ORIGINAL CLINICAL RESEARCH REPORT

Spectral Differences of Anesthetic Agents: Addressing Fundamental Problems With New Methods

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BACKGROUND: Processed electroencephalography parameters are used to guide anesthesia to adequate levels for surgical procedures. Despite known spectral differences between anesthetics, studies often assume similar anesthetic states when titrating to the same target values, presupposing a reductive one-size-fits-all approach for all anesthetic agents. We hypothesize this may introduce bias and aim to characterize the differences using conventional and new approaches.

METHODS: For this retrospective study, we included 108 patients undergoing surgery under general anesthesia with either fluranes or propofol. We analyzed steady-state frontal electroencephalography during surgery. Conventional approaches were compared with "fitting oscillations & one-over-f" and "variational mode decomposition" at clinically guided hypnotic and analgesic levels. After comparing the hypnotic drugs at the group level, we used 2 distinct ranges of spectral edge frequency (SEF) for further analyses (8–15 Hz vs 15–21 Hz).

RESULTS: Sevoflurane and desflurane ("flurane") demonstrated similar spectral patterns using both conventional methods and "fitting oscillations & one-over-f" and "variational mode decomposition." "Variational mode decomposition" presented a 1.5 Hz higher central frequency (area under the receiver operating characteristic [AUC]: 0.88, 95% confidence interval [CI], 0.81–0.94, $P < .001$) in the propofol group (10.8 Hz [10.4–11.6]), compared to the flurane group (9.26 Hz [8.51–9.41]). "Fitting oscillations & one-over-f" produced a 2.04 Hz higher center frequency (AUC: 0.82, 95% CI, 0.72–0.91, $P < .001$) in the propofol group (10.6 [9.8–11.3]) compared to the flurane group (8.56 [8.02–9.69]). The exponent was 0.26 Hz^{-1} lower (AUC: 0.76, 95% CI, 0.67–0.85, $P < .001$) in the propofol group (2.45 Hz^{-1} [2.45–2.71]) compared to the flurane group (2.71 Hz^{-1} [2.50–2.93]). At the lower SEF range, "variational mode decomposition" presented a 1.5 Hz higher central frequency (AUC: 0.83, 95% CI, 0.70–0.94, $P < .001$) in the propofol group (10.4 Hz [9.7–10.9]), compared to the flurane group (8.92 Hz [8.03–9.45]). "Fitting oscillations & one-over-f" produced a 1.5 Hz higher center frequency (AUC: 0.83, 95% CI, 0.68–0.95, $P = .002$) in the propofol group (10.3 [10.0–10.8]) compared to the flurane group (8.78 [7.63–9.66]). The exponent was 0.31 Hz^{-1} lower (AUC: 0.79, 95% CI, 0.65–0.91, $P = .002$) in the propofol group (2.57 Hz^{-1} [2.44–2.70]) compared to the flurane group (2.88 Hz^{-1} [2.66–3.05]). Similar differences were found in the higher SEF group. However, no significant difference was found in the exponent between the groups.

CONCLUSIONS: Differences between the electroencephalographic (EEG) spectral patterns under propofol anesthesia compared to anesthesia using fluranes were sensitively captured by 2 recent approaches to EEG analysis. This could potentially lead to establishing agent-specific anesthetic indices. (Anesth Analg 2026;142:249–260)

KEY POINTS

- **Question:** Do novel analysis methods of electroencephalographic (EEG) analysis offer deeper insights into spectral differences between EEG signatures of flurane and propofol general anesthesia compared to a commonly used spectral parameter?
- **Findings:** At comparable levels of spectral edge frequency parameters derived from fitting oscillatons & one-over-f and variational mode decomposition vary significantly between the different hypnotics.
- **Meaning:** Fitting oscillations & one-over-f and variational mode decomposition offer deeper insights into EEG analysis of propofol and fluranes anesthesia and show potential for refinement of future neuroanesthesia monitoring.

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Electroencephalographic (EEG) and processed EEG information, like spectral edge frequency (SEF), can help guide anesthetic administration for surgery under general anesthesia. Processed EEG indices are used to titrate the hypnotic drug to an unspecific anesthetic "depth" that is neither too "light" to risk intraoperative awareness nor too "deep" to increase the risk for postoperative neurocognitive disorders.[1,2] In clinical practice and research, following a one-size-fits-all approach, the same index ranges or parameter values are applied for different anesthetic regimes.[3] However, these indices might be overly reductive, and most commercial solutions display various technical limitations in accurately assessing the anesthetic level and, therefore, hinder the effort to optimize anesthesia navigation.[4,5] We know that different agents lead to unique EEG patterns. Sevoflurane, due to a broadband filling effect in the theta-band at higher concentrations caused most likely by the broader receptor activity compared to propofol. This causes a slower EEG with more theta-band activity than anesthesia adequately maintained with propofol. Still, both gamma-aminobutyric acid (GABAergic) agents are treated the same.[6] Based on this assumption, sometimes contradictory conclusions have been drawn about the specific anesthetics' benefits.

To evaluate how agent-specific differences may impact future EEG-based monitoring, we used EEG from 108 patients who received either fluranes or propofol as the primary anesthetic agent. These recordings were deconstructed using automated iterative methods, namely "fitting oscillations & one-over-f" (FOOOF) and "variational mode decomposition" (VMD), allowing the assessment of features beyond canonical frequency bands.[7,8] FOOOF determines periodic and aperiodic EEG components. VMD divides a signal into subordinate frequency- and time-modulated intrinsic mode functions (IMFs). Both methods offer less reductive processed EEG parameters than conventional spectral analysis. We hypothesized that VMD frequency band composition and aperiodic and oscillatory components differ between agents and can be used for agent-specific monitoring.

MATERIAL AND METHODS

Study Protocol and Patient Inclusion

We retrospectively analyzed published data from 201 patients recorded between April 2018 and November 2019. The primary goal was to investigate the possibility of predicting delirium from anesthesia emergence EEG. Ethical approval was obtained at the Klinikum rechts der Isar, TUM, Germany (213/17S, dated May 24, 2017). All patients gave written and informed consent. Our analysis included 108 patients without postoperative delirium according to the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) because it constitutes a confounding factor by itself.[2,9] We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for observational studies.

Anesthesia Protocol

In all patients included, anesthesia was induced with propofol and maintained either with sevoflurane or desflurane (ie, fluranes), or propofol. If required, paralysis was achieved with rocuronium or mivacurium in 1 case. Analgesia was provided with continuous remifentanil administration via a syringe pump or bolus application of sufentanil. Exact pharmacological dosages were not predefined but were left to the discretion of the responsible anesthesiologist to achieve a clinically adequate anesthetic level. Patient monitoring complied with the German Association of Anesthesiology and Intensive Care standards. The EEG was recorded for research purposes and did not impact clinical decisions.

EEG Recording

The EEG was recorded with the NIM-Eclipse Neuromonitoring system (Medtronic; sample-rate = 250 Hz; hardware 1 Hz high-pass-filter) using 10 electrodes positioned at Fp1/2, F1/2, C3/4, P3/4, O3/4, and Cz as the reference in accordance with the 10/20 nomenclature.

Missing Data

We conducted an available case analysis. The exclusion process yielded 108 ($N_{propofol}$ = 49, $N_{flurane}$ = 59) available recordings. Supplemental Digital Content, Supplemental Figure 1, http://links.lww.com/AA/F300, contains the inclusion protocol. There were no missing epidemiological data. Missing anesthetic and opioid concentrations are noted for each subgroup in Supplemental Digital Content, Supplemental Table 1, http://links.lww.com/AA/F300.

Corrupted Files, Artifacts, and Burst Suppression

We excluded corrupted EEG datasets. Two independent investigators visually inspected 180 seconds of EEG for a 60-second period free of artifacts and burst suppression at the midpoint between the incision and the termination of anesthetic delivery, representing a likely steady state of surgery.

Conventional EEG Power Spectrum Analysis and SEF

We used MATLAB 2023b (The Mathworks Inc) with the *eeglab* toolbox for processing.[10] After data import and applying a 47 Hz low-pass filter (Hamming windowed FIR filter; *pop_eegfiltnew*), we calculated power spectral densities (PSD) with the *pwelch* function with NFFT=500, resulting in a frequency resolution of 0.5

Hz. The relative spectra were calculated by normalizing PSDs to the total power between 1 and 47 Hz. The patient-averaged PSDs of both frontal channels (Fp1/Fp2) were used for further analysis, assuming a uniform interhemispheric effect of hypnotic agents on frontal EEG activity.

The SEF is a simple processed EEG parameter that correlates with the hypnotic level. It is implemented in multiple monitoring devices. However, a current narrative review concludes there is inconclusive evidence considering target ranges.[11] In our case, SEF is the frequency below which 95% of relative power is located. Using SEF, we formed 2 groups: light and deep anesthesia. We arbitrarily chose a SEF of 15 Hz for cutoff and compared spectral compositions as well as FOOOF and VMD between flurane- and propofol-based anesthesia maintenance at both SEF levels.

EEG Analysis With FOOOF

FOG represents a novel approach, and recent results offer possible mechanistic explanations for the underlying mechanisms.[12] The resulting PSDs (1–47 Hz) were input for the Python (v3.6) implementation.[7] The FOOOF method aims to split a PSD into an aperiodic power spectrum and to fit a predefined number of putative peaks to the periodic spectrum, identifying underlying oscillatory components. Fitting criteria were set to include a maximum of 3 peaks as we expected periodic peaks in the theta/alpha, beta, and gamma band with a minimum power height (absolute threshold) of 0.3 dB and a bandwidth ranging from twice the frequency resolution to 12 Hz. The peak (relative) threshold was kept at 2 standard deviations, and aperiodic fitting remained fixed.

Periodic components are parameterized by 3 items: center frequency, power of the peak, and bandwidth. As both anesthetics typically elicit a frontal alpha-band peak (8–13 Hz), we compared putative oscillatory peaks with center frequencies within the detected peak component. The bandwidth equals twice the standard deviation of the Gaussian peak function. The power of the peak is the height above the aperiodic component. Two parameters, offset (y-axis intercept) and exponent (slope) describe the aperiodic component. They define the linear equation that captures the PSD's 1/f behavior in the log–log space. 1/f describes the ubiquitous inversely correlated background noise signal, which decreases in amplitude with increasing frequency.

EEG Analysis Using Variational Mode Decomposition

VMD is a recent deconstruction method able to quantify the distinct, agent-specific, differences in EEG signatures.[13,14] The function *vmd (*Signal Processing Toolbox) was used to decompose the EEG into subordinate time and frequency-modulated IMFs. The modes' envelopes are positive and slowly varying, with a *frequency* oscillating around the *central frequency* of the IMF.[8,14] We predefined 5 IMFs, analogous to the 5 canonical bands (delta, theta, alpha, beta, and gamma) without the necessity to adhere to arbitrary bounds.[13] The maximum number of iterations was 10.000, and the penalty factor was 125 to reach iterative convergence and stricter data fidelity. The analytical amplitude was calculated with the Hilbert transformation (*hilbert*). Relative amplitudes were calculated by normalizing to the sum of all amplitudes in the corresponding EEG segment. Supplemental Digital Content, Supplemental Figures 2 and 3, http://links.lww.com/AA/F300, shows exemplary data from the analysis.

Comparing Fluranes

In a preliminary analysis using the conventional power spectrum analysis, the FOOOF and VMD methods were utilized to assess whether the spectra derived from desflurane and sevoflurane EEG segments could be merged into a single "flurane" group.

Statistical Analysis

We used MATLAB 2023b for statistical analyses. Differences in categorical variables sex and ASA status were analyzed using Fisher's exact tests. P values are supported by Risk-Ratios. Normal distributions were not assumed for continuous variables age, body mass index (BMI), anesthesia, and emergence time, and 2-sided Wilcoxon rank sum tests were applied. P-values were supported by effect sizes using the area under the receiver operating characteristic (AUC) and 10,000-fold bootstrapped 95% confidence intervals (CIs) supplied in the MES toolbox.[15] A 95% CI excluding AUC = 0.5 indicates a significant difference ($P < .05$).[15] AUC values can roughly be interpreted as excellent: 1≥ AUC ≥0.9; good: 0.9> AUC ≥0.8; fair: 0.8> AUC ≥0.7; poor: 0.7> AUC ≥0.6; or fail: AUC <0.6.[16] The process of calculating spectral differences in PSDs was similar to the continuous variables mentioned above. The corresponding group-level frequency/power bins were input to calculate the differences between agents using the AUC. As previously done, they were regarded as statistically significant when at least 2 adjacent frequencies showed significant AUC results.[6,17] Parameters from FOOOF and VMD were analyzed by treating them as continuous, not-normally distributed variables using the same approach described above.

RESULTS

Patient Characteristics

Supplemental Digital Content, Supplemental Table 2, http://links.lww.com/AA/F300, shows the results of

the univariable analysis. We found no significant differences between the groups regarding age, sex, BMI, American Society of Anesthesiologists (ASA) physical status, and anesthesia duration. Emergence time was 7 minutes [5–10] minutes in the propofol group and 10 minutes [8–14] in the flurane group (AUC: 0.65; 95% CI, 0.54–0.75; $P = .009$). Sufentanil concentrations were not statistically different between the propofol and the flurane group (Supplemental Digital Content, Supplemental Table 1, http://links.lww.com/AA/F300).

Conventional Spectral Analysis and Spectral Edge Frequencies

Our resulting group density spectral arrays (A–C) and the derived group PSDs (D–F) from the midsurgery period in Figure 1 showed similar results from previous publications that characterized sevoflurane and propofol anesthesia.[6] The propofol group had significantly lower absolute power in the delta (1–4 Hz) and theta (4–8 Hz) band than the desflurane group and additionally lower power in the beta and gamma range (Figure 1G, 1H) than the sevoflurane group. The sevoflurane group had significantly lower absolute power than the desflurane group spread across most bands, except for the alpha-band (Figure 1I). While corresponding SEFs were not significantly different between sevoflurane (14.5 Hz [12.5–16]) and desflurane (14 Hz [14–17]), SEFs for sevoflurane (AUC: 0.76, 95% CI, 0.65–0.86, $P < .001$) and desflurane (AUC: 0.75, 95% CI, 0.61–0.88, $P = .002$) groups were significantly lower compared to the propofol group (17 Hz [15–18.5]).

Comparing Fluranes

We did not find statistically significant differences between sevoflurane's and desflurane's spectral patterns with VMD, FOOOF, and SEFs (Supplemental Digital Content, Supplemental Figure 4 and Supplemental Table 3, http://links.lww.com/AA/F300). Hence, we combined both substances into 1 "flurane" group for all subsequent analyses.

Variational Mode Decomposition

The frequency ranges derived from the VMD were comparable to the conventional bands for both agents. Central frequencies were significantly higher for the propofol group across all but the slowest IMF (Figure 2A–E and Table). The Table contains the AUC values with 95% CI and p-values. In IMF 1, corresponding to the gamma and beta band, central frequencies were 10.44 Hz higher for propofol (35.1 Hz [27.0–47.9]) than for flurane (24.7 Hz [22.1–33.4]; "fair" discrimination). In IMF3, comparable to the alpha-band, central frequencies were 1.5 Hz higher for propofol (10.8 Hz [10.4–11.6]) than for flurane (9.26 Hz [8.51–9.94]; "good" discrimination). Absolute amplitudes were significantly lower for propofol across all IMFs, with "fair" and "good" discriminations (Figure 2F-J). In IMF4, corresponding to the theta band, relative analytical amplitudes were 5.6% lower for propofol (19.5% [18.1–20.8]) than for flurane (25.1% [23.2–26.5]; "excellent" discrimination).

Fitting Oscillations and One-Over-F

Offset values for propofol were 0.50 arbitrary units lower than for flurane. Propofol offsets were 2.03 [1.74–2.26], while flurane offsets were 2.54 [2.22–2.89] with "fair" discrimination (Figure 2P). Propofol exponents were 0.26 Hz^{-1} lower than for flurane with "fair" separation. Propofol exponents were 2.45 [2.28–2.58], while flurane exponents were 2.71 [2.50–2.94] (Figure 2Q). Regarding the properties of the oscillatory component within the canonical alpha-band, we found that the median center frequency (Figure 2R) of propofol was 2.0 Hz higher. Propofol center frequencies were 10.6 Hz [9.8–11.3] as compared to 8.56 Hz [8.02–9.69] for flurane with "good" discrimination. The power of the peak and peak width did not show significant differences. Supplemental Digital Content, Supplemental Figure 5, http://links.lww.com/AA/F300 shows the group-level PSDs of the periodic and aperiodic components and the differences between the substances.

Spectral Edge Frequency Ranges

Figure 3 presents the different spectral compositions of propofol (Figure 3A, 3B) and flurane (Figure 3D, 3E) anesthesia at 2 different SEF ranges ("deep anesthesia": 8–15 Hz and "light anesthesia": 15–21 Hz). Spectral differences between SEF levels in the propofol group are mostly attributable to a narrow-band increase in the low alpha range and a broadband decrease in the beta-to-gamma range (25–40 Hz). In contrast, variations between high and low SEF levels in the flurane group are due to a different spectral pattern. Absolute power in the beta/gamma range (15–47 Hz) decreased, and power in the delta/theta band increased, while alpha power did not change. Differences between the agents were similar for both SEF ranges. Absolute delta, theta, and low alpha (8–9 Hz) power was significantly lower in the propofol group than in the flurane group at both ranges (Figure 3G, 3H). Additionally, propofol had significantly lower absolute beta power (15–30 Hz) at the higher SEF range (Figure 3H).

FOOOF and VMD at Different SEF Ranges

The general trend was similar in both SEF ranges (Figures 4 and 5). Supplemental Digital Content, Supplemental Tables 4 and 5, http://links.lww.com/AA/F300 contain exact AUC values, 95% CI, and

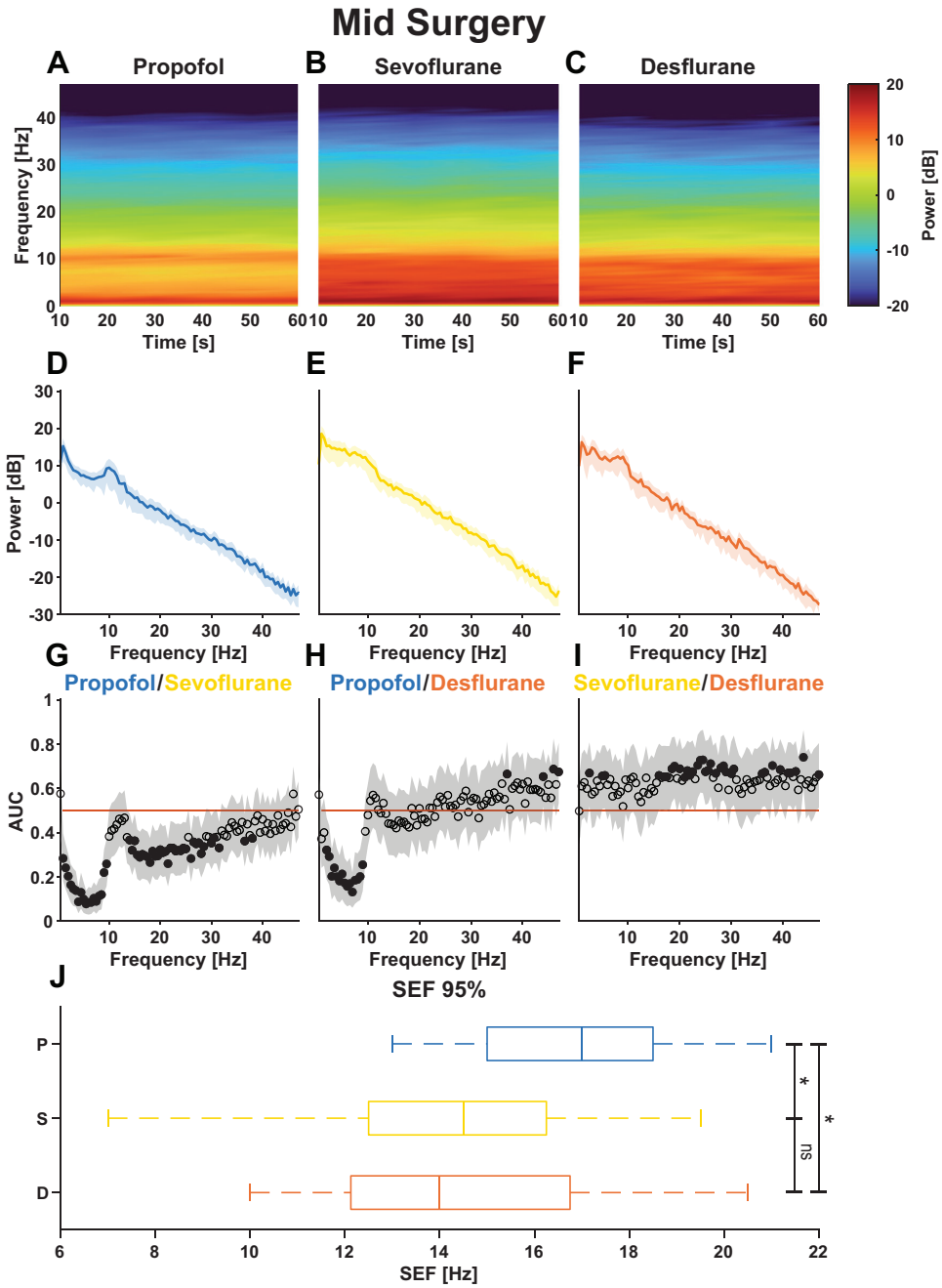

Figure 1. Conventional spectral power-based analysis of propofol, sevo- and desflurane general anesthesia at midsurgery. A–C, Groupwise median density spectral arrays for propofol (A), sevoflurane (B), and desflurane (C). D–F, Groupwise median absolute power spectrum densities for propofol (A), sevoflurane (B), and desflurane (C). G–I, Groupwise comparisons of power spectra: The propofol group had statistically significant lower absolute power in the delta (1–4 Hz) and theta (4–8 Hz) band than the desflurane group and additionally lower power in the beta and gamma range than the sevoflurane group. The sevoflurane group had statistically significant lower absolute power than the desflurane group spread across most bands, except for the alpha-band. J, spectral edge frequencies: The SEF was significantly higher (AUC: 0.76 [95% CI, 0.65–0.86], $P < .001$) in the propofol group (17 Hz [15; 18.5]) compared to the sevoflurane (14.5 Hz [12.5;16]) and the desflurane group (14 Hz [14;17]). AUC indicates area under the receiver operating characteristic; SEF, spectral edge frequency.

exact p-values. At SEF 8–15 Hz, central frequencies were significantly slower with fluranes in IMFs 1 to 5 and significantly faster in IMF 6 than with propofol (Figure 4A–E; Supplemental Table 4, http://links.lww.com/AA/F300). Central frequencies were 1.5 Hz faster in IMF3 with propofol (10.4 Hz [9.7–10.9]) than with fluranes (8.92 Hz [8.03–9.45]; "good" discrimination) (Figure 4C). Absolute amplitudes in IMF4 were 5.66 µV lower with propofol (4.90 µV [3.90–6.56]) than with fluranes (10.6 µV [7.4–14.0]) with "good" discrimination (Figure 4I). Relative amplitudes in IMF4 were 6.0% lower with propofol (19.2% [18.0–19.7]) than with fluranes (25.1% [23.2–26.4]) with "excellent" discrimination (Figure 4N). At SEF 15 to 21 Hz, central frequencies were significantly slower with fluranes in IMF 1 to 3 (Figure 5A-C). For IMF3, central frequencies were 1.2 Hz faster with propofol (10.8 Hz [10.6–11.6]) than with fluranes (9.57 Hz [8.90–10.12]) with "excellent" discrimination (Figure 5C). Absolute amplitudes were significantly lower across all IMFs, except IMF5 (Figure 5F–J). In IMF4, corresponding to the delta/theta bands, absolute amplitudes were 3.26 µV lower with propofol (4.45 µV [3.37–5.41]) than with fluranes (7.72 µV [6.25–9.60]) with "good" discrimination (Figure 5I). Relative amplitudes in IMF4 were 5.2% lower with propofol (19.6% [18.2–20.8]),

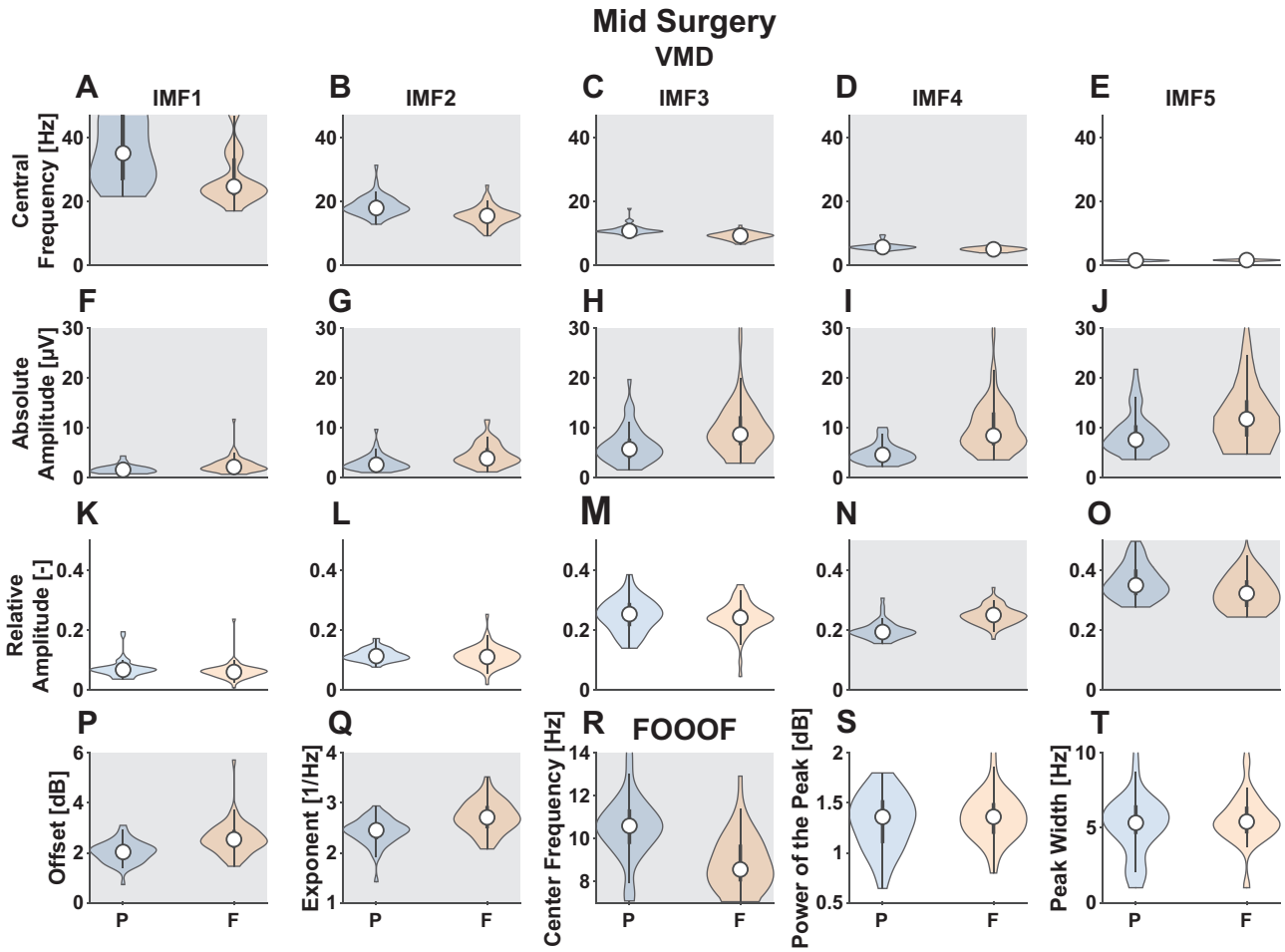

Figure 2. VMD and FOOOF analysis for propofol versus flurane groups: statistically significant differences are marked gray and indicated by bootstrapped 95% AUC confidence intervals not including AUC = 0.5 as well as *P* values <.05. Exact values are noted in the Table. A–E, Central frequencies in IMF 1 to 4 (B–D) are significantly lower in the Flurane group compared to the Propofol group. There is no statistically significant difference in IMF 5 (E). F–J, Absolute Amplitudes are significantly higher in the Flurane group compared to the Propofol group in all IMFs. K–O, In IMF 4 (N) relative power is significantly lower in the Propofol group compared to the Flurane group. In IMF 5 (O) relative power is significantly lower in the Flurane group compared to the Propofol group. P–T, Offset (P) and Exponent (Q) are significantly lower Propofol group compared to the Flurane group. Center Frequency (R) is significantly lower in the Flurane group compared to the Propofol group. There are no significant differences in the other FOOOF parameters. AUC indicates area under the receiver operating characteristic; FOOOF, fitting oscillations & one-over-f; IMF, intrinsic mode function; VMD, variational mode decomposition.

than with fluranes (24.8% [22.5–26.3]) with "good" discrimination (Figure 5N).

Differences in FOOOF parameters were comparable at both SEF ranges, so exemplary results are presented here for SEF 8 to 15 Hz (Supplemental Table 4, http://links.lww.com/AA/F300). Offset values for propofol power spectra were 0.37 arbitrary units lower than for fluranes with "fair" discrimination (Figure 4P). Propofol offsets were 2.20 [1.74–2.26], while flurane offsets were 2.57 [2.22–2.89]. Propofol exponents were 0.31 Hz^{-1} lower than for fluranes. Propofol exponents were 2.57 [2.44–2.70], while flurane exponents were 2.88 [2.66–3.05] with "fair" discrimination (Figure 4Q). Center frequencies of propofol were 1.54 Hz higher. Propofol center frequencies were detected around 10.3 Hz [10.0–10.8] as compared to 8.78 Hz [7.63–9.66] for fluranes with "good" discrimination (Figure 4R). The power of the peak and peak width did not show significant differences (Figure 4S–T). The corresponding SEF 15 to 21 Hz results can be found in Supplemental Digital Content, Supplemental Table 5, http://links.lww.com/AA/F300.

Agent-Specific Differences at 2 SEF Ranges

To assess how agent-specific spectral patterns change between light and deep anesthesia based on SEF, we compared propofol and flurane results from VMD and FOOOF at 8 to 15 Hz to results at 15 to 21 Hz. In the propofol group (Supplemental Digital Content, Supplemental Figure 6 and Supplemental Table 6, http://links.lww.com/AA/F300) central frequencies were 0.4 Hz higher in IMF3 of the high SEF group (10.8 Hz [10.6–11.6] than of the low SEF group (10.4 Hz [9.68–10.9]) with "fair" discrimination. No statistically significant differences in absolute

Table. VMD and FOOOF Analysis for Propofol versus Flurane Groups

VMD parameters		IMF1	IMF2	IMF3	IMF4	IMF5
Central frequencies	Propofol	35.14 [27.00–47.88]	17.96 [16.68–20.35]	10.76 [10.35–11.56]	5.67 [5.20–6.09]	1.47 [1.30–1.61]
	Flurane	24.71 [22.07–33.35]	15.51 [13.80–16.86]	9.26 [8.51–9.94]	4.98 [4.54–5.53]	1.57 [1.42–1.73]
	Median difference	**10.44**	**2.45**	**1.50**	**0.70**	−0.11
	AUC (95% CI)	**0.77 (0.67–0.85)**	**0.78 (0.69–0.87)**	**0.88 (0.81–0.94)**	**0.76 (0.66–0.84)**	0.65 (0.55–0.76)
	P value	**<.001**	**<.001**	**<.001**	**<.001**	.0597
Absolute amplitudes	Propofol	1.59 [1.07–2.12]	2.60 [1.87–3.62]	5.71 [4.05–7.69]	4.59 [3.47–5.62]	7.61 [6.01–10.39]
	Flurane	2.16 [1.58–3.09]	3.87 [3.13–5.80]	8.68 [6.65–12.21]	8.42 [6.62–12.96]	11.75 [8.38–15.40]
	Median difference	**–0.57**	**–1.27**	**–2.96**	**–3.83**	**–4.14**
	AUC (95% CI)	**0.70 (0.60–0.79)**	**0.74 (0.64–0.83)**	**0.73 (0.64–0.83)**	**0.88 (0.81–0.94)**	**0.73 (0.62–0.82)**
	P value	**.002**	**<.001**	**.001**	**<.001**	**.099**
Relative amplitudes	Propofol	6.84 [5.76–7.58]	11.41 [10.29–13.04]	25.42 [21.58–28.95]	19.45 [18.13–20.78]	35.07 [31.92–40.13]
	Flurane	6.09 [4.90–7.09]	11.13 [8.96–13.00]	24.24 [22.05–27.04]	25.13 [23.19–26.54]	32.33 [27.99–36.51]
	Median difference	0.75	0.27	1.19	**–5.59**	**2.74**
	AUC (95% CI)	0.61 (0.51–0.72)	0.55 (0.44–0.66)	0.55 (0.44–0.63)	**0.90 (0.82–0.96)**	**0.65 (0.55–0.75)**
	P value	.112	.433	.39	**<.001**	**.04**

FOOOF parameters	Offset (dB)	Exponent (Hz^{-1})	Center frequency (Hz)	Power of the peak (dB)	Peak width (Hz)
Propofol	2.03 [1.74–2.26]	2.45 [2.28–2.58]	10.59 [9.77–11.34]	1.36 [1.10–1.52]	5.34 [4.63–6.47]
Flurane	2.54 [2.22–2.89]	2.71 [2.50–2.93]	8.56 [8.02–9.69]	1.36 [1.20–1.49]	5.41 [4.67–6.38]
Median difference	**–0.50**	**–0.26**	**2.04**	<1e–3	–0.08
AUC (95% CI)	**0.78 (0.69–0.86)**	**0.76 (0.67–0.85)**	**0.82 (0.72–0.91)**	0.53 (0.41–0.65)	0.53 (0.40–0.65)
P value	**<.001**	**<.001**	**<.001**	.402	.420

We present median and 25th and 75th percentiles for FOOOF and VMD parameters well as the difference between medians. Statistically significant differences are marked bold and indicated by bootstrapped 95% AUC confidence intervals not including AUC = 0.5 as well as *P* values <.05 propofol (n = 49) vs flurane (n = 59).

Abbreviations: AUC, area under the receiver operating characteristic; CI, confidence interval; FOOOF, fitting oscillations & one-over-f; VMD, variational mode decomposition.

amplitudes were found. Relative amplitudes in IMF2 (beta band), were 1.7% lower in the low SEF group (10.3% [9.3–11.5]) than in the high SEF group (11.9% [10.7,13.4]) with "fair" discrimination. The FOOOF analysis showed a 0.15 Hz^{-1} higher exponent in the low SEF group (2.57 Hz^{-1} [2.44; 2.70] compared to the high SEF group (2.42 Hz^{-1} [2.27–2.54]) with "fair" discrimination. In contrast to the primary analysis between agents, the power of the peak was 0.15 dB higher in the low SEF group (1.45 dB [1.35–1.64]) compared to the high SEF group (1.30 dB [1.05–1.48]) with "fair" discrimination. In the flurane group (Supplemental Digital Content, Supplemental Figure 7 and Supplemental Table 7, http://links.lww.com/AA/F300) central frequencies were significantly slower across IMFs 2 to 4 in the low SEF group. In IMF3, central frequencies were 0.65 Hz slower in the low SEF group (8.92 [8.03–9.45]) than in the high SEF group (9.57 [8.90–10.1]) with "fair" discrimination. No significant results were found in absolute amplitudes. In IMF1, relative amplitudes were 1.12% lower in the low SEF group (5.93% [4.63–6.35]) compared to the high SEF group (7.06% [6.12–7.66]; "fair" discrimination). The FOOOF analysis showed a 0.29 Hz^{-1} higher exponent in the low SEF group (2.88 Hz^{-1} [2.66–3.05]) compared to the high SEF group (2.59 Hz^{-1} [2.41–2.68]; "good" discrimination).

DISCUSSION

State of the Art

As demonstrated in past studies flurane and propofol have distinct patterns of molecular target activation, which translate to different EEG signatures on a network level, despite undoubtedly sharing substantial mechanistic overlap.[6,18–21] We confirm and strengthen the finding, using conventional and state-of-the-art EEG interpretation algorithms: FOOOF and VMD, that during general anesthesia, the fluranes' EEG shows significantly more theta-band activity than for propofol.[6,18] To our knowledge, no processed EEG monitoring system currently adjusts the index to the agent. The one-size-fits-all used in contemporary anesthesia research, which employs canonical frequency bands with varying edge frequencies, might be overly reductive and could be substantially refined by approaches outlined and used here.[2,6,18,22]

Our Applied Methods

The FOOOF method provides new insights into the classical FFT by attributing spectral differences between anesthetics to differences in the periodic and aperiodic components.[7] For instance, a higher offset results from overall increasing power, while higher exponents indicate a steeper power distribution, with slow frequencies dominating. Possible explanations for the underlying

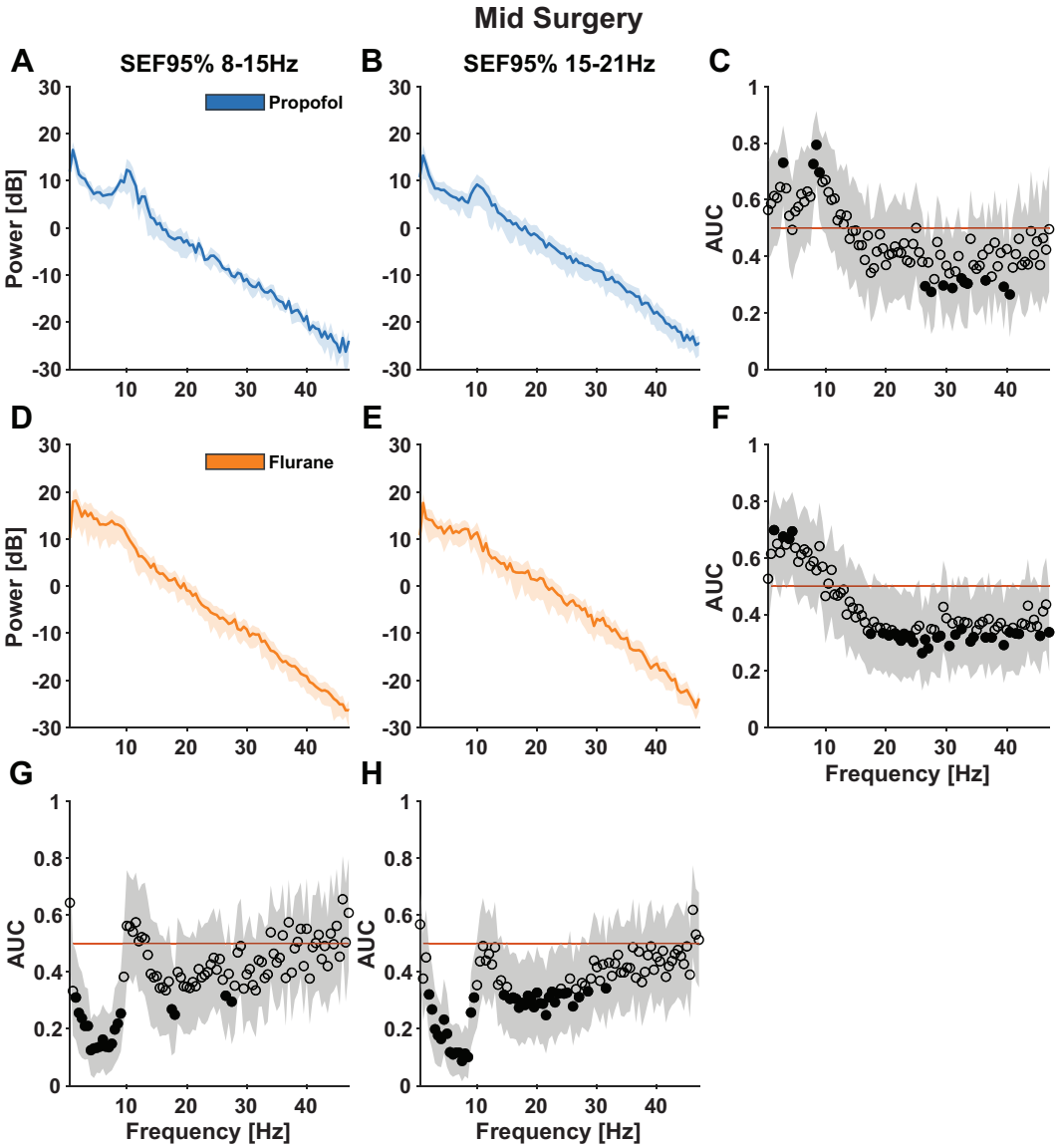

Figure 3. Spectral composition of propofol and flurane anesthesia at 2 SEF ranges. A, Propofol groupwise median power spectrum density at SEF 8 to 15 Hz. B, Propofol groupwise median power spectrum density at SEF 15 to 21 Hz. C, Differences in the propofol group are due to a statistically significant narrow-band increase in the low alpha range and a broad-band decrease in the beta to gamma range (25–40 Hz). D,Flurane groupwise median power spectrum density at SEF 8 to 15 Hz. EFlurane groupwise median power spectrum density at SEF 15 to 21 Hz. F,Differences in the flurane group are due to statistically significant differences in absolute power in the beta/gamma range (15–47 Hz) and delta/theta band. Alpha power did not change. G–H,Differences between the substances at both SEF ranges: Results are similar at both ranges. Absolute delta, theta, and low alpha (8–9 Hz) power was statistically significantly lower in the propofol group compared to the flurane group at both ranges. Additionally, propofol had statistically significant lower absolute beta power (15–30 Hz) at the higher SEF range. SEF indicates spectral edge frequency.

mechanistic processes were recently published.[12] The oscillatory (alpha-)peak frequency was significantly higher for propofol, with a difference >2 Hz, with similar results derived from the VMD analysis. This finding may impact index development, suggesting the need to define agent-specific alpha-bands. Currently, there is no alpha-band-based processed EEG parameter, even though alpha-power appears to correlate with anesthesia quality.[2,23,24] Processed EEG parameters react differently to changes in alpha oscillatory activity, compromising the indices' comparability and validity.[22]

Compared to FOOOF, VMD is a novel method that does not rely on FFT and is independent of user input regarding canonical bands. VMD iteratively searches for the best possible fit of "bands."[8] We found uniformly different absolute and relative amplitudes and center frequencies across different anesthetic regimes and different SEF ranges (equivalent to what may conventionally be considered light and deep anesthesia). We offer novel insights into the spectral composition of EEG patterns produced by different anesthetic agents. These patterns are currently, and potentially

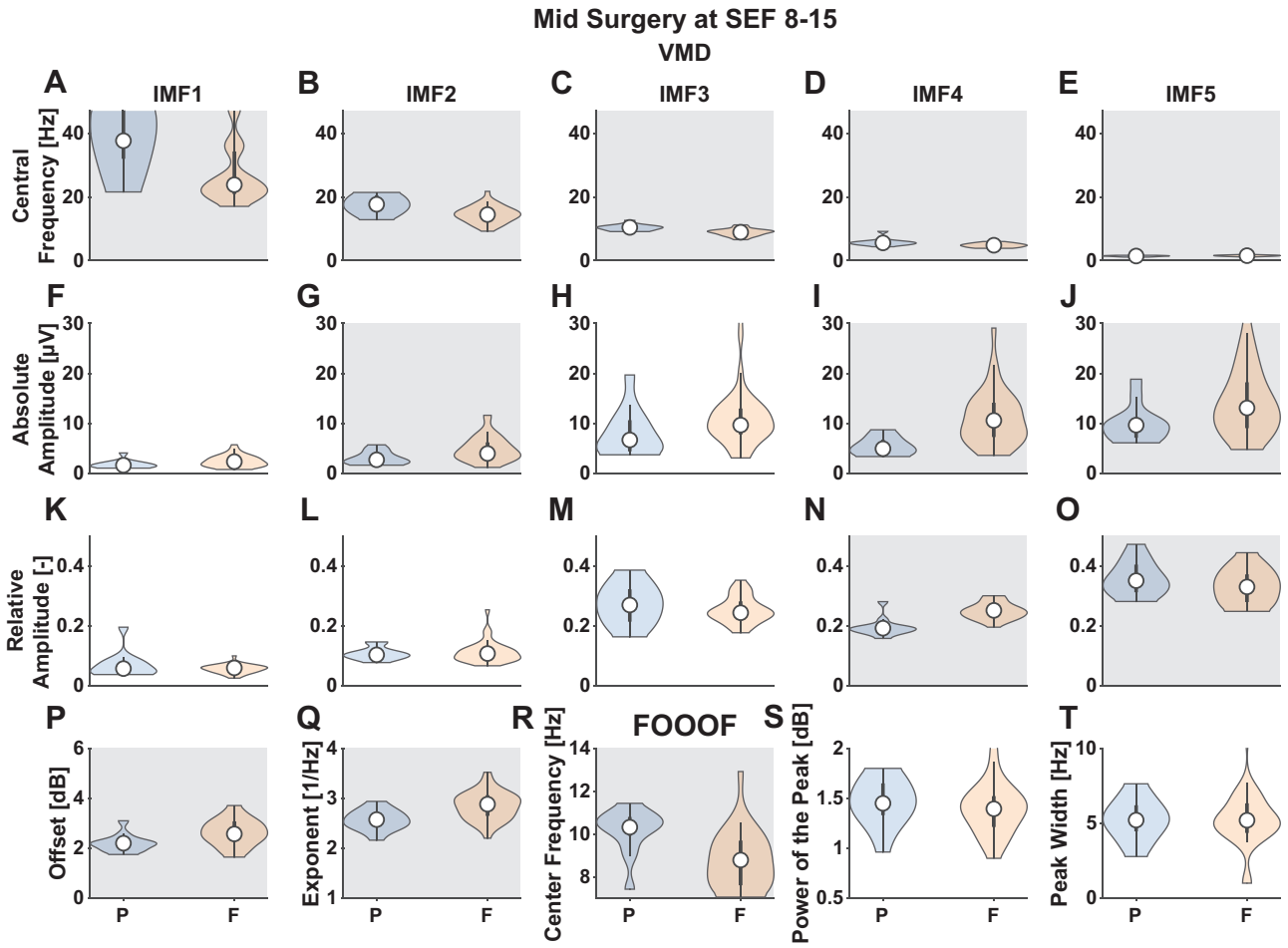

Figure 4. VMD and FOOOF analysis for propofol versus flurane groups at SEF 8 to 15 Hz: Statistically significant differences are marked gray and indicated by bootstrapped 95% AUC confidence intervals not including AUC = 0.5 as well as *P* values <.05. Exact values are noted in Supplemental Digital Content, Supplemental Table 4, http://links.lww.com/AA/F300. A–E, Central frequencies in IMF 1 to 4 (B–D) are significantly lower in the Flurane group compared to the Propofol group. The central frequency in IMF 5 (E) is significantly higher in the Flurane group compared to the propofol group. F–J, Absolute Amplitudes are significantly higher in the Flurane group compared to the Propofol group in all IMFs. K–O, In IMF 4 (N) relative power is significantly lower in the propofol group compared to the flurane group. In IMF 5 (O) relative power is significantly lower in the Flurane group compared to the Propofol group. P–T, Offset (P) and exponent (Q) are significantly lower in the Propofol group compared to the flurane group. Center frequency (R) is significantly lower in the Flurane group compared to the Propofol group. There are no significant differences in the other FOOOF parameters. AUC indicates area under the receiver operating characteristic; FOOOF, fitting oscillations & one-over-f; IMF, intrinsic mode function; SEF, spectral edge frequency; VMD, variational mode decomposition.

problematically, treated as essentially the "same" due to how processed EEG indices operate. FOOOF and VMD highlight the intrinsically different spectral compositions between adequate propofol and flurane anesthesia. The standard method involves dividing the EEG into a predefined number of frequency bands, which can, to some degree, be differently defined by the researcher or index designer. If an iterative algorithm, such as VMD, is used for deconstruction, the features for a defined number of "bands" can vary significantly among different agents and SEF ranges (corresponding to different hypnotic levels).

Impact on Monitoring and Possible Applications

All EEG-based anesthesia monitoring parameters in commercial use are derived from the power spectrum.[25–28] Our study confirms that anesthetic agents uniquely modulate the power spectrum, and differences are clearly distinguishable, firstly when comparing differences between anesthetics at different SEF target ranges and secondly when comparing within agent patterns at different target ranges. The intrinsic differences between fluranes and propofol may cause bias when titrating patients to the "same numbers," assuming the "same anesthetic level."[3,29–31] While other studies used set index limits to define different levels of light and deep anesthesia, there is evidence showing that patients receiving propofol had more burst suppression when titrated to the same SEF as patients receiving flurane anesthesia, suggesting excessive hypnotic levels.[32,33] At a clinically adequate level for surgical intervention, propofol anesthesia may be correlated with higher index values than flurane anesthesia. The agent-specific

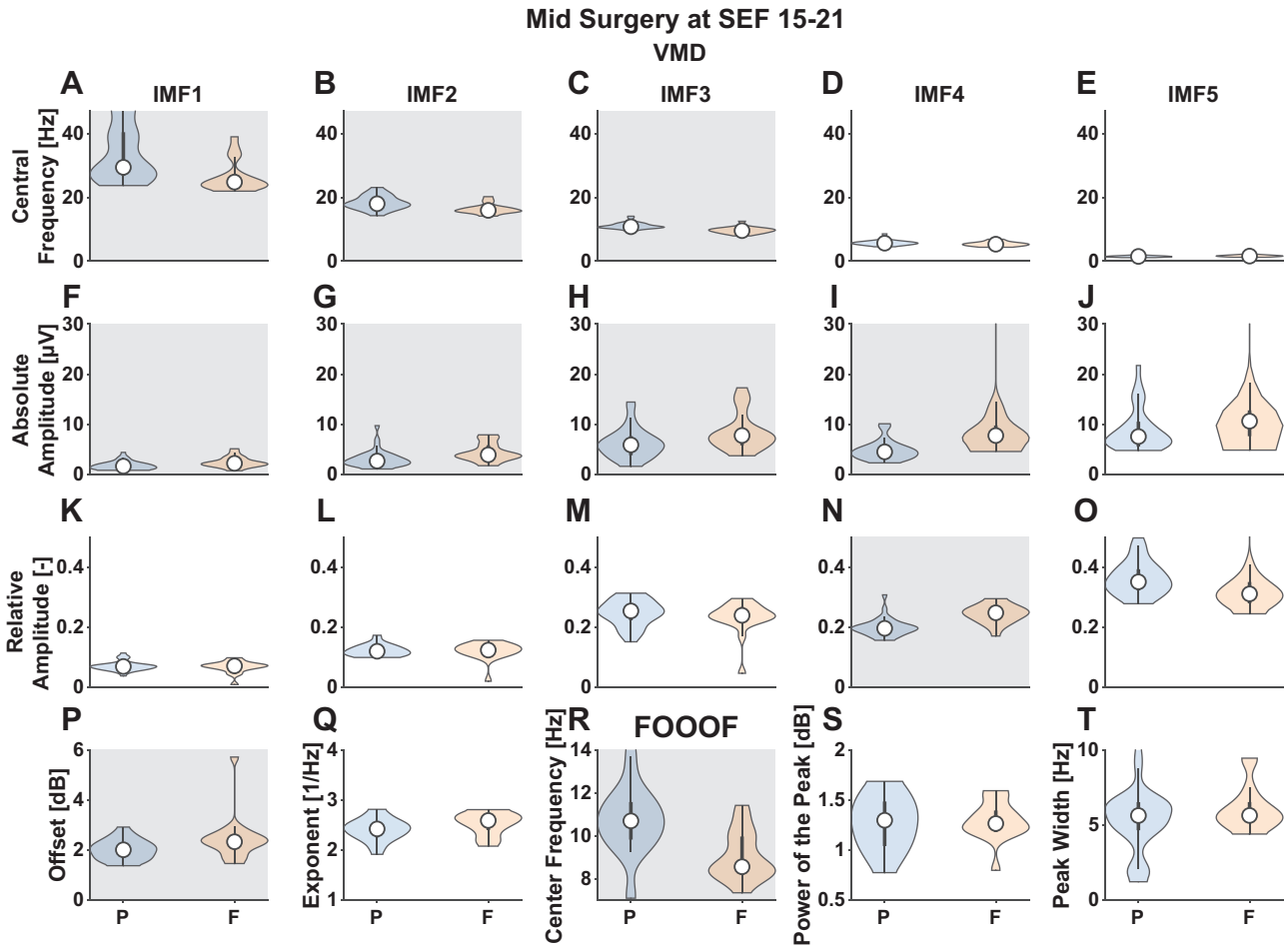

Figure 5. VMD and FOOOF analysis for propofol versus flurane groups at SEF 15 to 21 Hz, statistically significant differences are marked gray and indicated by bootstrapped 95% AUC confidence intervals not including AUC = 0.5 as well as *P* values <.05. Exact values are noted in Supplemental Digital Content, Supplemental Table 5, http://links.lww.com/AA/F300. A–E, Central frequencies in IMF 1 to 3 (B–D) are significantly lower in the Flurane group compared to the Propofol group. There are no significant differences in central frequencies in the other IMFs. F–J, Absolute Amplitudes are significantly higher in the Flurane group compared to the Propofol group in IMFs 1 to 4 (F–H). There is no significant difference in absolute amplitude in IMF 5. K–O, In IMF 4 (N) relative power is significantly lower in the Propofol group compared to the Flurane group. There is no significant difference in relative power in the other IMFs. P–T, The offset (P) is significantly lower in the propofol group compared to the flurane group. Center frequency (R) is significantly lower in the flurane group compared to the Propofol group. There are no significant differences in the other FOOOF parameters. AUC indicates area under the receiver operating characteristic; FOOOF, fitting oscillations & one-over-f; IMF, intrinsic mode function; SEF, spectral edge frequency; VMD, variational mode decomposition.

differences also add complexity when investigating the dependency of delirium on the anesthetic level. Several factors, that is, the indices' inaccuracy to reliably detect burst suppression, the different patterns of burst suppression between agents, the indices' dependency on age, and the indices' dependence on the agent, may interfere with using processed EEG information to identify patients at risk for a postoperative neurocognitive disorder.[22,34,35] Processed EEG indices, although overly simplifying the EEG signal, still may provide information regarding the hypnotic state. Slow and alpha waves are universal to propofol and flurane anesthesia, as well as other types of anesthetics.[36,37] However, the processed EEG indices may not sufficiently depict agent-specific differences primarily found in the frequencies outside these ranges.

Anesthetic "Depth"

Anesthetic depth is a term used to describe the hypnotic state, assuming comparability between different agents. Comparison of inhalational agents seems reasonable, as both sevoflurane and desflurane have similar MAC-awake/MAC values.[38] We found results comparable to those of previous studies conducted to compare MAC equivalent dosages of sevoflurane and desflurane.[39] While the spectral patterns did differ in absolute power terms, we found no significant differences in the underlying signal composition between sevoflurane and desflurane using FOOOF and VMD. There is a lack of a gold standard for comparing different agents and establishing comparable hypnotic levels. Struys et al. presented a carefully designed study with a surface plane model to quantify the comparability between propofol effect-site concentrations

and end-tidal sevoflurane concentrations for clinically relevant end points. For example, concentrations of 3.0 vol% of end-tidal sevoflurane were comparable to 7 µg/ml of propofol, considering the probability of reaction to laryngoscopy.[40] We assume that our patient population had clinically adequate anesthesia without adverse postoperative neurocognitive effects, using nonexcessive dosages of hypnotics and opioids. Based on this assumption, there are 2 possibilities for interpreting the results of this study: First, patients maintained with propofol or fluranes were, in fact, in different hypnotic states, and the observed differences in FOOOF and VMD parameters are merely reflective of the different hypnotic levels, but the other components of anesthesia were able to compensate for different levels of hypnosis. Second, both anesthesia regimes actually resulted in a comparable hypnotic state, meaning that different, agent-specific EEG patterns can produce similar hypnotic states. However, the lack of established dose-response curves on the synergistic effect of opioids with the simultaneous application of propofol and fluranes impedes comparability even more.

Limitations

One study limitation is whether we are comparing the EEG effects of propofol and fluranes at equivalent hypnotic drug concentrations. The statement is conceptually problematic as it assumes a progressive, monotonic increase in "hypnosis" with increasing hypnotic drug concentration and a comparable shape of the concentration-response curve between propofol and the fluranes. We have no practical measure of the degree of hypnosis beyond sedation scores, which are not applicable to general anesthesia. Therefore, as a proxy, we assumed that the anesthetist titrated the drugs to achieve a level of unconsciousness that resulted in acceptable surgical conditions for both groups. Obviously, the "depth" of surgical anesthesia will also be driven by cardiovascular and somatic movement responses to noxious stimuli, which are obtunded by the combination of hypnotic and analgesic drugs. As opioid doses were very similar between the groups, we can assume that the respective hypnotic drug delivery was also comparable. As fluranes, and probably less so propofol, have an antinociceptive effect, the "hypnosis" and "antinociception" components cannot be completely separated, and a different relative effect size may be possible. A possible solution would be a step-by-step criss-cross titration of a hypnotic and analgesic drug to clinically progressive states of hypnosis like loss-of-responsiveness, shake-and-shout, laryngoscopy, or tetanic stimulation. Lastly, this study was conducted and powered for the already published study. Consequently, all analyses were conducted post hoc.[24] We addressed this limitation by internally validating our findings using bootstrapping.

CONCLUSIONS

Our findings corroborate and enhance our understanding by characterizing them using FOOOF and VMD. By using the SEF as a proxy for hypnotic depth, we opened the possibility of quantifying a range of markers derived from VMD and FOOOF, possibly representative of adequate levels of hypnosis. Therefore, these methods may be useful in the future and provide the anesthesiologist with processed EEG information that is agent-specific. Furthermore, we provide additional proof that processed EEG information, that is, the numbers displayed, should not be treated as one-size-fits-all as automated methods can reliably differentiate signatures of anesthetic agents. Future studies are required to further explore these differences and new monitoring algorithms should account for them to truly establish comparable and adequate levels of hypnosis.

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DISCLOSURES

Conflicts of Interest: Drs Kreuzer, García, Schneider, Kratzer, and Dragovic are co-inventors on several patents related to intraoperative electroencephalographic analysis owned by Columbia and TUM. Dr García is a co-founder of a company, Lantern Laboratories, Inc. that has a license to build software and hardware for intraoperative monitoring. No other authors declared Conflicts of Interest. **Funding:** Support was provided solely from institutional and/or departmental sources. No external funding was received for this retrospective study. **This manuscript was handled by:** Peter A. Goldstein, MD.

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