ANESTHESIOLOGY

# Spectral and Entropic Features Are Altered by Age in the Electroencephalogram in Patients under Sevoflurane Anesthesia

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## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Age-related changes in the electroencephalograms of anesthetized surgical patients have been explored but not fully characterized

### What This Article Tells Us That Is New

- Older age is associated with a shift to a less predictable electroencephalogram, which could influence intraoperative monitoring approaches

## ABSTRACT

**Background:** Preexisting factors such as age and cognitive performance can influence the electroencephalogram (EEG) during general anesthesia. Specifically, spectral EEG power is lower in elderly, compared to younger, subjects. Here, the authors investigate age-related changes in EEG architecture in patients undergoing general anesthesia through a detailed examination of spectral and entropic measures.

**Methods:** The authors retrospectively studied 180 frontal EEG recordings from patients undergoing general anesthesia, induced with propofol/fentanyl and maintained by sevoflurane at the Waikato Hospital in Hamilton, New Zealand. The authors calculated power spectral density and normalized power spectral density, the entropic measures approximate and permutation entropy, as well as the beta ratio and spectral entropy as exemplary parameters used in current monitoring systems from segments of EEG obtained before the onset of surgery (*i.e.*, with no noxious stimulation).

**Results:** The oldest quartile of patients had significantly lower *1/f* characteristics ($P < 0.001$; area under the receiver operating characteristics curve, 0.84 [0.76 0.92]), indicative of a more uniform distribution of spectral power. Analysis of the normalized power spectral density revealed no significant impact of age on relative alpha ($P = 0.693$; area under the receiver operating characteristics curve, 0.52 [0.41 0.63]) and a significant but weak effect on relative beta power ($P = 0.041$; area under the receiver operating characteristics curve, 0.62 [0.52 0.73]). Using entropic parameters, the authors found a significant age-related change toward a more irregular and unpredictable EEG (permutation entropy: $P < 0.001$, area under the receiver operating characteristics curve, 0.81 [0.71 0.90]; approximate entropy: $P < 0.001$; area under the receiver operating characteristics curve, 0.76 [0.66 0.85]). With approximate entropy, the authors could also detect an age-induced change in alpha-band activity ($P = 0.002$; area under the receiver operating characteristics curve, 0.69 [0.60 78]).

**Conclusions:** Like the sleep literature, spectral and entropic EEG features under general anesthesia change with age revealing a shift toward a faster, more irregular, oscillatory composition of the EEG in older patients. Age-related changes in neurophysiological activity may underlie these findings however the contribution of age-related changes in filtering properties or the signal to noise ratio must also be considered. Regardless, most current EEG technology used to guide anesthetic management focus on spectral features, and improvements to these devices might involve integration of entropic features of the raw EEG.

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We are experiencing a strong shift in population demographics toward an aging society.[1] This shift is going to result in an increased number of surgeries in geriatric patients.[2] Older patients are at higher risk of developing adverse outcomes like delirious episodes after surgery with general anesthesia.[3,4] Electroencephalographic (EEG) monitoring devices may help to estimate the patients' level of neurophysiologic activity and to prevent episodes of excessively high administered doses of anesthesia as characterized by EEG burst suppression. The presence of these episodes seems to represent an independent risk factor for cognitive impairments after anesthesia[5,6]; however, some controversy

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exists regarding strategies designed to reduce the duration of burst suppression.[3,7]

Despite these possible advantages, the current generation of monitoring devices does not account for age-related changes in EEG characteristics. In general, EEG characteristics during general anesthesia vary greatly among patients of different age and cognitive performance.[8–10] Older patients exhibit lower EEG amplitudes (and consequently, lower power) during wakefulness,[11] sleep,[12] and general anesthesia.[8,9] Previous publications have described age-related changes in power spectral density under general anesthesia to some degree,[8,9] but a detailed description of age-related differences in other aspects of quantitative EEG analysis is still missing. We investigated age-related changes in EEGs recorded from patients aged 18 to 90 yr under general anesthesia with the goal to (1) characterize the EEG of older patients in more detail to further understand the neurophysiologic changes that occur with advanced age and to (2) estimate the influence of these changes on current EEG-based monitoring systems. We analyzed power spectral density, normalized power spectral density, and the *1/f* characteristics of the power spectrum, as well as the entropic measures of permutation entropy[13] and approximate entropy,[14] to investigate age-related changes in the EEG activity. The *1/f* characteristic and information extracted from power spectral density and normalized power spectral density analysis help to get a good (more broadband) overview of age-related changes. The entropic measures can help to identify subtler changes in the EEG. These analytical parameters were originally developed to characterize the complexity of a time-series signal and are reported as good measures to estimate the anesthetic level of a patient.[15–17] We also used two parameters (beta-ratio[18] and spectral entropy[19]) that are incorporated in current monitoring systems to estimate possible impact of age on the index that these systems generate to reflect the (hypnotic) level of anesthesia.

## Materials and Methods

We used frontal EEG records from 180 patients during general anesthesia, collected at the Waikato District Health Board Hospital in Hamilton, New Zealand. These patients gave written informed consent, and had previously contributed to an earlier observational study.[20] The ethical approval was specifically for the establishment of an anonymous EEG database that could be used for various *post hoc* analyses. We selected those patients who had received propofol for induction and sevoflurane for maintenance of anesthesia. For each patient, we selected 10 s of artifact-free, non–burst-suppression EEG, recorded 5 to 2 min before the onset of surgery, which represent a clinical level of general anesthesia without any surgical stimulation. We recorded the EEG with either the Bispectral Index ([BIS] Medtronic, Ireland) or the Entropy Module (GE Healthcare, Finland) monitors at 128 and 100 Hz, respectively. Raw EEG from the BIS was then resampled to 100 Hz for ease of comparison.

We estimated effect-site concentrations of sevoflurane, opioid, and propofol using standard pharmacokinetic models. We calculated the effect-site sevoflurane concentration (in minimum alveolar concentration [MAC]) using a simple end-tidal to brain delay model with a diffusion half-time constant of 144 s.[21] Based on these values, we calculated age-adjusted MAC values (referenced to 1 MAC in a 40-yr-old, *i.e.*, $MAC_{40}$) as described by Mapleson.[22] Opioid concentration (in fentanyl-equivalents; 1 ng/ml of fentanyl equals 20 ng/ml of morphine) was calculated using the two-compartment model parameters in Mazoit *et al.*[23] for morphine, and in Shafer and Varve[24] for fentanyl. We estimated effect-site propofol concentrations according to the model and parameters described by Wiczling *et al.*[25]

### EEG Analysis

***Spectral Analysis.*** We calculated the power spectral density using Thompson multitaper power spectral density estimate. We used the MATLAB R2015a (MathWorks Inc., USA) *pmtm* function (default settings and NFFT = 256). Based on power spectral density, we calculated the power in the 0.5 to 30 Hz range, the alpha-band power (7.8 to 12.5 Hz), and the beta-band power (12.5 to 25 Hz), as well as the lower frequency delta-band (0.4 to 3.9 Hz) and theta-band (3.9 to 7.8 Hz). We also computed a normalized power spectral density by dividing the power spectral density by the sum from 0.4 to 30.5 Hz. We used the Python-based *fitting oscillations & one over f* toolbox using the provided MATLAB wrapper[26] to identify periodic activity, as well as the aperiodic component of the EEG. The *fitting oscillations & one over f* algorithm decomposes the power spectral density into periodic components, as well as an aperiodic component that reflects *1/f* like characteristics. The aperiodic component is fitted according to $L=b-log(F^a)$ with $b$ being the (broadband) offset, $F$ being the frequency vector, and $a$ being the slope. We did not consider a "knee" parameter and therefore used the "fixed model" as described in the original publication.[26] We defined the range to detect possible oscillatory components from 1 to 30 Hz and focused on the detection of these peaks in the alpha range.

Furthermore, we obtained the relative alpha- and beta-band power by dividing the sum of power spectral density in the 8 to 12 Hz (alpha) or 12 to 25 Hz range (beta) by the sum of power spectral density in the 0.4 to 30.5 Hz range.

***Entropy Analysis.*** Entropic measures constitute a straightforward, time-domain approach to evaluate EEG features. We individually calculated approximate entropy and permutation entropy for the EEG 0.5 to 30 Hz range, the EEG alpha-band, and the EEG beta-band. We applied an adaptive filtering routine (Butterworth filter, order 3 to 5) using the MATLAB *filtfilt* functions that preserves the phase of the signal. So as not to include edge effects caused by filtering, we applied the filter to a 30-s EEG segment and used the central 10 s to calculate the entropies for the different frequency ranges.

For approximate entropy we used a custom routine and for permutation entropy we adapted the *my_permutation_entropy* function from MATLAB Central. We chose an embedding dimension $m = 3$ and a time delay $\tau = 1$ for permutation entropy,[15] and $m = 2$ / $\tau = 1$ together with tolerance $r = 0.2$ SD for approximate entropy.[27] These parameter settings are commonly used for EEG analyses.[15,16,27,28] A detailed description of how to calculate the parameters can be found in the papers initially presenting the methods by Steven M. Pincus for approximate entropy,[14] and Bandt and Pompe for permutation entropy.[13] Approximate entropy searches for similar amplitude patterns (of length $m$) in the EEG and calculates the probability of the patterns remaining similar if it is extended to a length of $m+1$. Similar, in this context, means that the amplitude values between the patterns do not differ by more than the defined tolerance $r$. Permutation entropy, as an ordinal measure, codes small segments of length $m$ according to their ranks, with the highest amplitude in the segment having the highest rank. Permutation entropy presents the Shannon entropy[29] of the probability distribution of the possible patterns (here 6, if $m = 3$). A graphical explanation for approximate entropy and permutation entropy can be found in the article by Kreuzer.[30]

*Phase-randomized Surrogate Analysis.* In order to clearly delineate the specific contribution of extracting information from the entropic measures *versus* the spectral measures of a signal, we used phase-randomized surrogate data. We calculated 200 phase-randomized surrogates for each of the 180 EEG episodes and compared the entropic measures to the spectral EEG band powers. For surrogate generation we used a modified version of the surrogate function for phase randomization of the PhysioNet Toolkit.[31] We modified this function such that no amplitude transformation, only a phase randomization, was performed. We then calculated the approximate entropy and permutation entropy for the alpha and beta range, as well as the relative alpha- and beta-band power for the surrogates.

*Parameters for Comparison to Available Monitors.* In order to estimate the influence of age on available monitoring systems like the BIS and Entropy module we calculated the *beta ratio* = log(sum[*power spectral density* $_{30\text{-}47\ Hz}$] / sum[*power spectral density* $_{11\text{-}20\ Hz}$]) as proxy for the subparameter BetaRatio of the BIS.[32] We further calculated the spectral entropy of the normalized power spectral density for settings mimicking the state entropy (to 32 Hz) and response entropy (47 Hz) for different lower band limits of 0.8 and 1.1 Hz.[19] We also had BIS indices available for 168 of 180 patients. In order to evaluate the influence of age on BIS, we used the last index value displayed within the 10-s analysis window used for spectral and entropic analysis.

*Statistical Analysis.* Because of the retrospective nature of our investigation, no statistical power calculation was conducted before the study and the sample size was based on the available number of patient EEG recordings. Our spectral analyses (except the spectral entropy with the 1.1 Hz lower limit) were *a priori* and the entropic analyses (approximate entropy, permutation entropy) were *post hoc* analyses after evaluating different parameter settings.

*Regression Analyses.* We generated models using the least squares method for linear regression analysis for each dependent variable with respect to age. For each linear model, we generated the regression curve and performed a one-sample *t* test comparing the slope coefficient against a slope of zero. Additionally, we determined the strength of the correlation, or rather the fit of the model, as an $R^2$ value.

*Evaluation of Interaction between Sevoflurane Concentration and EEG Parameters.* In order to evaluate if the EEG parameters (*i.e.*, permutation entropy and approximate entropy) differ significantly based on an interaction between age and age-adjusted MAC at a 5% significance level, we calculated the linear model interaction terms using the MATLAB *fitlm* function.

*Comparison of Youngest* versus *Oldest Quartiles.* For each parameter, we compared the youngest 25% (n = 46; first quartile) and the oldest 25% (n = 46; fourth quartile) of patients using a Mann–Whitney U test at a confidence level of 95% together with the area under the receiver operating characteristics curve (AUC) and 10,000-fold bootstrapped 95% CIs as effect size. We used the MATLAB-based MES toolbox for AUC and 95% CI calculation.[33] By including all subjects of a certain age our youngest and oldest quartiles each contained 46 subjects (not 45). Our excluded middle age range (44- to 72-yr-old) contained 88, instead of the expected 90, subjects. According to the traditional academic point system, AUC values can be interpreted as "excellent" (AUC between 1 and 0.9); "good" (AUC less than 0.9, but greater than or equal to 0.8); "fair" (AUC less than 0.8, but greater than or equal to 0.7); "poor" (AUC less than 0.7, but greater than or equal to 0.6); or "fail" (AUC less than 0.6). For the (normalized) power spectral density comparison, we only defined significant results if at least two neighboring frequencies showed significant differences between the young and old group. This procedure has been applied for similar studies, by other groups.[34]

All tests applied were two-tailed tests and we considered $P < 0.05$ to be significant.

## Results

Of 234 patients undergoing surgical intervention with propofol induction and sevoflurane maintenance, 54 patients were excluded from analysis due to missing EEG or incomplete volatile anesthetic concentrations data in the period before surgery onset, resulting in 180 patients being included in the final analysis. The subject ages ranged from 18 to 90 yr ([mean ± SD] 56.7 ± 18.4 yr). The age range for the youngest 25% was from 18 to 43 yr and for the oldest 25% from 73 to 90 years. Figure 1 presents a flow chart of patient and group selection. The results of all

linear regressions as well as all the comparisons between the youngest 25% and the oldest 25% are presented in table 1.

*Medications.* Despite the lack of any prescribed anesthetic protocol, the delivered sevoflurane concentration was lower in the older patients. We could eliminate this trend by age-adjusting the MAC according to Mapleson.[22] Similarly, the estimated propofol concentration decreased with age. By contrast, our data did not reveal any age-related difference in the opioid concentrations, measured in fentanyl equivalents. Figure S1 in the Supplemental Digital Content (http://links.lww.com/ALN/C254) presents the details and corresponding plots for describing the drug dose to age relationships. While the relationships for propofol and sevoflurane and age were statistically significant, the $R^2$ values were rather low ($R^2$ less than or equal to 0.06), indicating substantial contribution by other unmeasured factors. These results may reflect that the providers in our study consider age in their titration of dosages of propofol and sevoflurane, but other nuanced factors go into decisions of opioid administration (*e.g.,* surgery type, hemodynamic changes).

*Older Patients Exhibit More Uniform Distribution of Relative Spectral Power.* We obtained very similar age-to-power spectral density relationships, as presented in a previous study,[9] and provide the results and the corresponding plots in the Supplemental Digital Content (figs. S2 [http://links.lww.com/ALN/C255] and S3 [http://links.lww.com/ALN/C256]). The normalized power spectral density showed significant differences only in the low (0.5 to 5 Hz) and high (greater than 21 Hz) frequency ranges when comparing the youngest 25% *versus* the oldest 25% of patients (fig. 2A). Figure 2B presents exemplary traces from the youngest 25% and the oldest 25% groups.

We did not find significant differences between the youngest 25% and the oldest 25% in normalized power spectral density in the EEG alpha range ($P = 0.693$; AUC, 0.52 [0.42 to 0.63]; [fig. 3A]), but a "poor" and significant effect ($P = 0.041$; AUC, 0.62 [0.52 to 0.73]) in the EEG beta range (fig. 3B), as we did not observe a linear relationship of age with relative alpha and beta power and the difference in relative beta power. We take these results as evidence that age induces a change in the EEG, but that these changes may not be reliably detected by using the power in the classical frequency ranges. The evaluation of the relative power in the lower frequency delta and theta band did not show any age induced effects as well (fig. S4, Supplemental Digital Content, http://links.lww.com/ALN/C257).

The *fitting oscillations & one over f* analysis revealed that in 174 of 180 patients (97%), at least one oscillatory component in the 8 to 12 Hz alpha range could be observed. Because the six patients without such a periodic component were distributed over the age range, we decided to keep these patients included. The parameters of the aperiodic component of the normalized power spectral density changed with age (fig. 3C). For the comparison between the youngest 25% and the oldest 25% the exponent was affected significantly and strongly ($P < 0.001$, AUC, 0.84 [0.76 to 0.92]) by age as was the offset ($P < 0.001$, AUC, 0.81 [0.71 0.89]. Figure 2C shows the more uniform

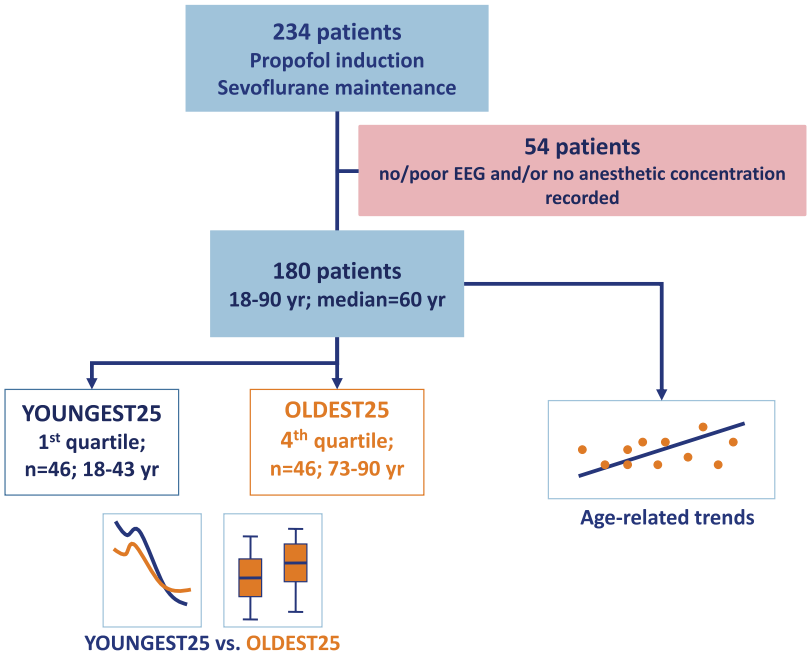


**Fig. 1.** Flow chart of the excluded patients and groups defined for analysis. EEG, electroencephalogram.

**Table 1. Comparison of Age to Spectral and Entropic Characteristics of EEG under Sevoflurane Anesthesia**

| Parameter | Intercept | Slope | 95% CI Slope | *t*-Stat | *P* Value Slope | $R^2$ | Youngest 25% | Oldest 25% | *P* Value (Ranksum) | AUC |
|---|---|---|---|---|---|---|---|---|---|---|
| EEG band power | | | | | | | | | | |
| Absolute delta | 37.66 | −0.15 | [−0.18 to −0.13] | −10.99 | < 0.001 | 0.40 | 32.72 [30.80–35.87] | 5.98 [23.90–28.36] | < 0.001 | 0.94 [0.89 to 0.98] |
| Absolute theta | 29.82 | −0.17 | [−0.20 to −0.15] | −13.13 | < 0.001 | 0.49 | 24.13 [22.33–26.93] | 16.02 [13.85–19.27] | < 0.001 | 0.93 [0.86 to 0.98] |
| Absolute alpha | 30.71 | −0.18 | [−0.20 to −0.15] | −12.25 | < 0.001 | 0.46 | 24.81 [21.85–28.19] | 17.77 [15.31–19.72] | < 0.001 | 0.92 [0.86 to 0.98] |
| Absolute beta | 23.02 | −0.13 | [−0.16 to −0.10] | −9.74 | < 0.001 | 0.35 | 18.30 [16.29–21.04] | 13.75 [10.02–15.24] | < 0.001 | 0.90 [0.83 to 0.96] |
| Relative delta | 0.69 | 0.000 | [−0.001 to 0.002] | 0.53 | 0.599 | 0.00 | 0.76 [0.69–0.82] | 0.75 [0.63–0.83] | 0.806 | 0.52 [0.40 to 0.63] |
| Relative theta | 0.11 | 0.000 | [−0.001 to 0.000] | −0.77 | 0.445 | 0.00 | 0.10 [0.07–0.12] | 0.09 [0.06–0.13] | 0.375 | 0.55 [0.43 to 0.68] |
| Relative alpha | 0.17 | −0.001 | [−0.002 to 0.000] | −1.36 | 0.176 | 0.01 | 0.10 [0.08–0.17] | 0.10 [0.07–0.17] | 0.693 | 0.52 [0.42 to 0.63] |
| Relative beta | 0.02 | 0.000 | [−0.000 to 0.001] | 1.78 | 0.077 | 0.02 | 0.03 [0.02–0.04] | 0.04 [0.02–0.06] | 0.041 | 0.62 [0.52 to 0.73] |
| *Fitting oscillations and one over f* | | | | | | | | | | |
| Exponent | 2.65 | −0.009 | [−0.011 to −0.007] | −8.14 | < 0.001 | 0.27 | 2.36 [2.19–2.60] | 2.00 [1.89–2.16] | < 0.001 | 0.84 [0.76 to 0.92] |
| Offset | −0.43 | −0.008 | [−0.009 to −0.006] | −8.27 | < 0.001 | 0.29 | −0.59 [−0.90 to −0.48] | −0.96 [−1.15 to −0.85] | < 0.001 | 0.81 [0.71 to 0.89] |
| Entropic Measures | | | | | | | | | | |
| Permutation entropy 0.5–30 Hz | 1.97 | 0.002 | [0.001–0.003] | 7.04 | < 0.001 | 0.22 | 2.02 [1.98–2.07] | 2.11 [2.06–2.15] | < 0.001 | 0.81 [0.71 to 0.90] |
| Permutation entropy delta | 1.34 | 0.000 | [−0.000 to 0.001] | 1.67 | 0.097 | 0.02 | 1.35 [1.32–1.37] | 1.36 [1.34–1.38] | 0.129 | 0.59 [0.48 to 0.70] |
| Permutation entropy theta | 1.72 | 0.000 | [−0.000 to 0.000] | 1.12 | 0.263 | 0.01 | 1.72 [1.70–1.75] | 1.73 [1.71–1.75] | 0.219 | 0.57 [0.44 to 0.71] |
| Permutation entropy alpha | 1.92 | 0.000 | [−0.000 to 0.000] | 0.69 | 0.489 | 0.00 | 1.92 [1.91–1.95] | 1.93 [1.91–1.95] | 0.384 | 0.55 [0.43 to 0.67] |
| Permutation entropy beta | 2.21 | 0.001 | [0.001–0.001] | 4.95 | < 0.001 | 0.12 | 2.24 [2.20–2.27] | 2.27 [2.24–2.29] | < 0.001 | 0.71 [0.61 to 0.80] |
| Approximate entropy 0.5–30 Hz | 0.76 | 0.002 | [0.001–0.003] | 4.87 | < 0.001 | 0.12 | 0.83 [0.77–0.89] | 0.93 [0.84–0.99] | < 0.001 | 0.76 [0.66 to 0.85] |
| Approximate entropy delta | 0.41 | −0.001 | [−0.001 to −0.001] | −2.20 | 0.029 | 0.03 | 0.40 [0.34–0.44] | 0.37 [0.33–0.41] | 0.088 | 0.60 [0.50 to 0.70] |
| Approximate entropy theta | 0.62 | 0.000 | [−0.000 to 0.000] | −1.95 | 0.052 | 0.02 | 0.61 [0.61–0.62] | 0.61 [0.60–0.62] | 0.143 | 0.59 [0.46 to 0.71] |
| Approximate entropy alpha | 0.55 | 0.001 | [0.000–0.001] | 4.18 | < 0.001 | 0.09 | 0.57 [0.56–0.59] | 0.60 [0.57–0.62] | 0.002 | 0.69 [0.60 to 0.78] |
| Approximate entropy beta | 1.01 | 0.001 | [0.001–0.001] | 2.44 | 0.016 | 0.03 | 1.05 [1.00–1.08] | 1.08[1.03–1.12] | 0.007 | 0.66 [0.55 to 0.77] |
| Monitoring parameter | | | | | | | | | | |
| BIS | 33.96 | 0.16 | [0.078–0.24] | 3.84 | < 0.001 | 0.08 | 42 [32–44] | 45 [40–51] | 0.026 | 0.65 [0.52 to 0.76] |
| Beta ratio | −4.74 | 0.02 | [0.01–0.02] | 5.00 | < 0.001 | 0.12 | −4.20 [-4.63 to −3.71] | −3.61 [−4.02 to −3.27] | < 0.001 | 0.73 [0.63 to 0.82] |
| Spectral entropy (1.1–32 Hz) | 2.73 | 0.007 | [0.005–0.01] | 5.81 | < 0.001 | 0.16 | 3.02 [2.78–3.17] | 3.25 [3.13–3.46] | < 0.001 | 0.79 [0.70 to 0.87] |
| Spectral entropy (1.1–47 Hz) | 2.73 | 0.007 | [0.005–0.010] | 6.08 | < 0.001 | 0.17 | 3.02 [2.79–3.18] | 3.29 [3.18–3.47] | < 0.001 | 0.80 [0.71 to 0.88] |
| Spectral entropy (0.8–32 Hz) | 2.64 | 0.002 | [−0.002 to 0.005] | 0.79 | 0.433 | 0.00 | 2.72 [2.31–2.91] | 2.78 [2.50–3.16] | 0.202 | 0.58 [0.47 to 0.68] |
| Spectral entropy (0.8–47 Hz) | 2.64 | 0.002 | [−0.002 to 0.006] | 0.37 | 0.372 | 0.00 | 2.73 [2.31–2.91] | 2.79 [2.51–3.16] | 0.161 | 0.58 [0.47 to 0.69] |

Included here are the outcomes for the comparison of patient age with specific EEG features under sevoflurane anesthesia. Specifically, the linear regression parameters identified for these relationships are presented, in addition to the median values of these characteristics for the youngest and oldest quartiles of patients used for direct comparison.

AUC, area under the receiver operating characteristics curve; BIS, bispectral index; EEG, electroencephalogram.

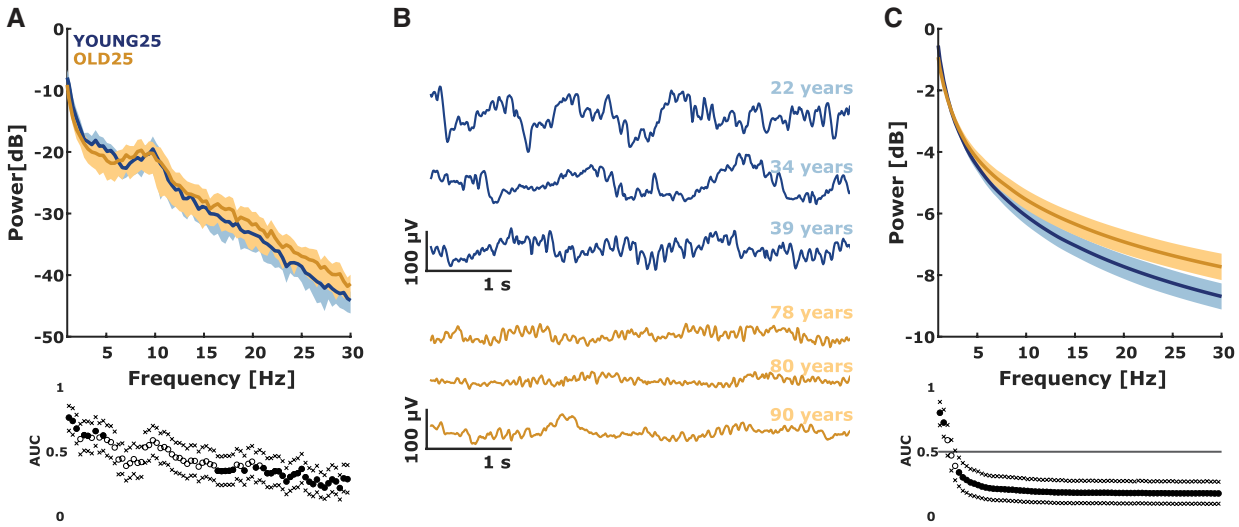


**Fig. 2.** Normalized power spectral density exemplary raw electroencephalogram (EEG) traces, and the aperiodic (*1/f*) component from young and old patients. (*A*) Median (± median absolute deviation) normalized power spectral density plots of EEG derived from the Y25 (*blue*) and O25 (*orange*) patients of the data set. power spectral density is presented with corresponding area under the receiver operating characteristics curve (AUC) values and bootstrapped 95% CIs. The relative power spectral density indicated a more uniform distribution of the EEG from the old group with lower relative power at low frequencies (0.5 to 5 Hz) and higher relative power at high frequencies (greater than 21 Hz). (*B*) Exemplary raw EEG traces from patients in the Y25 group (*blue*) and O25 group (*orange*). These traces highlight the age-induced differences on the EEG, especially fewer slow oscillations and an increased amount of high frequent activity. (*C*) Median (± median absolute deviation) of the exponential fit of the aperiodic (background) *1/f* component between the Y25 (*blue*) and O25 (*orange*) patients. In addition, the AUC values and 95% bootstrapped CIs are presented. In general, the aperiodic component of the power spectral density was more uniformly distributed in the old patients. *Filled circles* indicate a significant difference, between Y25 and O25 evaluated by AUC CIs, excluding 0.5. The areas of light colors indicate the median absolute deviation.

distribution of the aperiodic *1/f* component of the power spectral density in the old patients.

*Age-related Changes Can Be Observed Using Entropy-based Analyses.* Permutation entropy increased with age in the 0.5 to 30 Hz range, as well as in the EEG beta range, but not in the EEG alpha range EEG (fig. 4, A to C). Comparing the youngest 25% and the oldest 25%, we found a strong and significant ($P < 0.001$; AUC, 0.81 [0.71 to 0.90]) effect of age on the (0.5 to 30 Hz) filtered EEG and a fair and significant ($P < 0.001$; AUC, 0.71 [0.61 to 0.81]) effect on the beta-band EEG. We found no significant difference for the alpha band EEG ($P = 0.384$; AUC, 0.55 [0.43 to 0.67]). These results signify that permutation entropy tracks the shift toward higher-frequency EEG activity with age.

Approximate entropy of all three frequency ranges increased with age (fig. 5, A to C). The comparisons of approximate entropy for the youngest 25% and the oldest 25% patients revealed a significant and moderate to strong effect of age in the 0.5 to 30 Hz range ($P < 0.001$; AUC, 0.76 [0.66 to 0.85]), in the EEG alpha range ($P = 0.002$; AUC, 0.69 [0.60 to 0.78]), as well as in the EEG beta range ($P = 0.007$; AUC, 0.66 [0.55 to 0.77]). The fact that approximate entropy, in contrast to permutation entropy, revealed an effect on the alpha-band possibly indicates a higher sensitivity of approximate entropy to lower frequencies.

The entropic parameters did not undergo an age-related change in the slower dynamics, *i.e.*, when applied to the EEG filtered to the delta and theta ranges. We present the detailed statistical parameters in table 1 and the corresponding regression and box plots in figure S5 of the Supplemental Digital Content (http://links.lww.com/ALN/C258).

*Surrogates.* The surrogate analysis revealed a lower regression line for approximate entropy in the alpha and beta-band as well as for permutation entropy in the beta-band for the original signals. The phase randomization had no influence on the relative alpha- and beta-band power. Figure S6 of the Supplemental Digital Content (http://links.lww.com/ALN/C259) shows the corresponding plots.

*Monitoring Parameters Shows Age-related Changes.* We used the beta ratio and spectral entropy to estimate a possible influence of age on neurophysiologic measures as implemented in commonly used monitoring systems. The BIS revealed a strong dependence on age, as did the spectral entropy for the 1.1 to 32 Hz and 1.1 to 47 Hz range (table 1 and fig. S7 of the Supplemental Digital Content [http://links.lww.com/ALN/C260]). The comparison of the youngest 25% and the oldest 25% revealed significant and fair effects of age on beta ratio ($P < 0.001$; AUC, 0.73 [0.63 to 0.82]) and spectral entropy (1.1 to 32 Hz: $P < 0.001$; AUC, 0.79 [0.70 to 0.87]; 1.1 to 47 Hz: $P < 0.001$; AUC, 0.80 [0.71 to 0.88]). For 0.8 Hz to 32 Hz

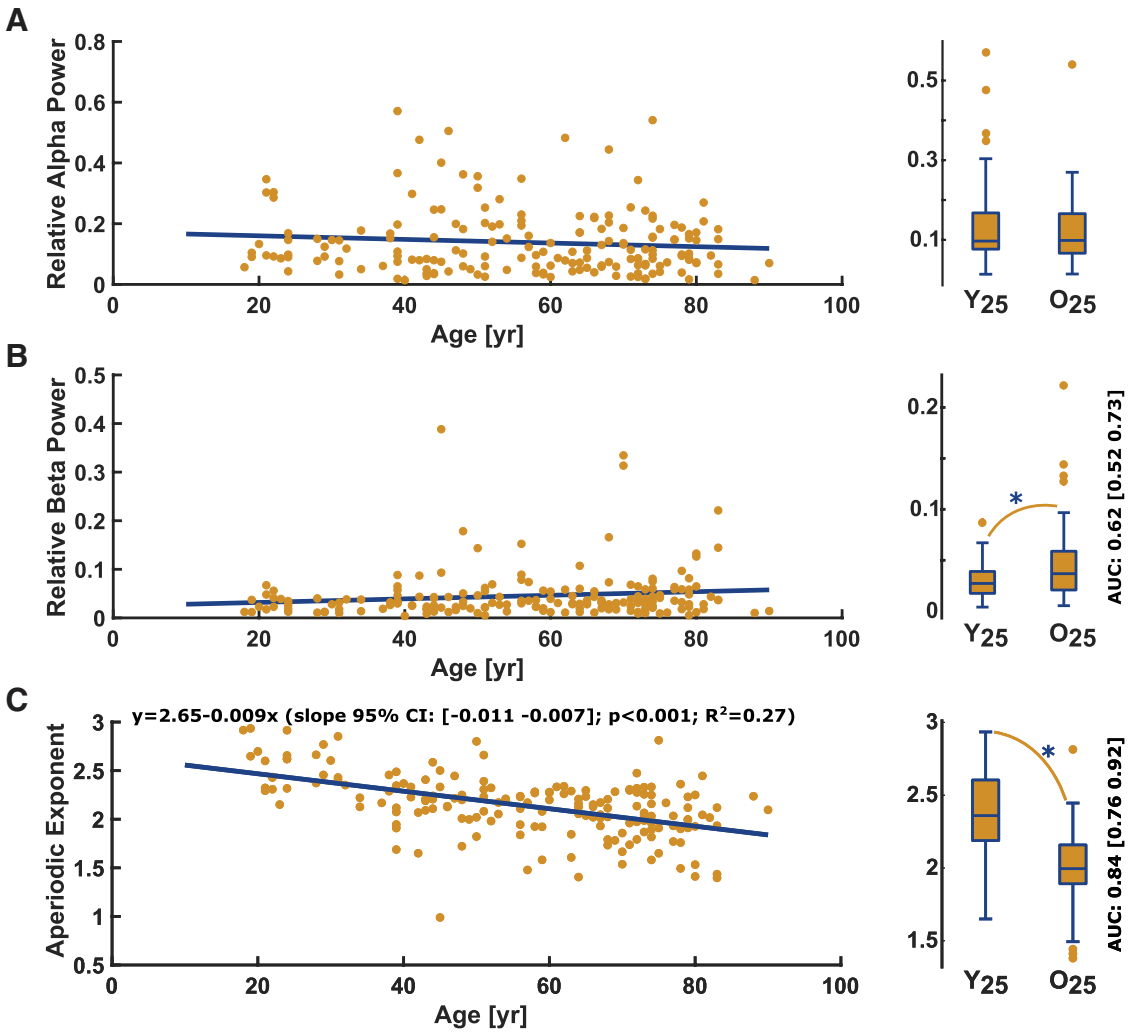


**Fig. 3.** Linear regression and box plots of the youngest *versus* the oldest quartile for (*A*) the relative (normalized) electroencephalogram (EEG) alpha power, (*B*) the relative EEG beta power, and (*C*) the slope of the aperiodic *1/f* component with corresponding box plots. (*A*) Relative power in the alpha-band EEG did not significantly ($P = 0.176$; *t*-statistic, −1.36) change with age. There was no significant difference ($P = 0.693$; AUC, 0.52 [0.42 to 0.63]) in relative alpha power between Y25 (0.10 [0.08 to 0.17]) and O25 (0.10 [0.07 to 0.17]). (*B*) Relative EEG beta power did not significantly ($P = 0.077$; *t*-statistic, 1.78) change with age, but there was a significant difference ($P = 0.041$) in relative beta power between Y25 (0.03 [0.02 to 0.04]) and O25 (0.04 [0.02 to 0.06]). The AUC, 0.62 [0.52 to 0.73] as effect site indicated a "poor" effect. (*C*) The slope of the aperiodic *1/f* component derived by the *fitting oscillations & one over f* algorithm significantly decreased with age ($P < 0.001$; *t*-statistic, −8.14). The box plot indicates a significant flatter ($P < 0.001$) slope in O25 patients (2.00 [1.89 to 2.16]) compared to the Y25 (2.36 [2.19 to 2.60]). AUC, 0.84 [0.76 to 0.92] at effect site indicated a "good" effect. In the regression plots, the *yellow dots* represent the single patients and the *blue line* represents the linear fit. AUC, area under the receiver operating characteristics curve; O25, oldest 25%; Y25, youngest 25%; yr, year.

($P = 0.202$; AUC, 0.58 [0.47 to 0.68]) or 47 Hz ($P = 0.161$; AUC, 0.58 [0.47 to 0.69]), we could not observe a significant difference with age. These results indicate an influence of age on the (sub-) parameters that are used to track neurophysiological changes in EEG-based monitoring systems, which seems strongly dependent on the frequency range. For the sample of 168 patients we could observe an increase of the recorded BIS with age (linear regression: $P > 0.001$; *t*-statistic, 3.84; youngest 25% *vs.* oldest 25%: $P = 0.026$; AUC, 0.65 [0.52 to 0.76]; fig. S6 of the Supplemental Digital Content, http://links.lww.com/ALN/C259).

## Discussion

Our results show that age-dependent changes in EEG characteristics during general anesthesia extend beyond a mere decrease in EEG amplitude. Our demonstrable changes in power spectral density of the EEG recorded under

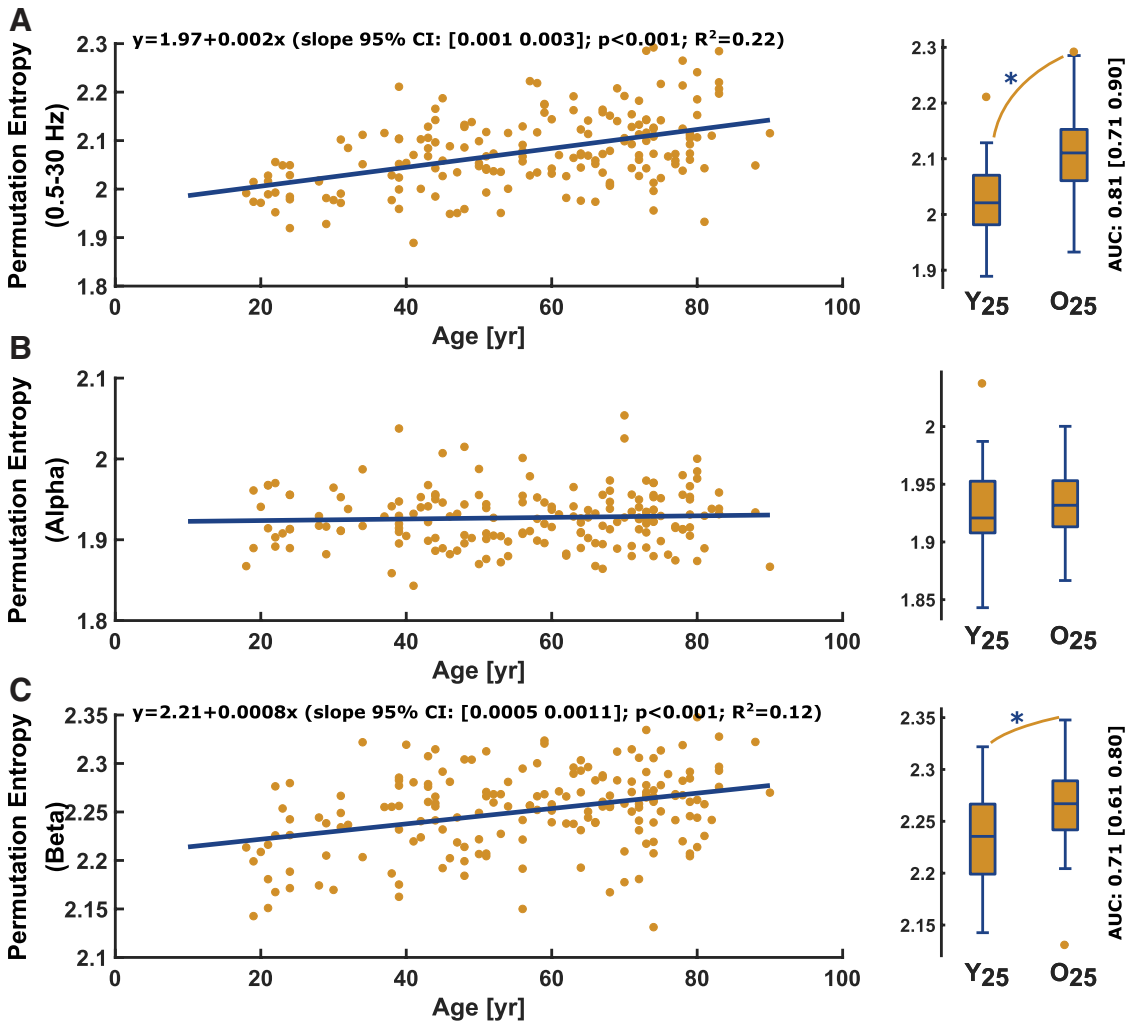


**Fig. 4.** Permutation entropy ($m = 3$, $\tau = 1$): Linear regression and box plots of the youngest *versus* the oldest quartile for the (*A*) 0.5 to 30 Hz range, (*B*) the alpha range, and (*C*) the electroencephalogram (EEG) beta range. (*A*) Permutation entropy of the 0.5 to 30 Hz filtered EEG significantly increased ($P < 0.001$; *t*-statistic, 7.04) with age. Age had a "good" and significant ($P < 0.001$; AUC, 0.81 [0.71 to 0.90]) effect on permutation entropy as depicted in the comparison between Y25 (2.02 [1.98 to 2.07]) and O25 (2.11 [2.06 to 2.15]). (*B*) Permutation entropy of the alpha-band EEG showed no significant age-related effect ($P = 0.489$; *t*-statistic, 0.69) and the AUC for the comparison between Y25 and O25 indicated no effect ($P = 0.384$; AUC, 0.55 [0.43 to 0.67]). (*C*) Permutation entropy of the beta-band EEG significantly ($P > 0.001$; *t*-statistic, 4.95) increased with age. Age had a "fair" and significant ($P < 0.001$; AUC, 0.71 [0.61 to 0.80]) effect on permutation entropy as depicted in the comparison between Y25 (2.24 [2.20 to 2.27]) and O25 (2.27 [2.24 to 2.29]). In the regression plots, the *yellow dots* represent the single patients and the *blue line* represents the linear fit. In the boxplots, the *circles* indicate outliers as defined by the MATLAB plotting routine. They were not excluded from analysis. AUC, area under the receiver operating characteristics curve; O25, oldest 25%; Y25, youngest 25%; yr, year.

general anesthesia have been reported by other groups.[8,9] The absolute power decreases with age in every frequency range. After normalization, we found that delta oscillations contributed less to total power with age, while (high) beta oscillations contributed more. The change in the *1/f* characteristics as revealed by the *fitting oscillations & one over f* analysis confirm this finding. We did not observe a significant change in the relative power in the specific bands, but the additional usage of entropic parameters revealed that these parameters are capable of tracking subtler changes in the oscillatory composition of the EEG that are not detected by power spectral density based approaches, also in the alpha- and beta-band. The entropic parameters seem to analyze additional content in the signal as shown by surrogate analysis. The higher entropies in the surrogates point toward a loss in deterministic signal properties, as has also been reported previously.[35] The monitoring parameters BIS, BetaRatio, and spectral entropy were also affected by

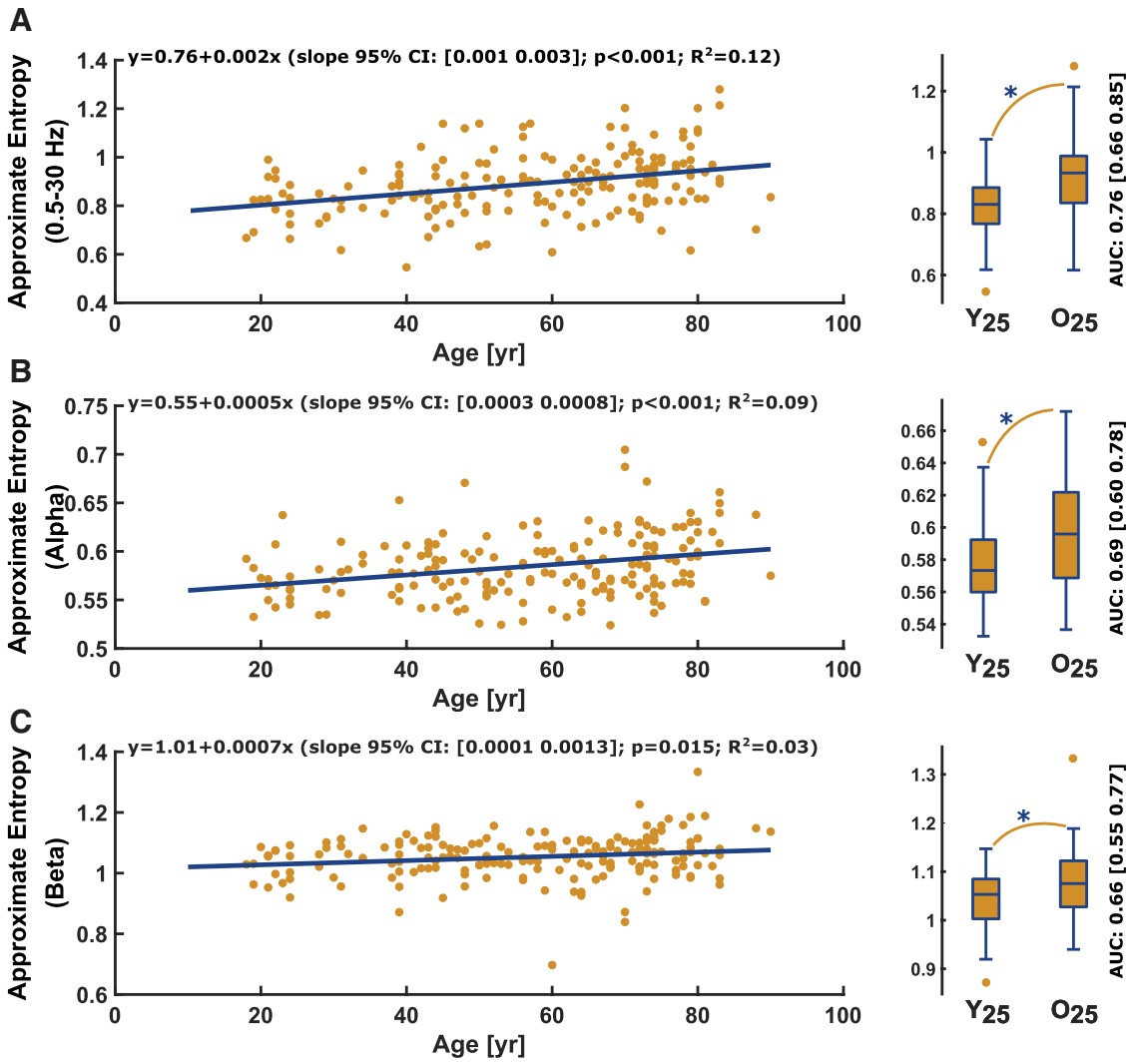


**Fig. 5.** Approximate entropy ($m = 2$; $r = 0.2$ SD; $\tau = 1$) *versus* age and corresponding youngest *versus* oldest quartile box plot for the (*A*) 0.5 to 30 Hz electroencephalogram (EEG) range, (*B*) the EEG alpha range, (*C*) and the EEG beta range. (*A*) Approximate entropy of the 0.5 to 30 Hz filtered EEG significantly ($P < 0.001$; *t*-statistic, 4.87) increased with age. Age had a "fair" and significant ($P < 0.001$; AUC, 0.76 [0.66 to 0.85]) effect on approximate entropy as depicted in the comparison between Y25 (0.83 [0.77 to 0.89]) and O25 (0.93 [0.84 to 0.99]). (*B*) Approximate entropy of the alpha-band EEG significantly ($P < 0.001$l; *t*-statistic, 4.18) increased with age. Age had a "poor"/"fair" and significant ($P = 0.002$; AUC, 0.69 [0.60 to 0.78]) effect on approximate entropy as depicted in the comparison between Y25 (0.57 [0.56 to 0.59]) and O25 (0.60 [0.57 to 0.62]). (*C*) Approximate entropy of the beta-band EEG significantly increased with age ($P = 0.015$; AUC, 0.66 [0.55 to 0.77]). Age had a "fair" and significant effect on approximate entropy as depicted in the comparison between O25, (1.08[1.03 to 1.12]) and Y25, (1.05 [1.00 to 1.08]) of the data set. In the regression plots, the *yellow dots* represent the single patients and the *blue line* represents the linear fit. In the boxplots, the *circles* indicate outliers as defined by the MATLAB plotting routine. They were not excluded from analysis. AUC, area under the receiver operating characteristics curve; O25, oldest 25%; Y25, youngest 25%; yr, year.

age, a finding that highlights that age adjustments should be considered for monitoring.

*Influence of Age on EEG Amplitude and Power Spectral Density.* Reductions in grey matter, including cortical thinning,[36–40] or a decrease in skull conductance[41] with age, cause a decrease in EEG amplitude, and hence lower power spectral density. Furthermore, the EEG amplitude also depends somewhat on neuronal synchrony, but it is unknown at present to what extent this is altered by aging.[42]

*Age Influences EEG Spectral Power.* Our power spectral density analyses are in line with previously published findings (*i.e.*, power spectral density decreases with age).[9] The body of knowledge we can add to these results is the more uniformly distributed normalized power spectral density that

is reflected by a flatter (aperiodic) *1/f* slope. Schultz *et al.*[8] reported changes in relative band power for propofol anesthesia and other groups for non–rapid eye movement sleep.[12,43] Age-related cortical activation during non–rapid eye movement sleep seems to increase relative beta power,[12] a scenario that sounds plausible for our findings under general anesthesia as well. Further, older women had lower relative EEG delta-band and higher beta-band power during wakefulness and rapid eye movement sleep compared to the middle-aged group.[44] In general, there may be a number of potential explanations that cause the observed shift in the relative power spectrum. An increase of neural noise may be one of them. Older test subjects had a flatter *1/f* slope during visual tasks, due to increased neural noise.[42,45] This increase does not have to represent a more aroused brain state since recent research found increased higher beta frequencies to be associated with poorer memory test outcomes in geriatric women.[46] Volunteers with eyes closed exhibited higher beta-coherence with age, indicative of higher synchrony in this frequency range.[47] But, besides a possible increase in neural noise, the changes in spatiotemporal filtering properties may be due to age-related, physiologic changes affecting the cortex[40] (*e.g.*, the extracellular space, which can act as *1/f* filter).[48] Further, age and the decline in EEG power also reduce the signal to noise ratio, as shown in experiments with event-related potentials.[49] Our findings may either reflect increased cortical neural noise (*i.e.*, spiking not correlated to oscillatory activity in the elderly brain), the age-induced change of physiological *1/f* filtering properties, changes in the signal to noise ratio of the EEG with age, or a combination of these factors. Our observational study was not designed to closely investigate the cause for the flatter slope. The results further showed that the relative alpha- and beta-band power was not affected by age. This information could become important for the design of future monitoring devices, but also leads to questions about the use of this approach to investigate age-related changes. Entropic measures in the time domain, like approximate entropy and permutation entropy, provide information separate from spectral features.[15–17,27] An understanding of both spectral and entropic features may broaden our clinical model of estimations regarding consciousness in patients under general anesthesia.

*Older Patients Express Higher Signal Entropy.* Our findings showed increasing approximate entropy and permutation entropy (except in the alpha-band) values with age. The results of approximate entropy and permutation entropy differ to some degree because both parameters may target different EEG characteristics.[50] Permutation entropy is regarded as superior to approximate entropy in distinguishing conscious from unconscious EEG,[16,17,51] while approximate entropy performs better than permutation entropy in tracking different levels of anesthesia.[17] These differences are in accordance with the strong effect of age on permutation entropy in the high frequencies (beta-band), as well as the ability of approximate entropy to identify differences in the alpha-band, where permutation entropy showed no contrast. The age-related increase in entropic measures seem to apply to other vigilance states and encephalographic modalities as well: in a magnetoencephalography study, permutation entropy increased with age in volunteers that were awake with their eyes closed.[52] In general, the increase of entropic measures with age probably reflects the effect on the *1/f* slope by indicating a more uniform distribution of ordinal EEG patterns (permutation entropy), and a decreased signal predictability (approximate entropy) in the elderly. In this regard, an association between permutation entropy (for $m = 3$) and the spectral centroid of the (weighted) power spectral density was recently described.[53] This proposition may eventually add a general link between spectral analytical approaches and permutation entropy, such that ordinal irregularity may become usable as a proxy for changes in the oscillatory EEG composition. Admittedly, this link is still missing for approximate entropy, though. But these measures seem to track deterministic properties in the signal, in contrast to power spectral density measures. Although other settings of permutation entropy could have tracked age-related changes with higher precision, we do not know the underlying cause for that and hence we refrained from presenting the results in this article. Since using lags of $\tau > 1$ could lead to unintended distortions in the signal,[53] we chose to apply permutation entropy with $\tau = 1$ to EEG filtered to the different frequency bands. In any case, our analyses demonstrate the sensitivity of entropic measures to subtle changes in the EEG.

*Reasons for Altered EEG Characteristics.* There is evidence that the aged brain reacts to general (sevoflurane) anesthesia differently than the young brain. In young brains, usually, a peak in the EEG alpha range develops under general anesthesia[34] as a marker of adequate anesthesia. This peak in the EEG alpha-band, as well as strong interhemispheric EEG alpha-band coherence,[34] most probably is associated with thalamocortical pacemaker cells and their activity spreading to the cortex.[54] Older and cognitively impaired patients express lower alpha power and alpha coherence during general anesthesia.[9,10,55] We did not observe an influence of age using the relative alpha-band power, a finding that is in line with Schultz *et al.,* who found age-related differences in relative alpha power only at very profound levels of propofol anesthesia.[8] Hence, the described decrease in alpha power may be due to the general decrease in EEG amplitude with age.

Although we did not see an influence of age in relative alpha-band power in our results, approximate entropy of the alpha-band revealed a significant change. Because strong and synchronous (*i.e.*, low approximate entropy) alpha oscillations may correlate with good cognitive function and better outcomes after general anesthesia,[10,56,57] this parameter may be useful to identify patients with a "frail" brain using EEG recordings during general anesthesia in the future. For

both entropic parameters we observed changes in the EEG beta range. This frequency range seems associated with an activated cortex and intracortical, as well as corticocortical, information processing.[54,58] Hence, our findings of a flatter *1/f* slope may reflect a state of higher cortical activation in the elderly, or a higher influence of noise. During visual tasks the flatter *1/f* slope may represent a decoupling of (cortical) population spiking activity from an oscillatory regimen.[42] Furthermore, findings from sleep research indicate that the EEG of older subjects during sleep may be closer to the wake state than in middle-aged to young subjects.[44] At the same time, age seems to affect thalamocortical regulatory mechanisms during sleep, as expressed by lower sleep spindle density, duration, and amplitude.[59] In general, the EEG of older patients may have a smaller dynamic range. During the awake state, the EEG is slower in the older population[8] and shows increased relative beta power during general anesthesia. Hence, the aged brain may not be capable of expressing activated or synchronized activity to the same degree that the young adult brain is capable of. In conclusion, a difference between chronologic *versus* functional brain age should be considered to reveal functional age-related differences in the EEG in more detail. Young patients with potential for having a frail brain can express EEG activity typical for an old patient.[55] Furthermore, (mild) cognitive impairments like early-stage Alzheimer seem to change the EEG architecture in a fashion similar to aging.[60]

*Implications for Titration of Anesthesia.* We utilized BIS, beta ratio, and spectral entropy to estimate the presumed behavior of existing monitoring systems. In general, these parameters exhibited an increase with age. Consequently, our results hint at a possible influence of age on the indices of commonly used EEG monitors (BIS and GE Entropy) toward a lower dose, but the presented BIS values may not correlate with our analyzed EEG segments because of a considerable time delay of up to 60 s.[61,62] Still, recent findings from Ni *et al.* show higher BIS in older adults, hence emphasizing our results.[63] At least some of the commercially available monitors were developed using data from rather young adult subjects.[64] A study found that at the propofol-induced loss of consciousness, older patients expressed higher BIS and state entropy values, projecting a "more awake" EEG by means of the indices.[65] These findings, and our own, imply that future EEG-based "depth of anesthesia" monitoring systems should account for patient age or use parameters not affected by age. In our data limited to EEG during unstimulated unconsciousness, relative alpha and beta power did not change with age, but did show considerable variability. Hence, a possible use for monitoring purposes has to be investigated more thoroughly.

*Limitations.* General anesthesia was not conducted by any strict protocol but navigated by best clinical practice. For sevoflurane, we could overcome a possible limitation of age and drug requirement by using age-adjusted MAC estimates.[22] While we did find a decrease in residual propofol concentration with age, lower propofol requirements with age have previously been reported.[66] Some patients also received opioids, but these concentrations did not show any age-related trends. We did not evaluate the EEG characteristics during general anesthesia with surgical stimulation. We also cannot make a statement regarding age-related EEG changes for other anesthetic drugs, such as ketamine or dexmedetomidine, that trigger different EEG patterns and have different receptor targets. Although, we did not observe any consistent age-related differences in the sevoflurane MAC and the opioid concentration, we cannot completely exclude a complex confounding relationship between age and anesthetics or opioids. To tease out these relationships would require some specific, tightly controlled, prospective interventional studies. Another limitation is that we only recorded single-channel EEG, thus, we could not evaluate the influence of age on multivariate parameters, and cannot add information to reported changes in spectral coherence with age.[9] And ultimately, the EEG is a signal originating from a large number of (mainly) cortical neurons and transmitted through layers of cerebrospinal fluid, bone, skin, and hair.[67] Hence, we refrain from drawing mechanistic conclusions on the receptor level. Still, an age-related influence on inhibitory network activity is highly likely.

In conclusion, we demonstrated that the EEG under general anesthesia changes with age toward activity patterns of higher frequencies that cause a flatter *1/f* slope of power spectral density, as well as an increase of entropic measures. These changes may be due to changes in neurophysiological filtering properties or the signal to noise ratio, but in general, patient age should be taken into account when using the EEG. Currently, EEG-based monitoring approaches do not seem to correct for it.

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## Competing Interests

Drs. Kreuzer and Garcia are named as inventors for a patent recently filed (through Columbia University, New York, New York) on a method for intraoperative EEG monitoring that accounts for spectral and entropic features of age (application No. 62914183, filed on January 20, 2020, "Method and Computer-Accessible Medium Which Takes into Consideration Change(s) of Spectral and Entropic Features Age in the Electroencephalogram in Patients under Sevoflurane Anesthesia"). The other authors declare no competing interests.

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## References


1. Delafuente JC: The silver tsunami is coming: Will pharmacy be swept away with the tide? Am J Pharm Educ 2009; 73:1
2. Etzioni DA, Liu JH, Maggard MA, Ko CY: The aging population and its impact on the surgery workforce. Ann Surg 2003; 238:170–7
3. Fritz BA, Kalarickal PL, Maybrier HR, Muench MR, Dearth D, Chen Y, Escallier KE, Ben Abdallah A, Lin N, Avidan MS: Intraoperative electroencephalogram suppression predicts postoperative delirium. Anesth Analg 2016; 122:234–42
4. Radtke FM, Franck M, Hagemann L, Seeling M, Wernecke KD, Spies CD: Risk factors for inadequate emergence after anesthesia: emergence delirium and hypoactive emergence. Minerva Anestesiol 2010; 76:394–403
5. Watson PL, Shintani AK, Tyson R, Pandharipande PP, Pun BT, Ely EW: Presence of electroencephalogram burst suppression in sedated, critically ill patients is associated with increased mortality. Crit Care Med 2008; 36:3171–7
6. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD: Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 2013; 110 Suppl 1:i98–105
7. Wildes TS, Mickle AM, Ben Abdallah A, Maybrier HR, Oberhaus J, Budelier TP, Kronzer A, McKinnon SL, Park D, Torres BA, Graetz TJ, Emmert DA, Palanca BJ, Goswami S, Jordan K, Lin N, Fritz BA, Stevens TW, Jacobsohn E, Schmitt EM, Inouye SK, Stark S, Lenze EJ, Avidan MS; ENGAGES Research Group: Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: The ENGAGES randomized clinical trial. JAMA 2019; 321:473–83
8. Schultz A, Grouven U, Zander I, Beger FA, Siedenberg M, Schultz B: Age-related effects in the EEG during propofol anaesthesia. Acta Anaesthesiol Scand 2004; 48:27–34
9. Purdon PL, Pavone KJ, Akeju O, Smith AC, Sampson AL, Lee J, Zhou DW, Solt K, Brown EN: The ageing brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. Br J Anaesth 2015; 115 Suppl 1:i46–57
10. Giattino CM, Gardner JE, Sbahi FM, Roberts KC, Cooter M, Moretti E, Browndyke JN, Mathew JP, Woldorff MG, Berger M; MADCO-PC Investigators: Intraoperative frontal alpha-band power correlates with preoperative neurocognitive function in older adults. Front Syst Neurosci 2017; 11:24
11. Polich J: EEG and ERP assessment of normal aging. Electroencephalogr Clin Neurophysiol 1997; 104:244–56
12. Carrier J, Land S, Buysse DJ, Kupfer DJ, Monk TH: The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20-60 years old). Psychophysiology 2001; 38:232–42
13. Bandt C, Pompe B: Permutation entropy: A natural complexity measure for time series. Phys Rev Lett 2002; 88:174102
14. Pincus SM: Approximate entropy as a measure of system complexity. Proc Natl Acad Sci U S A 1991; 88:2297–301
15. Olofsen E, Sleigh JW, Dahan A: Permutation entropy of the electroencephalogram: A measure of anaesthetic drug effect. Br J Anaesth 2008; 101:810–21
16. Jordan D, Stockmanns G, Kochs EF, Pilge S, Schneider G: Electroencephalographic order pattern analysis for the separation of consciousness and unconsciousness: An analysis of approximate entropy, permutation entropy, recurrence rate, and phase coupling of order recurrence plots. Anesthesiology 2008; 109:1014–22
17. Schneider G, Jordan D, Schwarz G, Bischoff P, Kalkman CJ, Kuppe H, Rundshagen I, Omerovic A, Kreuzer M, Stockmanns G, Kochs EF; European Multicenter EEGAEP Anesthesia Monitoring Study Group and Research Group Knowledge-based Signal Processing: Monitoring depth of anesthesia utilizing a combination of electroencephalographic and standard measures. Anesthesiology 2014; 120:819–28
18. Rampil IJ: A primer for EEG signal processing in anesthesia. Anesthesiology 1998; 89:980–1002
19. Viertiö-Oja H, Maja V, Särkelä M, Talja P, Tenkanen N, Tolvanen-Laakso H, Paloheimo M, Vakkuri A, Yli-Hankala A, Meriläinen P: Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. Acta Anaesthesiol Scand 2004; 48:154–61
20. Hight D, Voss LJ, Garcia PS, Sleigh J: Changes in alpha frequency and power of the electroencephalogram during volatile-based general anesthesia. Front Syst Neurosci 2017; 11:36
21. McKay ID, Voss LJ, Sleigh JW, Barnard JP, Johannsen EK: Pharmacokinetic-pharmacodynamic modeling the hypnotic effect of sevoflurane using the spectral entropy of the electroencephalogram. Anesth Analg 2006; 102:91–7

22. Mapleson WW: Effect of age on MAC in humans: A meta-analysis. Br J Anaesth 1996; 76:179–85
23. Mazoit JX, Butscher K, Samii K: Morphine in postoperative patients: pharmacokinetics and pharmacodynamics of metabolites. Anesth Analg 2007; 105:70–8
24. Shafer SL, Varvel JR: Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology 1991; 74:53–63
25. Wiczling P, Bienert A, Sobczyński P, Hartmann-Sobczyńska R, Bieda K, Marcinkowska A, Malatyńska M, Kaliszan R, Grześkowiak E: Pharmacokinetics and pharmacodynamics of propofol in patients undergoing abdominal aortic surgery. Pharmacol Rep 2012; 64:113–22
26. Haller M, Donoghue T, Peterson E, Varma P, Sebastian P, Gao R, Noto T, Knight RT, Shestyuk A, Voytek B: Parameterizing neural power spectra. bioRxiv 2018: 299859
27. Bruhn J, Röpcke H, Hoeft A: Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. Anesthesiology 2000; 92:715–26
28. Nicolaou N, Houris S, Alexandrou P, Georgiou J: Entropy measures for discrimination of 'awake' Vs 'anaesthetized' state in recovery from general anesthesia. Conf Proc IEEE Eng Med Biol Soc 2011; 2011:2598–601
29. Shannon C: A mathematical theory of communication. Bell Syst. Tech. J 1948; 27: (379-423):623–56
30. Kreuzer M: EEG based monitoring of general anesthesia: Taking the next steps. Front Comput Neurosci 2017; 11:56
31. Goldberger AL, Amaral LA, Glass L, Hausdorff JM, Ivanov PC, Mark RG, Mietus JE, Moody GB, Peng CK, Stanley HE: PhysioBank, PhysioToolkit, and PhysioNet: Components of a new research resource for complex physiologic signals. Circulation 2000; 101:E215–20
32. Schneider G, Schöniger S, Kochs E: Does bispectral analysis add anything but complexity? BIS sub-components may be superior to BIS for detection of awareness. Br J Anaesth 2004; 93:596–7; author reply 596–7
33. Hentschke H, Stüttgen MC: Computation of measures of effect size for neuroscience data sets. Eur J Neurosci 2011; 34:1887–94
34. Akeju O, Westover MB, Pavone KJ, Sampson AL, Hartnack KE, Brown EN, Purdon PL: Effects of sevoflurane and propofol on frontal electroencephalogram power and coherence. Anesthesiology 2014; 121:990–8
35. Jordan D, Stockmanns G, Kochs EF, Schneider G: Is detection of different anesthetic levels related to nonlinearity of the electroencephalogram? 4th European Conference of the International Federation for Medical and Biological Engineering. Edited by Sloten J, Verdonck P, Nyssen M, Haueisen J, Springer Berlin Heidelberg, 2009, pp 335–9
36. Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D, Acker JD: Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. Cereb Cortex 2005; 15:1676–89
37. Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, Morris JC, Dale AM, Fischl B: Thinning of the cerebral cortex in aging. Cereb Cortex 2004; 14:721–30
38. Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, Brewer JB, Dale AM: One-year brain atrophy evident in healthy aging. J Neurosci 2009; 29:15223–31
39. Fjell AM, Westlye LT, Amlien I, Espeseth T, Reinvang I, Raz N, Agartz I, Salat DH, Greve DN, Fischl B: High consistency of regional cortical thinning in aging across multiple samples. Cereb. Cortex 2009: bhn232
40. Thompson PM, Hayashi KM, Dutton RA, Chiang MC, Leow AD, Sowell ER, De Zubicaray G, Becker JT, Lopez OL, Aizenstein HJ, Toga AW: Tracking Alzheimer's disease. Ann NY Acad Sci 2007; 1097:183–214
41. Hoekema R, Wieneke GH, Leijten FS, van Veelen CW, van Rijen PC, Huiskamp GJ, Ansems J, van Huffelen AC: Measurement of the conductivity of skull, temporarily removed during epilepsy surgery. Brain Topogr 2003; 16:29–38
42. Voytek B, Kramer MA, Case J, Lepage KQ, Tempesta ZR, Knight RT, Gazzaley A: Age-related changes in 1/f neural electrophysiological noise. J Neurosci 2015; 35:13257–65
43. Chinoy ED, Frey DJ, Kaslovsky DN, Meyer FG, Wright KP Jr: Age-related changes in slow wave activity rise time and NREM sleep EEG with and without zolpidem in healthy young and older adults. Sleep Med 2014; 15:1037–45
44. Bruce EN, Bruce MC, Vennelaganti S: Sample entropy tracks changes in EEG power spectrum with sleep state and aging. J. Clin. Neurophysiol. 2009; 26: 257
45. Dave S, Brothers TA, Swaab TY: 1/f neural noise and electrophysiological indices of contextual prediction in aging. Brain Res 2018; 1691:34–43
46. Kaiser AK, Doppelmayr M, Iglseder B: EEG beta 2 power as surrogate marker for memory impairment: A pilot study. Int Psychogeriatr 2017; 29:1515–23
47. Vysata O, Kukal J, Prochazka A, Pazdera L, Simko J, Valis M: Age-related changes in EEG coherence. Neurol Neurochir Pol 2014; 48:35–8
48. Bédard C, Kröger H, Destexhe A: Does the 1/f frequency scaling of brain signals reflect self-organized critical states? Phys Rev Lett 2006; 97:118102
49. Hämmerer D, Li SC, Völkle M, Müller V, Lindenberger U: A lifespan comparison of the reliability, test-retest stability, and signal-to-noise ratio of event-related potentials assessed during performance monitoring. Psychophysiology 2013; 50:111–23

50. Keller K, Mangold T, Stolz I, Werner J: Permutation entropy: New ideas and challenges. Entropy 2017; 19: 134
51. Brown EN, Lydic R, Schiff ND: General anesthesia, sleep, and coma. N Engl J Med 2010; 363:2638–50
52. Shumbayawonda E, Fernández A, Hughes MP, Abásolo D: Permutation entropy for the characterisation of brain activity recorded with magnetoencephalograms in healthy ageing. Entropy 2017; 19: 141
53. Berger S, Schneider G, Kochs EF, Jordan D: Permutation entropy: Too complex a measure for EEG time series? Entropy 2017; 19: 692
54. John ER, Prichep LS: The anesthetic cascade: A theory of how anesthesia suppresses consciousness. Anesthesiology 2005; 102:447–71
55. Kreuzer M, Whalin MK, Hesse SDW, Riso MA, García PS: Anesthetic management of a patient with multiple previous episodes of postanesthesia care unit delirium: A case report. A A Case Rep 2017; 8:311–5
56. Chander D, García PS, MacColl JN, Illing S, Sleigh JW: Electroencephalographic variation during end maintenance and emergence from surgical anesthesia. PLoS One 2014; 9:e106291
57. Hesse S, Kreuzer M, Hight D, Gaskell A, Devari P, Singh D, Taylor NB, Whalin MK, Lee S, Sleigh JW, García PS: Association of electroencephalogram trajectories during emergence from anaesthesia with delirium in the postanaesthesia care unit: An early sign of postoperative complications. Br J Anaesth 2019; 122:622–34
58. Bassett DS, Bullmore ET, Meyer-Lindenberg A, Apud JA, Weinberger DR, Coppola R: Cognitive fitness of cost-efficient brain functional networks. Proc Natl Acad Sci U S A 2009; 106:11747–52
59. Crowley K, Trinder J, Kim Y, Carrington M, Colrain IM: The effects of normal aging on sleep spindle and K-complex production. Clin Neurophysiol 2002; 113:1615–22
60. Frantzidis CA, Ladas A, Diamantoudi MD, Semertzidou A, Grigoriadou E, Tsolaki A, Liapi D, Papadopoulou A, Kounti F, Vivas AB: What are the symbols of Alzheimer? A permutation entropy based symbolic analysis for the detection of early changes of the electroencephalographic complexity due to mild Alzheimer, Bioinformatics & Bioengineering (BIBE), 2012 IEEE 12th International Conference on, IEEE, 2012, pp 282–287
61. Pilge S, Zanner R, Schneider G, Blum J, Kreuzer M, Kochs EF: Time delay of index calculation: Analysis of cerebral state, bispectral, and narcotrend indices. Anesthesiology 2006; 104:488–94
62. Zanner R, Pilge S, Kochs EF, Kreuzer M, Schneider G: Time delay of electroencephalogram index calculation: Analysis of cerebral state, bispectral, and Narcotrend indices using perioperatively recorded electroencephalographic signals. Br J Anaesth 2009; 103:394–9
63. Ni K, Cooter M, Gupta DK, Thomas J, Hopkins TJ, Miller TE, James ML, Kertai MD, Berger M: Paradox of age: Older patients receive higher age-adjusted minimum alveolar concentration fractions of volatile anaesthetics yet display higher bispectral index values. Br J Anaesth 2019; 123:288–97
64. Prichep LS, Gugino LD, John ER, Chabot RJ, Howard B, Merkin H, Tom ML, Wolter S, Rausch L, Kox WJ: The Patient State Index as an indicator of the level of hypnosis under general anaesthesia. Br J Anaesth 2004; 92:393–9
65. Lysakowski C, Elia N, Czarnetzki C, Dumont L, Haller G, Combescure C, Tramèr MR: Bispectral and spectral entropy indices at propofol-induced loss of consciousness in young and elderly patients. Br J Anaesth 2009; 103:387–93
66. Dundee JW, Robinson FP, McCollum JS, Patterson CC: Sensitivity to propofol in the elderly. Anaesthesia 1986; 41:482–5
67. Teplan M: Fundamentals of EEG measurement. Meas. Sci. Rev. 2002; 2: 1–11