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NEUROSCIENCES AND NEUROANAESTHESIA

Behaviour of spectral entropy, spectral edge frequency 90%, and alpha and beta power parameters during low-dose propofol infusion

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Background. In this study we analyse the behaviour, potential clinical application and optimal cortical sampling location of the spectral parameters: (i) relative alpha and beta power; (ii) spectral edge frequency 90%; and (iii) spectral entropy as monitors of moderate propofol-induced sedation.

Methods. Multi-channel EEG recorded from 12 ASA 1 (American Society of Anesthesiologists physical status 1) patients during low-dose, target effect-site controlled propofol infusion was used for this analysis. The initial target effect-site concentration was 0.5 μg ml^{-1} and increased at 4 min intervals in increments of 0.5 to 2 μg ml^{-1}. EEG parameters were calculated for 2 s epochs in the frequency ranges 0.5–32 and 0.5–47 Hz. All parameters were calculated in the channels: P4–O2, P3–O1, F4–C4, F3–C3, F3–F4, and Fp1–Fp2. Sedation was assessed clinically using the OAA/S (observer's assessment of alertness/sedation) scale.

Results. Relative beta power and spectral entropy increased with increasing propofol effect-site concentration in both the 0.5–47 Hz [$F(18, 90) = 3.455$, $P<0.05$ and $F(18, 90) = 3.33$, $P<0.05$, respectively] and 0.5–32 Hz frequency range. This effect was significant in each individual channel ($P<0.05$). No effect was seen of increasing effect-site concentration on relative power in the alpha band. Averaged across all channels, spectral entropy did not outperform relative beta power in either the 0.5–32 Hz [Pk=0.79 *vs* 0.814 ($P>0.05$)] or 0.5–47 Hz range [Pk=0.81 *vs* 0.82 ($P>0.05$)]. The best performing indicator in any single channel was spectral entropy in the frequency range 0.5–47 Hz in the frontal channel F3–F4 (Pk=0.85).

Conclusions. Relative beta power and spectral entropy when considered over the propofol effect-site range studied here increase in value, and correlate well with clinical assessment of sedation.

The number of standard indications for moderate sedation or 'monitored anaesthesia care' to facilitate surgical or medical procedures has increased greatly over the past decade.[1] This continuing trend is due in part to the evidence based movement to minimally invasive procedures and ambulatory surgery.

Moderate sedation shortens procedure duration and allows patients to tolerate unpleasant procedures by relieving anxiety and discomfort.[2] Excessive sedation and the resulting upper airway and cardiovascular effects present avoidable risk to patients and particular difficulties to practitioners who are less skilled in airway management. Inadequate sedation resulting in pain, disinhibition, and cardiovascular stress is of particular concern in the paediatric and elderly populations. The inter-patient variability in response to sedating drugs makes the use of

clinical endpoints essential. Sedation scales were designed to standardize assessment and minimize inter-observer variation in a reliable way.[3 4] The obvious disadvantage of these instruments is the repeated verbal and tactile stimulation of the patient required to administer them. A reliable EEG-based monitor could potentially remove this need.

Currently available depth-of-sedation monitors designed primarily for use in anaesthesia practice are regularly evaluated by both anaesthetists and non-anaesthetists alike in the context of moderate sedation.[2 5] Evaluated over the entire sedation-anaesthesia continuum these monitors appear to correlate well with clinical evaluation when endpoints such as loss of verbal response and loss of consciousness (and regain) are assessed.[6–8] However, when observations are confined to levels of sedation before loss of consciousness associated with loss of response to verbal command [such as the observer's assessment of alertness/sedation (OAA/S) levels 4 and 3] the performance of at least two of these monitors deteriorates.[2 5]

The EEG changes that occur during low-dose propofol infusion before loss of consciousness have previously been investigated using topographic EEG power mapping studies.[9 10] Specific brain EEG changes occur at different plasma propofol concentrations. Over the propofol effect-site concentration range 0–1.2 μg ml^{-1} increased frontal fast (beta) activity and a reduction in the predominantly occipital alpha rhythm (a rhythm best seen in the relaxed eyes closed state) occurs.[9] The increase in frontal beta activity appears to be a reliable indicator of increasing sedation.[9–11]

The ideal descriptor of the sedation-anaesthesia continuum should decrease in a monotonic fashion with increasing depth of sedation.[12] EEG descriptor variables, including Approximate, Shannon, and Spectral entropy demonstrate monotonic behaviour and good correlation with drug effect-site concentrations in the context of depth-of-anaesthesia monitoring when comparatively large doses of anaesthetic agents are administered over a short period of time.[13–15]

In day-to-day practice, this means that, when a hypnotic drug is administered, the value of the depth-of-sedation indicator should decrease. In the context of a prolonged induction period (10 min), biphasic behaviour (i.e. an initial increase followed by a decrease in value) of EEG amplitude and spectral edge frequency (SEF) 95% has been reported.[11] Recent work demonstrates spectral entropy to behave in a similar manner during a prolonged propofol infusion period leading to loss of consciousness.[16] Over the entire sedation–anaesthesia continuum, spectral entropy had a low prediction probability (0.56) for the OAA/S score.[16]

Using clinical and EEG data obtained from a previous prospective observational study we set out to determine the behaviour and potential application of the spectral parameters: relative alpha and beta power, spectral edge frequency 90% (SEF 90), and spectral entropy as monitors of moderate sedation in adult patients during target effect-site controlled propofol infusion.[17] The range of propofol effect-site concentrations is limited to that previously

associated with increasing beta activity and calculated spectral entropy, that is, the ascending limb of the biphasic EEG propofol response curve.[9 16]

Commercially available depth-of-sedation monitors tend to use forehead mounted electrode arrays that acquire a frontal channel of the EEG. As a secondary endpoint we simultaneously studied frontal, fronto-central and occipito-parietal EEG to investigate the optimum cortical location from which to acquire EEG for parameter calculation.

Methods

Recruitment

We used EEG data recorded in a previous study which was performed by our research group after approval by the Clinical Research Ethics Committee of the Cork Teaching Hospitals.[17] After providing written informed consent, 12 adult unpremedicated patients were studied. Inclusion criteria were: patients undergoing elective surgery aged 18–65 yr, and American Society of Anesthesiologists (ASA) physical status 1. Exclusion criteria were: diseases affecting the central nervous system (CNS), concurrent medication with CNS effects, hearing defect, history of drug abuse, at increased risk of pulmonary aspiration or obesity (body mass index >30 kg m^{-2}).

Experimental setup

The study took place in a quiet, temperature-controlled anaesthetic induction room. Twenty gold cup EEG scalp electrodes (Nicolet Biomedical, Madison, WI, USA) filled with Ten20^{TM} (D.O. Weaver and Co., Aurora, CO, USA) conductive paste were applied to the patient's scalp using the international 10–20 electrode mapping system. Nineteen channels of EEG were recorded using an Alliance digital EEG machine (Nicolet/Alliance Biomedical, Madison, WI, USA). State and response entropy (SE/RE) values were recorded simultaneously using a standard disposable Entropy^{TM} sensor and an M-Entropy^{TM} module for the Datex/Ohmeda S/5^{TM} compact monitor (GE Healthcare, Helsinki, Finland).

A target effect-site infusion of propofol was administered using the Base Primea Infusion System (Fresenius-Vial, Brezins, France). This system uses Schnider's pharmacokinetic model. In this model, the plasma effect-site equilibrium rate constant (K_{eo}) of 0.45 min^{-1} is used, resulting in a time to peak effect of 1.7 min.[18 19] The initial target effect site concentration was set to 0.5 μg ml^{-1}. This was increased in 0.5 μg ml^{-1} increments every 4 min to a maximum of 2 μg ml^{-1}.

Each patient was asked to keep his/her eyes closed from the outset, and remained in a semi-recumbent position for the study duration. Blood pressure, ECG, and peripheral arterial oxygen saturation were monitored. The

responsiveness component of the OAA/S scale was administered at 1 min intervals. OAA/S assessment was based on the scale 5=alert; 4=lethargic response to name spoken in a normal tone; 3=response only after name is called loudly or repeatedly; 2=response only after mild prodding or shaking; 1=no response to mild prodding or shaking.[4] For the purposes of analysis the OAA/S score recorded at the end of each 4 min, propofol effect-site equilibrium period was used to assess the accuracy of the derived EEG parameters to predict the clinical state of the patient.

All EEG parameters were calculated in the bipolar channels: occipito-parietal P4–O2 and P3–O1, prefrontal Fp1–Fp2, frontal F3–F4, and frontocentral F4–C4 and F3–C3. Even numbers by convention refer to the right side of the scalp. The occipito-parietal locations were chosen as alpha rhythm (which originates in the posterior occipital cortex) is best seen in this area. Fp1-Fp2 represents an extreme frontal montage likely to be contaminated by EMG artifact from the frontalis muscle. The recording electrode array of the Entropy™ monitor is in a similar position.[20] The remaining three channels F3–F4, F4–C4 and F3–C3 were chosen to represent frontal and fronto-central cortical activity. Channel positions are shown in Figure 1.

Signal processing

The EEG for each channel was considered in epochs of 2 s duration and band-pass filtered in the frequency ranges 0.5–32 Hz and 0.5–47 Hz using a fifth order type II Chebyshev IIR filter. The following parameters were calculated for each 2 s EEG epoch for each channel:

- Spectral entropy (H_s);
- SEF 90;
- Relative power in the alpha band (8–13 Hz);
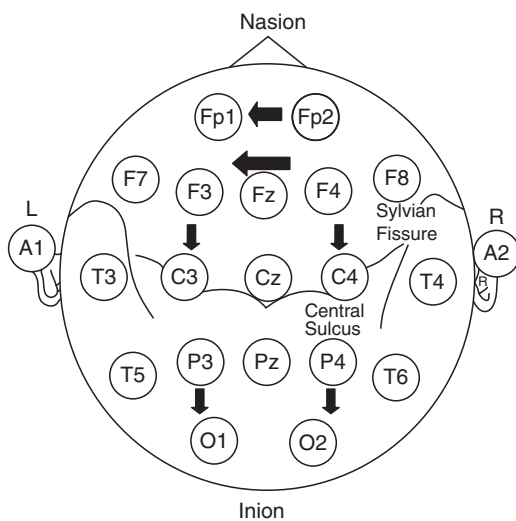- Relative power in the beta band (14–40 Hz).

Fig 1 International 10–20 electrode positions. Block arrows show the bipolar montages used for comparison.

Relative rather than absolute power bands were used as the EEG exhibits large intra-individual power variation.

As relative power bands are calculated over the entire spectrum studied, that is, 0.5–47 Hz, the possibility exists that contamination from electrical sources other than EEG (such as the EMG) might result in a disproportionately low power value for alpha and beta activity and hence an erroneous result. To overcome this potential confounding problem all parameters were also calculated for the frequency range 0.5–32 Hz (a range considered to be confined to pure EEG activity).[20] In considering this frequency range the upper limit of the beta band was taken to be 32 Hz. Thus the relative power in the alpha and beta frequency band was defined as the ratio of the power in each frequency band to the total power in the band 0.5–47 or 0.5–32 Hz, respectively.

The SEF was calculated as that frequency below which 90% of the total spectral power resided in each of the respective frequency bands.

To compute the spectral entropy of each 2 s epoch we adopted the method used by Viertio-Oja and coworkers,[20 21] which applies a power spectral density (PSD) based estimate of the probability density function (PDF) to the Shannon entropy equation:

$$H_s(X) = -\frac{1}{\log N_f} \sum_f P_f(X) \log_e P_f(X) \qquad (1)$$

After the fast Fourier transform (FFT) of the EEG for each epoch, the PSD was calculated by multiplying the FFT estimate for each epoch by its conjugate. The power spectrum estimate was then divided by the total spectral power in the range 0.5–32 or 0.5–47 Hz to yield an estimate of the PDF. Multiplying this PDF estimate [$P_f(X)$] by the natural logarithm of the PDF [$\log_e P_f(X)$] and summing over all frequency components, f, produced a spectral entropy value for each epoch of EEG. The spectral entropy value is then divided by the factor $\log N_f$, where N_f is equal to the total number of frequency components in the range 0.5–47 or 0.5–32 Hz. This normalization step confines H_s to the range 0–1, where unity represents maximum irregularity and zero complete regularity.

Artifact rejection

The recorded EEG was first subjected to artifact detection and rejection. Each recording contained only small amounts of eye-blink artifact as each patient was asked to keep their eyes closed for the duration of the recording. Movement artifacts, which are large signal spikes caused by movement of the patient and electrode leads, were identified and excluded from further analysis using a previously reported method.[22] To identify the artifact sections of the EEG, a zero mean EEG signal was first calculated for each EEG channel by subtracting the mean of the EEG from each sample and then processing this signal as follows:

The standard deviation (SD) of the absolute value of the signal was calculated and any signal samples >10 times the SD of this zero-mean signal were flagged as 'movement' artifact.

This artifact measure was then associated with each 2 s epoch for each channel. Any epoch in a given channel, considered to contain >1% artifact was excluded from subsequent analysis.

Statistical analysis

Mean relative alpha and beta power, spectral edge frequency, and spectral entropy parameter values were compared across four levels of target effect-site propofol concentration. A repeated measures multivariate analysis of variance (MANOVA) was conducted for each of the four EEG parameters to examine the effect of propofol effect-site concentration on measurements in the six EEG channels. As this method is specifically designed to gauge the effect of an independent variable (i.e. propofol effect-site concentration) on multiple dependent variables (EEG channels), potential problems arising from multiple comparisons are overcome. As several MANOVAs were conducted on the data, *P*-values produced after Bonferroni correction are reported. Probability values <0.05 were deemed significant.

The ability of the EEG parameters relative beta power, SEF 90%, and spectral entropy (H_s) in distinguishing between 'clinically sedated' (OAA/S<5) and 'clinically not sedated' (OAA/S=5) at the end of each 4 min propofol effect-site equilibrium period was assessed using prediction probability values (Pk). Developed by Smith *et al.*,[23] prediction probability compares the performance of independent variables having different units of measurement. In this case the gold standard measurement of sedation depth was OAA/S score, against which relative beta power, SEF 90, and spectral entropy were compared. A Pk value of 1 for the independent variable means that variable always increases or decreases according to the gold standard. A Pk value of 0.5 implies there is no correlation between the direction of change of the gold standard and the independent variable. Pk values were calculated using Smith's custom spreadsheet; Pk MACRO. The standard error of the estimate was computed using the jackknife method.[23] Smiths's PkDMACRO custom spreadsheet was used to compute the *t* value for comparison of Pk values between different EEG parameters.

Results

The EEG records of all 12 patients were analysed [(M:F::4:8); aged 37 (SD 9) yr (range 26–50); height: 168 (6) cm and weight: 71 (10) kg]. The mean EEG recording length was 19.8 min. The lowest recorded OAA/S score at any time during the study was three.

Relative alpha power

When relative alpha power was calculated based on averaging across all six EEG channels no significant effect of propofol effect-site concentration on relative alpha power was observed after a repeated measures MANOVA in either the 0.5–32 or 0.5–47 Hz frequency range [$F(18, 90)=1.302$, $P>0.05$ and $F(18, 90)=1.38$, $P>0.05$, respectively]. Subsequent inspection of the univariate analyses for each channel in both frequency ranges indicated no significant relationship between effect-site concentration and the relative alpha power in any of the six channels.
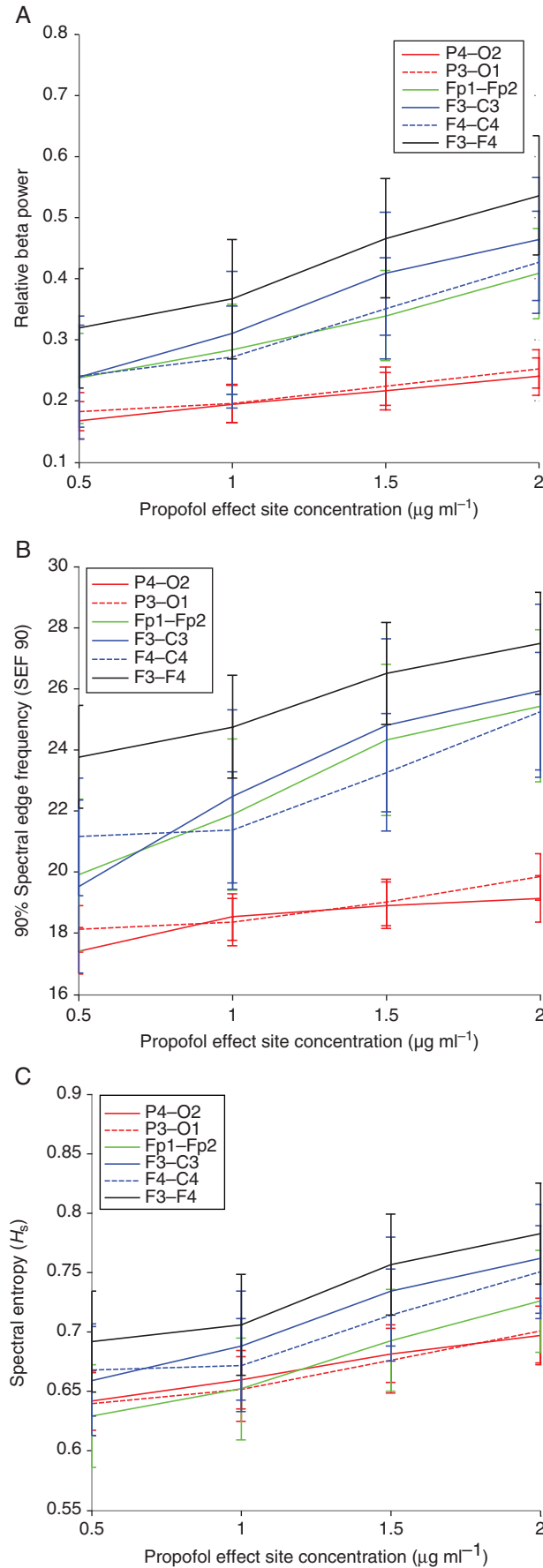
Relative beta power

Multivariate analysis indicated a significant effect of propofol target-effect site concentration on relative power in the beta band when calculated based on averaging across all six EEG channels in both the 0.5–32 and 0.5–47 Hz frequency range [$F(18, 90)=2.338$, $P<0.05$ and $F(18, 90)=3.455$, $P<0.05$, respectively]. An examination of the univariate analyses demonstrated that increasing propofol effect-site concentration was significantly associated with an increase in relative beta power in each of the six channels over the frequency ranges 0.5–47 Hz (Fig. 2A) and 0.5–32 Hz ($P<0.05$ respectively). Raw values calculated for relative alpha and beta power over the frequency range 0.5–47 Hz are shown in Table 1.

Spectral edge frequency

Effect-site concentration had a significant effect on SEF 90, whereby increasing effect-site concentration resulted in an increasing value of the frequency below which 90% of the EEG power resides. This was true for both the 0.5–32 and 0.5–47 Hz frequency ranges [$F(18, 90)=3.5$, $P<0.001$ and $F(18, 90)=2.424$, $P<0.001$, respectively]. Examination of the univariate analyses suggested that the significant relationship was restricted to the prefrontal channel Fp1–Fp2 ($P<0.001$) and the fronto-central channels F3–C3 ($P<0.001$) and F4–C4 ($P<0.05$) for the frequency range 0.5–47 Hz (Fig. 2B). Over the more limited frequency range (0.5–32 Hz) increasing propofol effect-site concentration resulted in increased SEF 90 in all but the F3–F4 channel ($P=0.057$).

Spectral entropy

Increasing propofol effect-site concentration resulted in a significant increase in spectral entropy in the frequency ranges 0.5–32 Hz and 0.5–47 Hz [$F(18, 90)=2.48$, $P<0.05$ and $F(18, 90)=3.33$, $P<0.05$, respectively]. This relationship reached statistical significance ($P<0.05$) in all six channels in both frequency ranges when inspected individually (Fig. 2C). Mean spectral entropy values (averaged over the six bipolar channels) are presented on a per-patient basis in Table 2.

Fig 2 (A) Relative beta power *vs* propofol target effect-site concentration in each of the six individual bipolar channels averaged across all patients over the frequency range 0.5–47 Hz. Values shown at each effect-site concentration are mean (standard error), averaged across all patients. (B) Spectral edge frequency 90 (SEF 90) *vs* propofol target effect-site concentration in each of the six individual bipolar channels for the frequency range 0.5–47 Hz. The effect was significant in channels: Fp1–Fp2, F4–C4, and F3–C3. Values shown at each effect-site concentration are mean (standard error), averaged across all patients. (C) Spectral entropy (H_s) *vs* propofol target effect-site concentration in each of the six individual bipolar channels for the frequency range 0.5–47 Hz. Values shown at each effect-site concentration are mean (standard error), averaged across all patients. The effect was significant in all channels.

State and response entropy

SE and RE indices (Entropy™ Monitor; GE Healthcare, Helsinki, Finland), appeared to change little in the majority of patients with increasing target effect-site concentration.[17] Both SE and RE values varied by 1–6 arbitrary units in 11 of 12 patients over the effect-site concentration range studied. The greatest change occurred in Patient 11 whose SE and RE values declined by 28 and 25 arbitrary units, respectively, over the target effect-site range. Spectral entropy when averaged across all channels in Patient 11 increased with target effect-site concentration (Table 2). PSD functions from both frontal and occipital-parietal locations in this patient show total power spread over a broad range of frequencies (Fig. 3). Derived spectral entropy value thus increases in tandem with the increase in high frequency (beta) activity.

Prediction probability

The prediction probability values for the parameters: spectral entropy, SEF 90%, and relative beta power to predict 'sedated/not sedated' based on OAA/S score were highest in the frontal channels (Table 3). The highest value

Table 1 Mean relative alpha and beta power averaged across all six channels (i.e. frontal, fronto-central, and occipito-parietal regions) in individual patients with increasing propofol target effect-site concentration

Patient ID	Effect-site concentration (µg ml^{-1})							
	Relative alpha power (0.5–47 Hz)				Relative beta power (0.5–47 Hz)			
	0.5	1	1.5	2	0.5	1	1.5	2
1	0.04	0.06	0.06	0.06	0.23	0.27	0.30	0.50
2	0.08	0.06	0.11	0.11	0.10	0.11	0.20	0.35
3	0.09	0.14	0.12	0.15	0.17	0.21	0.17	0.35
4	0.05	0.05	0.19	0.13	0.20	0.25	0.29	0.30
5	0.14	0.16	0.13	0.13	0.19	0.29	0.45	0.51
6	0.31	0.36	0.34	0.28	0.13	0.17	0.28	0.33
7	0.22	0.19	0.22	0.14	0.28	0.39	0.35	0.37
8	0.15	0.09	0.16	0.20	0.29	0.25	0.41	0.42
9	0.12	0.10	0.07	0.07	0.38	0.38	0.46	0.41
10	0.24	0.20	0.15	0.14	0.27	0.24	0.29	0.46
11	0.19	0.24	0.19	0.15	0.17	0.26	0.33	0.40
12	0.21	0.20	0.22	0.17	0.21	0.36	0.36	0.28
Mean	0.15	0.15	0.16	0.14	0.22	0.27	0.32	0.39

A   3D PSD plot, Patient 11, Channel: F4–C4

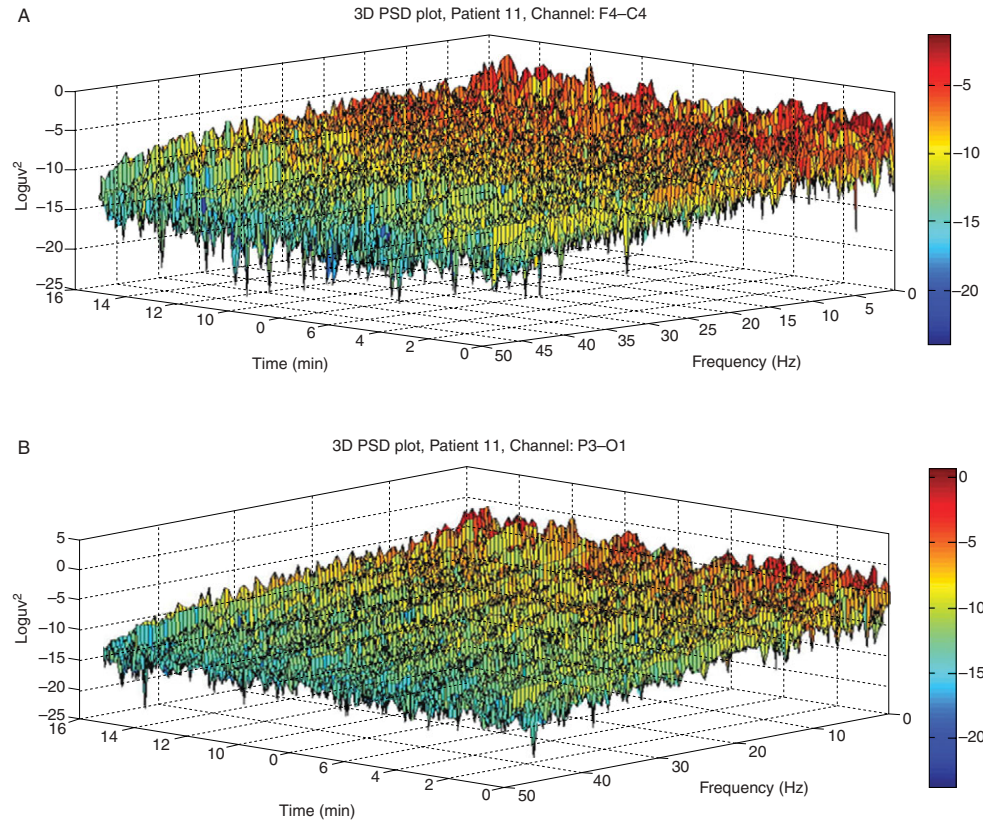B   3D PSD plot, Patient 11, Channel: P3–O1

Fig 3 Three-dimensional power spectral density (PSD) function from Patient 11: (A) fronto-central channel F4–C4 and (B) the occipito-parietal channel P3–O1. The time axis corresponds to propofol effect-site concentration 0.5–2 μg ml^{-1} (increased in 4 min increments). High frequency activity is a clear feature resulting in a broad power spectrum demonstrating a leftward shift as high frequency (beta) activity increases with increasing effect-site concentration.

recorded for any parameter in any single channel was for spectral entropy (Pk=0.85) in the fronto-central channel F3–F4 over the frequency range 0.5–32 Hz. This was significantly greater ($P<0.01$) than that achieved over the frequency range 0.5–47 Hz. Averaged across all channels, spectral entropy did not demonstrate greater predictive value than relative beta power in either the 0.5–32 Hz [Pk=0.79 *vs* 0.814 ($P>0.05$)] or 0.5–47 Hz range [Pk=0.81 *vs* 0.82 ($P>0.05$)].

Discussion

We have demonstrated that spectral entropy increases during propofol infusion over the target effect-site concentration range 0.5–2.0 μg ml^{-1}. This finding may appear counter-intuitive in that many clinical practitioners might assume that spectral entropy should decrease as the patient demonstrates clinical evidence of sedation. The direction of the correlation should thus be negative. Previous work on this data set demonstrated a small though significant decrease in SE and RE values when EEG or clinical evidence of sedation was present at the end of each 4 min propofol equilibrium period.[17]

Our findings are consistent with earlier reports of investigators who documented the dramatic increase in beta activity that occurs particularly in frontal EEG channels during low-dose propofol sedation.[9] [10] Consistent with increasing beta activity, we found that SEF 90 increased

Table 2 Mean spectral edge frequency 90 (SEF 90) and spectral entropy (H_s) averaged across all six EEG channels (i.e. frontal, fronto-central, and occipito-parietal regions) in individual patients with increasing propofol target effect-site concentration. *Patient 11 is specifically discussed in the results section: 'State and response entropy'

Patient ID	Effect-site concentration (μg ml^{-1})							
	SEF 90 (Hz) (0.5–47 Hz)				H_s (0.5–47 Hz)			
	0.5	1	1.5	2	0.5	1	1.5	2
1	21.71	22.01	23.43	26.68	0.66	0.68	0.70	0.75
2	11.21	10.44	16.15	23.39	0.55	0.54	0.61	0.71
3	14.93	16.30	15.82	23.75	0.59	0.61	0.61	0.71
4	16.84	20.47	23.08	21.08	0.60	0.63	0.74	0.72
5	16.92	22.79	24.25	24.76	0.62	0.69	0.75	0.76
6	16.57	19.41	23.65	24.18	0.67	0.66	0.70	0.72
7	24.28	28.36	25.79	25.59	0.74	0.77	0.78	0.78
8	24.70	19.41	23.66	23.18	0.71	0.65	0.76	0.76
9	31.05	29.43	32.09	28.98	0.74	0.73	0.76	0.75
10	22.10	19.66	20.49	25.28	0.69	0.68	0.70	0.76
11*	16.49	21.42	21.79	22.82	0.67	0.73	0.73	0.75
12	20.05	26.18	22.96	18.98	0.68	0.74	0.74	0.69
Mean	19.74	21.32	22.76	24.06	0.66	0.68	0.71	0.74

Table 3 Prediction probabilities of the EEG measures with respect to observer's assessment of alertness/sedation (OAA/S) score for the frequency ranges 0.5–32 and 0.5–47 Hz. OAA/S score dichotomized to: sedated (OAA/S<5)/not sedated (OAA/S=5) for each channel studied. Cross-channels (X) is the Pk value obtained when the parameter was first averaged across all six channels. Data are prediction probability (Pk) (standard error). H_s, spectral entropy

Parameter	Fp1–Fp2	F3–F4	F4–C4	F3–C3	P4–O2	P3–O1	X Channels
0.5–32 Hz							
Relative beta power	0.74 (0.08)	0.78 (0.07)	0.77 (0.07)	0.80 (0.06)	0.76 (0.08)	0.64 (0.08)	0.81 (0.06)
SEF 90%	0.70 (0.09)	0.78 (0.07)	0.74 (0.07)	0.78 (0.07)	0.65 (0.08)	0.58 (0.08)	0.76 (0.07)
H_s	0.76 (0.08)	0.85 (0.06)	0.74 (0.07)	0.81 (0.07)	0.74 (0.08)	0.68 (0.08)	0.79 (0.08)
(0.5–47 Hz)							
Relative beta power	0.74 (0.09)	0.79 (0.07)	0.77 (0.07)	0.79 (0.06)	0.72 (0.08)	0.63 (0.08)	0.82 (0.06)
SEF 90%	0.63 (0.08)	0.56 (0.08)	0.63 (0.08)	0.71 (0.07)	0.61 (0.08)	0.54 (0.08)	0.64 (0.08)
H_s	0.75 (0.08)	0.73 (0.07)	0.70 (0.08)	0.78 (0.07)	0.71 (0.09)	0.65 (0.08)	0.81 (0.06)

with target effect-site concentration. This increase was significant in the frontal and fronto-central channels when considered over the frequency range 0.5–47 Hz. Confined to the frequency range 0.5–32 Hz this increase also reached significance in the more posterior channels consistent with the fact that the frequency below which 90% of the spectral power was contained remained significantly less than the 32 Hz taken as the upper limit of the beta band in this instance. No significant change occurred in relative alpha power in individual bipolar channels or when averaged across all channels with increasing effect-site concentration. We had anticipated that a decrease in alpha power might occur in the posterior-occipital channels, as decreased alpha amplitude and drop out in these regions is known to occur with deepening sedation.[24][25] Kishimoto et al.[9] demonstrated a decrease in alpha1 (7.75–10 Hz) and an increase in alpha2 (10.25–12.5 Hz) in patients receiving low dose propofol sedation to a maximum plasma concentration of 1.2 μg ml^{-1}. We did not subdivide the Alpha band rather we defined the alpha band as the 8–13 Hz part of the spectrum.

The increase in spectral entropy shown in our results may be explained by the changes occurring in the underlying PSD, with increasing propofol effect-site concentration. In the Shannon function all power components of the PSD influence the final calculated entropy value.[21] This effect is seen in Figure 3A. As propofol dose increases, the PSD becomes more elongated and flattened as EEG power spreads to frequencies greater than those confined to the alpha (awake relaxed) band. The spectral entropy value associated with a 'flat' or less skewed PSD is greater than that where total power is confined to a narrow or 'peaked' frequency range.

A simultaneous PSD from a more posterior channel in the same patient is also shown (Fig. 3B). It can be seen that a marked decrease in total power occurs with increasing propofol dose in this channel (consistent with the well-known phenomenon of 'frontal anteriorization'). As spectral entropy is normalized to total power, this makes calculated values relatively insensitive to the dramatic decreases seen here, allowing valid comparison of spectral entropy values derived within and between channels.

Recent work has shown the behaviour of EEG-based measures to be highly sensitive to the frequency band of the EEG signal underlying their calculation. Ferenets et al.[16] investigated the behaviour of spectral entropy during step-wise target effect-site controlled propofol infusion. When the frequency band used for the calculation of spectral entropy was varied, the performance of the calculated parameter changed. Over the range 0.5–47 Hz (as used in this study), spectral entropy appeared to increase and reach a plateau at approximately 2 μg ml^{-1} and subsequently decrease. When a frequency range of 6–47 Hz was used for calculation, spectral entropy was stationary or decreased over the same effect-site range.

Given this we choose to consider spectral entropy primarily over the frequency range 0.5–47 Hz in that spectral entropy appeared to exhibit a consistent unidirectional effect up to the effect-site concentration of approximately 2.0 μg ml^{-1}.

In calculating the *SyncFastSlow* and the *Beta Ratio* the BIS^{TM} monitor (Aspect Medical, Norwood, MA, USA) also relies on a similar frequency range. The possible importance and role of beta activity and the *Beta Ratio* in the final BIS calculation has been demonstrated.[26] The RE parameter in the Entropy^{TM} monitor (GE Healthcare, Helsinki Finland) is calculated over the frequency range 0.8–47 Hz.

This study is limited in that the data used were collected for a previous clinical study. The OAA/S scale was administered at 1 min intervals, thus stimulating the patient. Had this contaminated the measured EEG parameters, we would have expected this to result in a unidirectional effect within patients. In many of the patient records, the value of measured EEG parameters increased and decreased with drug dose, as a result OAA/S administration could not be found to have unidirectional effect. Examination of the raw EEG indicated little movement artifact at the times the OAA/S scale was administered. Ocular artifact such as eye blinks generates signals that have amplitude 10 times larger than cortical signals.[27] Repetitive unfiltered eye blink artifact could therefore contribute to a change in spectral entropy by itself. From the outset of the study, patients were requested to keep

their eyes gently shut. The raw EEG itself contained little blink artifact.

The forehead location is favoured for the positioning of electrode arrays manufactured for depth-of-sedation monitors. Presumably this represents a trade off between clinical convenience and EEG acquisition. The international '10–20' bipolar channel F3–F4 is located more posterior on the scalp (and usually within the hairline of individuals).

Spectral entropy calculated in this cross-hemispheric channel (F3–F4) over the frequency range 0.5–32 Hz offers the best correlation with the clinical scoring system used here (Pk=0.85). Averaged across all channels spectral entropy did not offer a significantly better prediction probability than the simple measure of relative beta power.

This study serves to highlight the utility of simple EEG measures such as relative beta power. Neither spectral entropy nor relative beta power parameters behave in a monotonic fashion over the entire sedation-anaesthesia continuum. This may result in apparently poor performance of the indicator when assessed over a greater range of effect-site concentrations resulting in loss of consciousness.[16] The unidirectional increase in both relative beta power and spectral entropy when considered over the frequency and propofol-effect site ranges studied here offers potential as a monitor of moderate or 'conscious' propofol-induced sedation.

Multiparameter EEG monitors sensitive to the 'clinical context', that is, sedation *vs* anaesthesia via clinician feedback should offer the best correlation with observed sedation depth.

Acknowledgement

Funding

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