coherent alpha oscillations with similar maximum power and coherence occurring at $\sim 10\text{--}12\text{ Hz}$; (ii) Also similar to propofol, sevoflurane is associated with slow oscillations at frequencies $< 1\text{ Hz}$; (iii) In contrast to propofol, sevoflurane is associated with increased power and coherence in the theta band.

These similarities in sevoflurane- and propofol- induced electroencephalogram dynamics are consistent with the notion that similar GABAergic neural circuit mechanisms are involved.^{2–5,14} This suggests that sevoflurane, like propofol, may also induce highly structured thalamocortical oscillations that interfere with cortical information processing, as well as slow oscillations that fragment cortical activity.^{7,9–12} Preliminary studies from our laboratory suggest that these electroencephalogram signatures are also representative of the ether derivatives, isoflurane and desflurane, suggesting that these oscillatory patterns may be used as electroencephalogram signatures of general anesthesia induced loss of consciousness. It is important to note that intracortical mechanisms may also be necessary for the generation and propagation of coherent oscillations.²³

The coherent theta oscillations (~5 Hz) characteristic of sevoflurane anesthesia, to our knowledge, have not been previously reported. Speculating on the possible significance of these theta oscillations, we note that pathological theta oscillations have been linked to dysfunction of low-threshold T-type calcium channels in thalamic neurons, leading to a thalamocortical dysrhythmia.^{23–26} Volatile anesthetics have been reported to modulate T-type calcium channels at clinically relevant concentrations in the dorsal root ganglia, hippocampal and thalamic relay neurons.^{27–31} These parallels lead us to hypothesize that sevoflurane-induced theta oscillations may be indicative of profound thalamic deafferentation. If true, this electroencephalogram signature along with those of slow and alpha oscillations may be useful to monitor depth of anesthesia in real-time. In the future, it would be important to study the spatio-temporal dynamics of this oscillatory dynamic with respect to depth of anesthesia.

Our findings suggest that propofol and sevoflurane, despite quantitative differences in the electroencephalogram power spectrum, both exhibit highly coherent frontal alpha oscillations that have been associated with entrainment of thalamocortical communications. However, sevoflurane also exhibits a theta-band coherence that was not present under propofol. Coherent theta oscillations are not generally present in the awake eyes closed state,^{7,9} leading us to conclude that this coherence signature is sevoflurane induced. Also, we were able to observe these similarities and differences in electroencephalogram spectra and coherences in data recorded during routine care of patients undergoing a variety of surgical procedures, and under different coadministered medications, suggesting that these effects are robust.

The electroencephalogram recordings analyzed in this paper were obtained from frontal channels; as a result, our analysis was unable to examine anterior-posterior connectivity³² that have been reported as other cortical dynamics underlying anesthesia induced unconsciousness. Because this study was performed in the clinical setting with concomitant administration of opioids, we were unable to perform detailed characterizations of changing behavior and consciousness during controlled induction and emergence, limiting our inferences to a clinically unconscious state. Future studies employing high-density electroencephalogram and behavioral tasks will allow us to analyze connectivity and phase-amplitude coupling under sevoflurane and other inhaled anesthetics and their relation to varying degrees of consciousness.

In summary, the present analysis suggests a potential shared GABAergic mechanism for propofol and sevoflurane at clinically-relevant doses. Furthermore, it details electroencephalogram signatures that can be used to identify and monitor the shared and differential effects of anesthetic agents, providing a foundation for future analyses.

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The authors Oluwaseun Akeju, Emery N. Brown, and Patrick L. Purdon have submitted a provisional patent application describing the use of the electroencephalogram measures described in this manuscript for monitoring sedation and general anesthesia.

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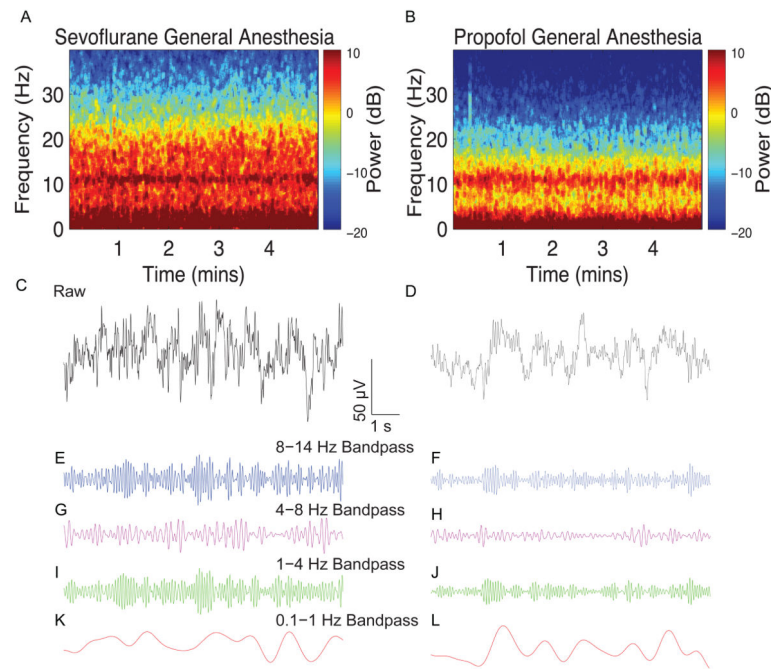


Figure 1.

Representative individual spectrogram and the time-domain electroencephalogram data obtained during sevoflurane general anesthesia (GA), and propofol GA. A. Spectrogram of a patient who received sevoflurane GA. B. Spectrogram of a patient who received propofol GA. The spectrogram displays the frequency content of signals as they change over time. Frequency is plotted on the y-axis, time is plotted on the x-axis, and the energy or power in the signal is indicated in color. Both spectrograms show power in the slow and alpha frequency bands. However, sevoflurane GA is further characterized by increased power in the theta and beta frequency bands. C. Representative 10-s electroencephalogram traces of sevoflurane GA. D. Representative 10-s electroencephalogram traces of propofol GA illustrating the gross similarities in electroencephalogram signal amplitudes in fig. 1C. E–L. Bandpass filtered electroencephalogram signals from the raw tracings to more clearly illustrate gross similarities in the electroencephalogram.

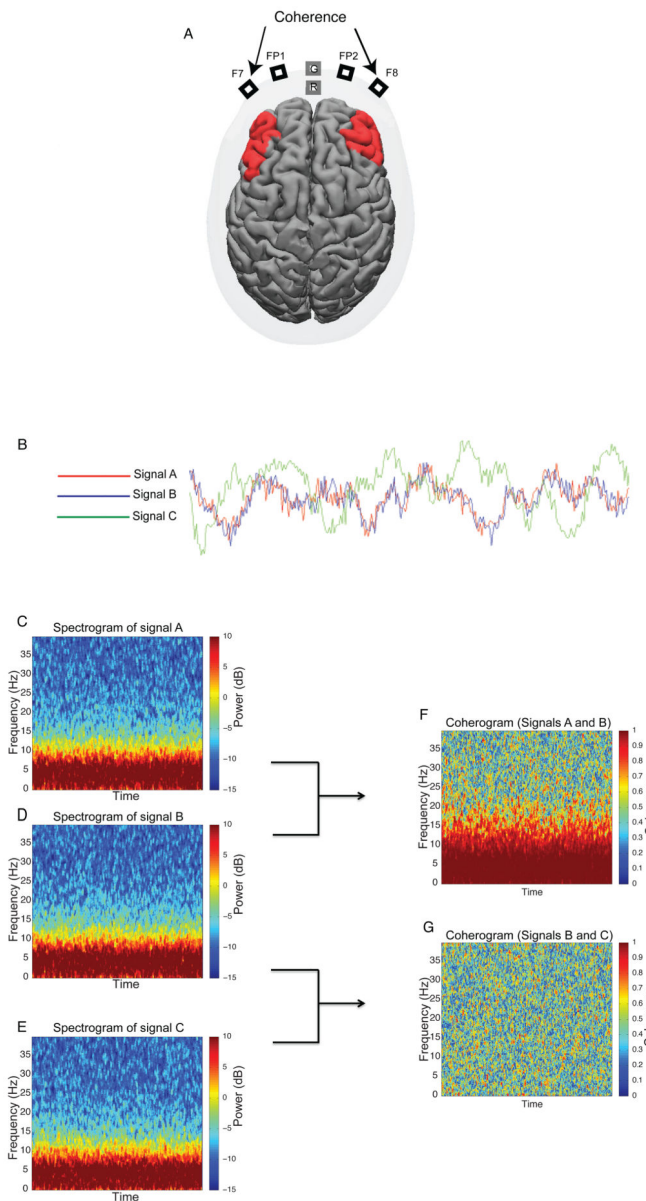


Figure 2.

Illustration of electroencephalogram channels, and coherence measurement. A. Visual representation of channel locations and the two bipolar frontal channels, F7 and F8, which we used for coherence analysis. Areas in red are purely illustrative for the explanation of coherence. The bipolar frontal channels overlaying these regions may not record signals solely from the underlying cortex. B. Simulated signals to illustrate interpretation of coherence. Signal “A” and signal “B” appear highly correlated in time, whereas signal “C” appears uncorrelated with both signals A and B. C–E. Spectrogram for simulated signals in 2B. The spectrogram plots signal power or energy as a function of time and frequency. Signals A, B and C produce almost identical spectrograms, however their coherograms will reflect differences in functional connectivity that may otherwise be overlooked. F–G. The coherence indicates the correlation coefficient between two signals as a function of

frequency (0 for no correlation, with a maximum value of 1 for perfect correlation). The coherogram plots the coherence as function of time, much like the spectrogram. This example shows how the simulated signals have identical spectrograms, but very different coherograms, consistent with the degree of correlation evident in the time domain traces shown in 2B. The coherogram also indicates the frequencies over which two signals are correlated. In this example, signals A and B are correlated at frequencies below approximately 20 Hz.

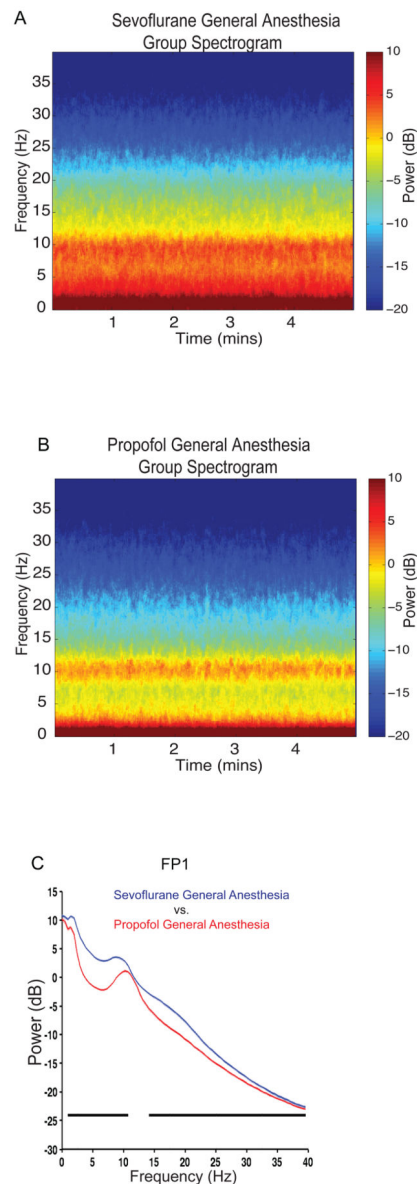


Figure 3.

Group level spectral analysis comparing sevoflurane general anesthesia (GA) to propofol GA. A. Group level spectrogram of sevoflurane GA ($n = 30$), showing increased power in slow, delta, theta and alpha, beta frequency bands. B. Group level spectrogram of propofol GA ($n=30$), showing increased power in slow, delta, and alpha frequency bands. C. Power spectra of sevoflurane GA *versus* propofol GA. Electroencephalogram power is significantly greater with sevoflurane GA over propofol GA across a broad frequency range spanning the alpha, delta, theta and beta frequency bands (fig. 3C; 0.4–11.2 Hz, 14.7–40Hz; $P < 0.001$, two group test for spectra). Median spectra presented with 95% jackknife confidence intervals. Horizontal solid black lines represent frequency ranges at which there was significant difference.

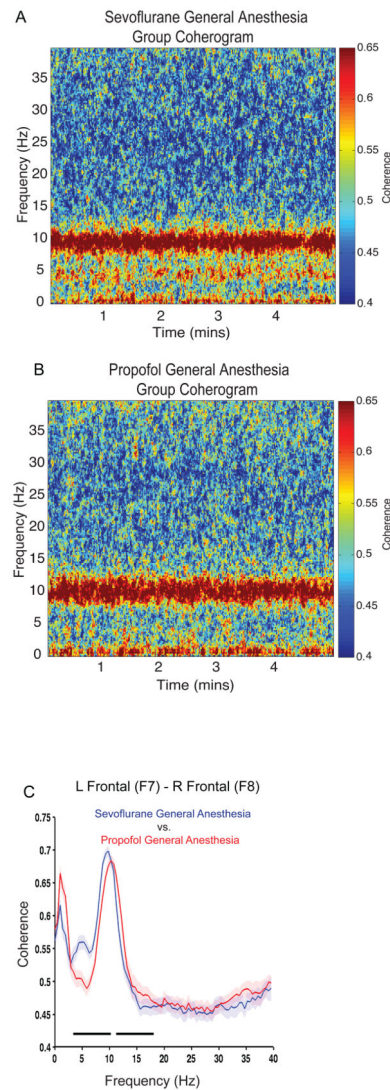


Figure 4.

Group level coherence analysis comparing sevoflurane general anesthesia (GA) to propofol GA. A. Group level coherogram of sevoflurane GA ($n = 30$) showing coherence in the theta and alpha frequency bands. B. Group level coherogram of propofol GA ($n = 30$), showing coherence in the alpha frequency band. C. Coherence of sevoflurane GA *versus* propofol GA. Qualitatively, the alpha coherence between the two groups appeared similar. However, sevoflurane exhibited a theta coherence peak. Sevoflurane GA coherence across was higher than propofol GA at 3.41–10.7 Hz (two group test for coherence, $P < 0.001$). Propofol GA coherence across was higher than sevoflurane GA at 11.7–19.5 Hz (two group test for coherence, $P < 0.001$). Median coherence presented with 95% jackknife confidence intervals. Horizontal solid black lines represent frequency ranges at which there was significant difference.

Table 1

Characteristics of Patients Studied

	Sevoflurane (n = 30)	Propofol (n = 30)
Age (years), mean (\pm SD)	43 (17)	45 (16)
Sex (male), n (%)	11 (36.7)	11 (36.7)
Weight (kg), mean (\pm SD)	83 (23)	81 (18)
BMI (kg/m ²), mean (\pm SD)	30 (9)	30 (7)
Surgery type, n (%)		
General	16 (53.3)	17 (56.7)
Gynecologic	3 (10.0)	2 (6.7)
Orthopedic	3 (10.0)	1 (3.3)
Plastic	4 (13.3)	5 (16.7)
Thoracic	0 (0)	1 (3.3)
Urologic	4 (13.3)	4 (13.3)
Length of Surgery (minutes), mean (\pm SD)	126 (72)	126 (109)

BMI = body mass index; kg = kilogram; m = meter; SD = standard deviation.

Table 2

General Anesthesia Induction and Maintenance Agents

Sevoflurane (n = 30)		Propofol (n = 30)	
Induction agent (mg), mean (\pm SD)	Propofol (n = 28) 205 (66) Methohexital (n = 1) 250 Etomidate (n = 1) 30	Induction agent (mg), mean (\pm SD)	Propofol (n = 30) 198.3 (44)
Maintenance sevoflurane* (% inspired), mean (\pm SD)	2.21 (0.44)	Maintenance propofol* (mcg/kg/min), mean (\pm SD)	117.2 (26)

* Maintenance anesthetic during the selected epoch. SD = standard deviation.

Table 3

Adjunct Medications Administered*

	Sevoflurane (n = 30)	Propofol (n = 30)
Midazolam (mg), mean (\pm SD)	1.9 (0.4) (n = 23)	1.9 (0.7) (n = 14)
Fentanyl (mcg), mean (\pm SD)	210 (80) (n = 28)	192 (97) (n = 24)
Propofol-postinduction (mg), mean (\pm SD)	20.0 (n = 1)	55 (27) (n = 12)
Remifentanyl (mcg/kg/hr), mean (\pm SD)	(n = 0)	0.09 (0.04) (n = 24)
Hydromorphone (mg), mean (\pm SD)	0.74 (0.53) (n = 8)	0.6 (0.3) (n = 6)
Keterolac (mg), mean (\pm SD)	(n = 0)	30.0 (n = 1)
Morphine (mg)	5.0 (n = 1)	(n = 0)
Neuromuscular blocker, n (%)	27 (90.0)	30 (100)

* Medications administered from beginning of anesthetic until end of selected epoch.

hr = hour; kg = kilogram; mcg = microgram; mg = milligram; SD = standard deviation.