British Journal of Anaesthesia **86 (1)**: 50–8 (2001)

Comparison of changes in electroencephalographic measures during induction of general anaesthesia: influence of the gamma frequency band and electromyogram signal

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Recent research has shown that high-frequency, gamma-band electroencephalographic (EEG) oscillations (40–60 Hz) may be an important marker of the conscious state. We compared the ability of the bispectral index (BIS) to distinguish the awake and anaesthetized states during the induction of general anaesthesia with: (i) components of the BIS (BetaRatio, SynchFastSlow); (ii) a new EEG variable—the median frequency of the first time derivative of the EEG signal (SE50d); and (iii) the SE50d derived from an EEG signal that has had the frequencies above 30 Hz removed ($SE50d_{30Hz}$). Two groups of subjects were studied: (i) nine volunteers undergoing a short propofol infusion until loss of response to verbal command, and (ii) 84 patients undergoing routine anaesthesia for a variety of surgical procedures. In the volunteer group, the changes in the BetaRatio and SE50d were comparable with changes in the BIS. The changes in the $SE50d_{30Hz}$ were less consistent. In the patient group, the BIS components were equivalent to the BIS in separating the awake from the surgically anaesthetized states (area under receiver operating curve: BIS 0.95, SE50d 0.95, BetaRatio 0.96). Using the submental electromyogram (EMG) signal to estimate the frontalis EMG (30–47 Hz) signal, the changes in EMG signal were, on average, about one-tenth the magnitude of the EEG. We conclude that: (i) there exist simpler derived EEG variables that are similar in accuracy to the BIS; (ii) it is important to avoid filtering out the EEG frequencies above 30 Hz; and (iii) in most patients the confounding effects of the frontalis EMG on the EEG are minimal.

Br J Anaesth 2001; **86**: 50–8

Keywords: monitoring, electroencephalography; anaesthesia, general; monitoring, electromyography

Accepted for publication: August 19, 2000

By visual inspection there are obvious electroencephalographic (EEG) changes that occur as general anaesthesia is induced in a patient. It is believed that the EEG reflects, to some degree, the level of cortical information processing, and that this changes during the abrupt transition from the state of conscious awareness to that of unconsciousness. Over the years, many putative methods of extracting this information quantitatively from the EEG signal have been proposed.[1 2] These methods usually involve quantifying the increase in low-frequency components of the EEG signal that occurs as anaesthesia deepens. None has been found to be an ideal measure of the depth of anaesthesia. Recent neurophysiological and anaesthetic research has highlighted the importance of the so-called gamma-band EEG oscillations (40–60 Hz) as a marker of the conscious state.[3–7] These are recognized as an irregular, broad-band, high-frequency, low-amplitude (so-called desynchronized) EEG pattern. This pattern is characteristically present when the subject is engaged in specific conscious tasks; it is indicative of the spotlight of attention.[8 9] Experimentally, these gamma rhythms have also been detected at the level of neuronal networks, and have been postulated to be an important part of the process by which the brain binds together sensory input into a conceptual whole that is necessary in the formation of consciousness.[10] Because the spectral power of the scalp EEG signal has a small amplitude at these relatively high frequencies, these contributions to the spectrum have often been ignored when various parameters derived from the EEG power spectrum have been tested as potential monitors of the depth of anaesthesia. One potential problem with using these high-frequency components is that interpretation of the EEG

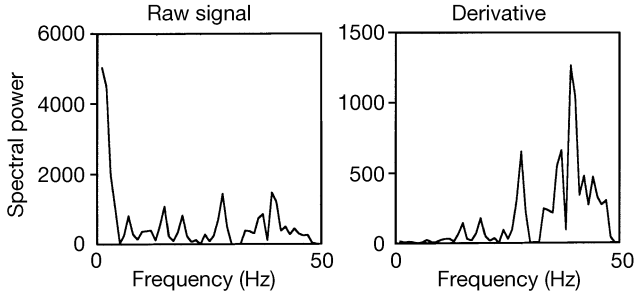

Fig 1 Comparison of typical power spectra of the raw EEG signal with that of the first time-derivative of the same 1 s segment of the EEG signal in an awake patient. The spectral power density of the raw EEG (left) is in units of $(\mu V)^2$ Hz^{-1} and that of the first derivative (right) in units of $(\mu Vs^{-1})^2$ Hz^{-1}. The signal has been digitally band-pass filtered 0.1 to 47 Hz.

signal could be confounded by significant frontalis electromyographic (EMG) spectral power.

However, in recent years the introduction of the bispectral index (BIS) by Aspect Medical Systems (Natick, Massachusetts, USA) has achieved success as an EEG monitor of the conscious state.[11] With the publication of some of the algorithms involved in the derivation of the BIS,[12] it is apparent that one feature that sets this monitor apart from previous monitors is that it recognizes the importance of the higher EEG frequencies (up to 47 Hz) as indicators of the state of consciousness. The details of the calculation and significance of the components of the BIS are discussed in Appendix 1.

There is a large number of possible alternative estimators that could be used to quantify the higher frequencies. In this paper we take a simple approach and use the first time-derivative of the raw EEG signal. Taking the derivative is mathematically equivalent to scaling the EEG signal by its frequency, thus markedly increasing the relative contribution of the higher frequency components and reducing that of the low-frequency components in a linear fashion. Figure 1 compares the power spectrum of the raw EEG signal (left) against that of the first time-derivative of the EEG signal (right).

From our initial discussion we hypothesize that: (i) it is important to include information above 30 Hz when designing an EEG measure of the conscious state, and (ii) simple frequency-related EEG measures may perform comparably with the full BIS in identifying when loss of consciousness occurs. Therefore, in this study we compared the ability of the BIS to differentiate between the awake and anaesthetized states during the induction of anaesthesia, by the use of: (i) components of the BIS (the BetaRatio and the SynchFastSlow); (ii) a new EEG variable—the median frequency of the first time-derivative of the EEG signal (called the SE50d); and (iii) the SE50d, derived from an EEG signal that has had the frequencies above 30 Hz removed (called $SE50d_{30Hz}$). In addition, we have attempted to estimate the degree to which the derived EEG variables (specifically the BetaRatio) may be influenced by changes in the EMG signal that occur as the patient is undergoing general anaesthesia.

Table 1 Clinical details of the patient group

Age (mean (SD))	57 (9) yr	
Sex (female:male)	52:32	
Oral premedication (2 h before induction)	Midazolam (7.5 mg)	*n*=3
Intravenous premedication (5 min before induction)	Midazolam (1–4 mg)	*n*=42
	Fentanyl (50–100 μg)	*n*=67
	Droperidol (1.25 mg)	*n*=5
Induction agents	Propofol (70–200 mg)	*n*=63
	Thiopentone (200–450 mg)	*n*=13
	Etomidate (14–20 mg)	*n*=8
Muscle relaxants	Suxamethonium (100 mg)	*n*=7
	Rocuronium (30–50 mg)	*n*=31

Methods

Clinical procedures

After obtaining permission from the Regional Ethical Committee and informed written consent from participants, we studied EEG changes in two separate groups. The first group (termed the 'volunteer group') consisted of nine fit (ASA I or II) volunteers undergoing light anaesthesia with a slow i.v. infusion of propofol (150 ml h^{-1}) in tightly controlled conditions, as described previously.[13] The EEG data were compared at each of three clinically defined points: (i) start; (ii) loss of consciousness (LOC); (iii) reawakening (responding to verbal command as the effects of the propofol wore off). Encouraged by the results from the volunteer group, we then studied a second, more heterogeneous group (termed the 'patient group'). This group consisted of 84 patients undergoing routine surgery under general anaesthesia. Because we wanted to compare the EEG changes in the varying conditions of routine clinical anaesthesia, the choice of anaesthetic technique was decided entirely on clinical grounds. The clinical anaesthetist was blinded to the EEG monitoring. The various anaesthetic techniques are shown in Table 1.

The patients had no history of neurological disorders. A total of 90 patients (ASA I–III) were recruited but only 84 had complete data sets (two were excluded from the data set because they were unable to respond appropriately to verbal command before induction of anaesthesia, and four had unacceptably high electrode impedances). The clinical stages during the induction of anaesthesia were defined as follows: (i) AWAKE = start time; (ii) LOC = time of loss of consciousness as determined by failure to respond to verbal command ('move your thumb') repeated twice; (iii) LOC60 = LOC + 60 s; and (iv) SURG = start of surgery.

EEG acquisition and analysis

To reduce electrode–skin impedance, the skin over the forehead of each subject was cleaned with an abrasive cleaning fluid (Omniprep; DO Weaver, Aurora, Colorado, USA), and low-impedance electrode paste (Grass EC2 electrode cream; Astro-Med, Warwick, Rhode Island, USA) was placed under disposable adhesive silver–silver chloride electrodes (Meditrace 200; Graphic Controls, Buffalo, NY, USA). We have found previously that, using this arrangement, we are able to obtain electrode impedances similar to, or better than, those obtained with the proprietary disposable EEG electrodes. The EEG was monitored using a bipolar bifrontal montage format (Fp1–Fp2, 10/20 system). The ground electrode was placed at the mid-forehead (Fz) position. In the volunteer group, a second bipolar EEG channel was recorded from the temporoparietal region (T3–P3). In a subset of 30 of the patient group, the second channel consisted of a bipolar pair of electrodes recording the submental EMG signal. The subjects and patients were asked to close their eyes to reduce ocular and blink artefact. An Aspect A-1000 EEG monitor (software version 3.12; Aspect Medical Systems) was used to collect the EEG data. The processed BIS output was recorded at 5 s intervals on a laptop computer, while the raw EEG data were downloaded (sampling frequency 256 samples s^{-1}) onto a second computer for later analysis. Electrode impedance was less than 5000 ohms, and the low- and high-frequency filters were set at 0.5 and 70 Hz with the mains notch filter set at 50 Hz. This filtering applied to the processed output from the Aspect Monitor, but not the raw EEG output. All subsequent processing and analysis were done using purpose-written computer programs in Matlab (Matlab 5.3; Mathworks, Natick, Massachusetts, USA).

SE50d, BetaRatio and SynchFastSlow

The data were processed in 2 s epochs. The signal was low-pass filtered using a phase-preserving 12th-order elliptical digital filter (cutoff frequencies 47–49 Hz, 100 dB roll-off, <2 dB ripple). Then, the signal was processed to reject gross artefacts by excluding epochs in which the absolute magnitude of the signal was greater than 200 μV. The BetaRatio and SynchFastSlow were obtained using the published formula described by Rampil.[12] The exact algorithm for the calculation of the burst suppression ratio (QUAZI Suppression Index) is not in the public domain, and therefore the calculation was not done. In any case, the depth of anaesthesia was such that no burst suppression (as indicated by the Aspect Monitor) was achieved in any patient. The first time-derivative of the EEG signal was then taken and the spectral density of each 2 s epoch obtained (Hanning window). From this, the median frequency of the derivative of the signal (SE50d) could be calculated as the frequency which bisected the area under the derivative-power spectral density curve. The $SE50d_{30Hz}$ was also calculated using a version of the EEG signal that had been additionally digitally low-pass filtered to 30 Hz. This was done because it is common for commercial EEG systems to use this more severe filtering of higher frequencies. The 2 s epochs of all three variables were then smoothed using a moving five-point median window.

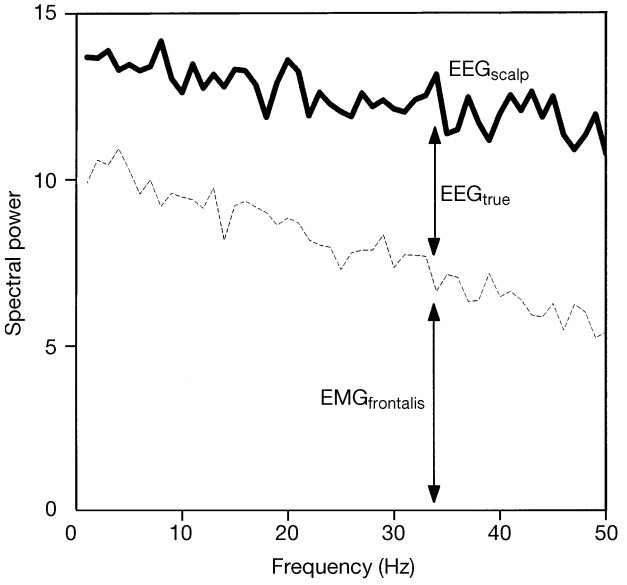

Fig 2 Pictorial representation of how the power spectrum of the observed EEG signal (EEG_{scalp}) consists of the sum of power spectra of the frontalis EMG signal ($EMG_{frontalis}$) and that of the true EEG signal (EEG_{true}).

EMG influence

There has been some criticism that the high-frequency component (30–47 Hz) of the BetaRatio is particularly susceptible to the influence of EMG interference. It is usual to consider the power spectrum of the observed scalp EEG signal (EEG_{scalp}) as the sum of (i) the power spectrum of the true EEG signal (EEG_{true}) and (ii) the power spectrum of the frontalis EMG signal ($EMG_{frontalis}$) (diagrammatically displayed in Fig. 2).

To observe the EEG_{true} signal reliably it would be necessary to have the patient awake and paralysed, which was clearly problematical ethically! However, although we could not measure the $EMG_{frontalis}$ directly, we were able to measure the EMG signal from a bipolar electrode pair sited submentally ($EMG_{submental}$). This pair detects the electrical activity in the muscles of the floor of the mouth and upper neck. This montage is used routinely in sleep monitoring to quantify muscle tone for the evaluation of periods of rapid-eye-movement sleep. An example of the unfiltered $EMG_{submental}$ power spectrum in a conscious patient is shown in Fig. 3. It can be seen that the power spectrum is relatively flat in the frequency range 15–90 Hz (once the 50 Hz mains interference is filtered out).

It is possible to use the spectral power of the $EMG_{submental}$ to estimate the amount of $EMG_{frontalis}$ spectral power that is present in the EMG_{scalp}. The details and assumptions of this method are discussed further in Appendix 2.

Statistical techniques

Unless stated otherwise, data are presented as mean (SD). The changes in the various EEG parameters at each time-point were compared statistically using paired *t*-tests with Bonferroni's correction for multiple comparisons, if the data satisfied normality criteria. In the patient group the data were often skewed, and therefore the Wilcoxon test was used. Receiver operating curve (ROC) analysis was used to compare the ability of the EEG parameters to distinguish the awake and anaesthetized states and to determine the appropriate cutoff values.[14] The anaesthetized state (at the time of surgery) was coded as positive. All the spectral powers were expressed as the 10·base 10 logarithm [i.e. dB relative to 1 $(\mu V)^2$ Hz^{-1}]. It is important to remember that subtraction of logarithms is equivalent to division, and that a difference of one logarithmic unit is the equivalent of a tenfold difference in absolute value.

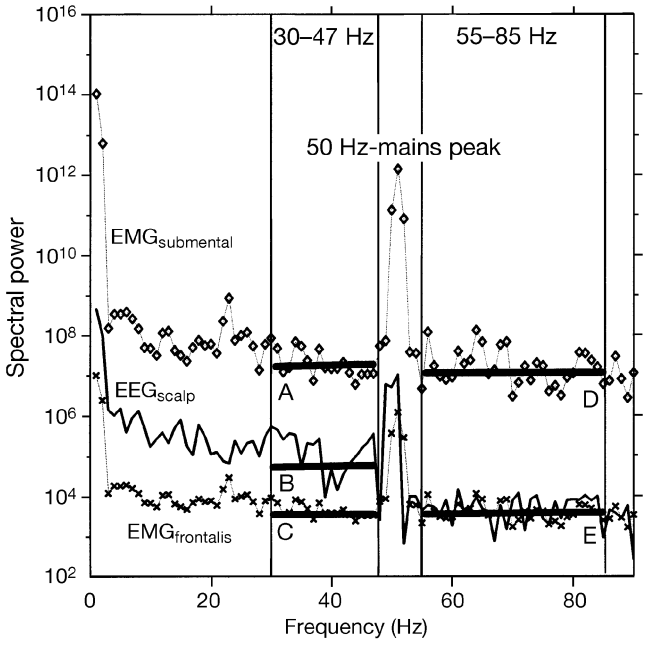

Fig 3 Example of the power spectra of the submental EMG signal and scalp EEG from an awake patient. The $EMG_{frontalis}$ signal cannot be measured directly, but is in fact the same $EMG_{submental}$ signal suitably scaled to give a diagrammatic representation of the various ratios as described in the text. The unit of spectral power is $(\mu V)^2$ Hz^{-1}.

Results

Volunteer group

Figure 4 shows typical changes of the four indices with time in a single volunteer during and recovering from a propofol infusion. He slowly became more drowsy (the infusion was stopped at the point of loss of consciousness, i.e. at 401 s) and then reawakened (822 s). At the light levels of anaesthesia obtained in this study, both the SE50d and the BetaRatio show relative changes that closely track those of the BIS. The changes in the $SE50d_{30Hz}$ are less pronounced than the SE50d.

We found that the SE50d compared favourably with the BIS in distinguishing the awake and asleep states. As shown in Table 2, in the volunteer group the values of both indices decreased from the starting point to the point of loss of consciousness and then increased at the point of reawaken-

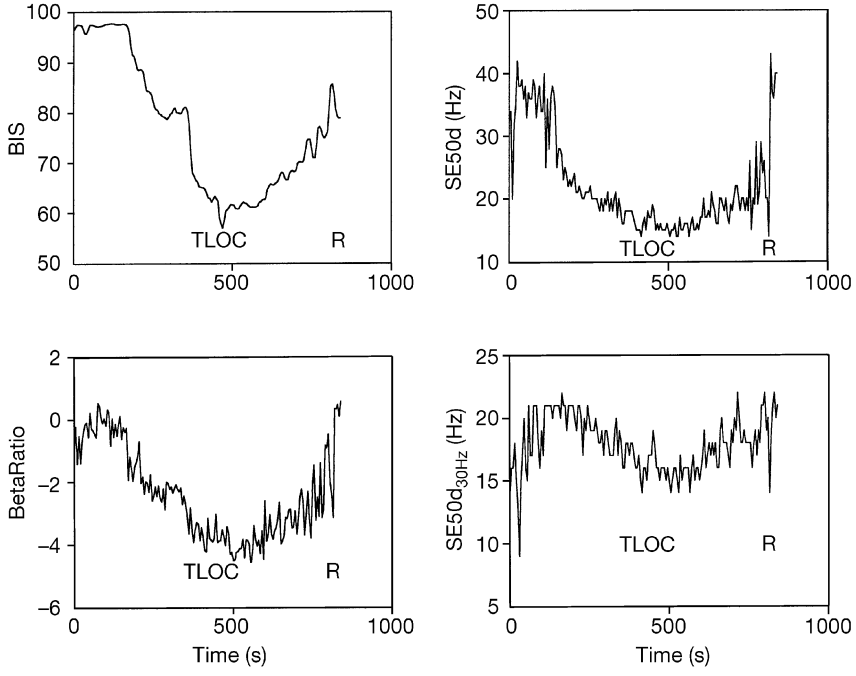

Fig 4 Graphs showing typical changes in EEG indices (BIS, SE50d, $SE50d_{30Hz}$ and BetaRatio) with time for a single volunteer. TLOC is the time of loss of consciousness and R is the time of reawakening.

ing (P<0.03). There were no statistically significant differences between data from the frontal and parietal EEG channels. The SE50d demonstrated significant hysteresis (P=0.0035) when comparing the values at which subjects awoke with the values when they went to sleep.

Patient group

The clinical details of the patient group are summarized in Table 1. Typical changes of the BIS, SE50d, SynchFastSlow, bispectral power in the bands 0.5–47 and 40–47 Hz, submental EMG power and BetaRatio during induction of anaesthesia in one patient are shown in Fig. 5.

Table 2 Comparison of changes in EEG parameters in the volunteer group (mean (5th to 95th centile))

	BIS	SE50d
Start	96 (94–98)	33 (28–37)
LOC	71 (49–94)	18 (13–27)
Reawakening	78 (61–96)	27(21–35)

It can be seen that the response of the BIS tends to lag behind the other parameters (BetaRatio, SynchFastSlow and SE50d). Whether this lag is due to the pronounced smoothing incorporated in the BIS algorithm or some other cause is not clear.[12] This graph illustrates the decrease in EMG power during induction, and its close correlation with all the other parameters. Figure 5E shows the changes in bispectral power over the whole frequency range (0.5–47 Hz, labelled 'Total') and the high-frequency range (40–47 Hz, labelled 'High'). It demonstrates that the changes in the SynchFastSlow during induction consist of the progressive decrease in high-frequency bispectral power (which closely follows the decline in EMG spectral power) combined with a relatively unchanged, or even increased, total bispectral power at the point of loss of consciousness. The relative changes amongst the different frequency bands of the bispectrum are qualitatively remarkably similar to those seen in the simple power-spectral frequency measures (as quantified by the SE50d and BetaRatio).

A statistical comparison of the changes in the variables is shown in Table 3. All the variables decreased significantly during induction of anaesthesia (P<0.001). In all the raw

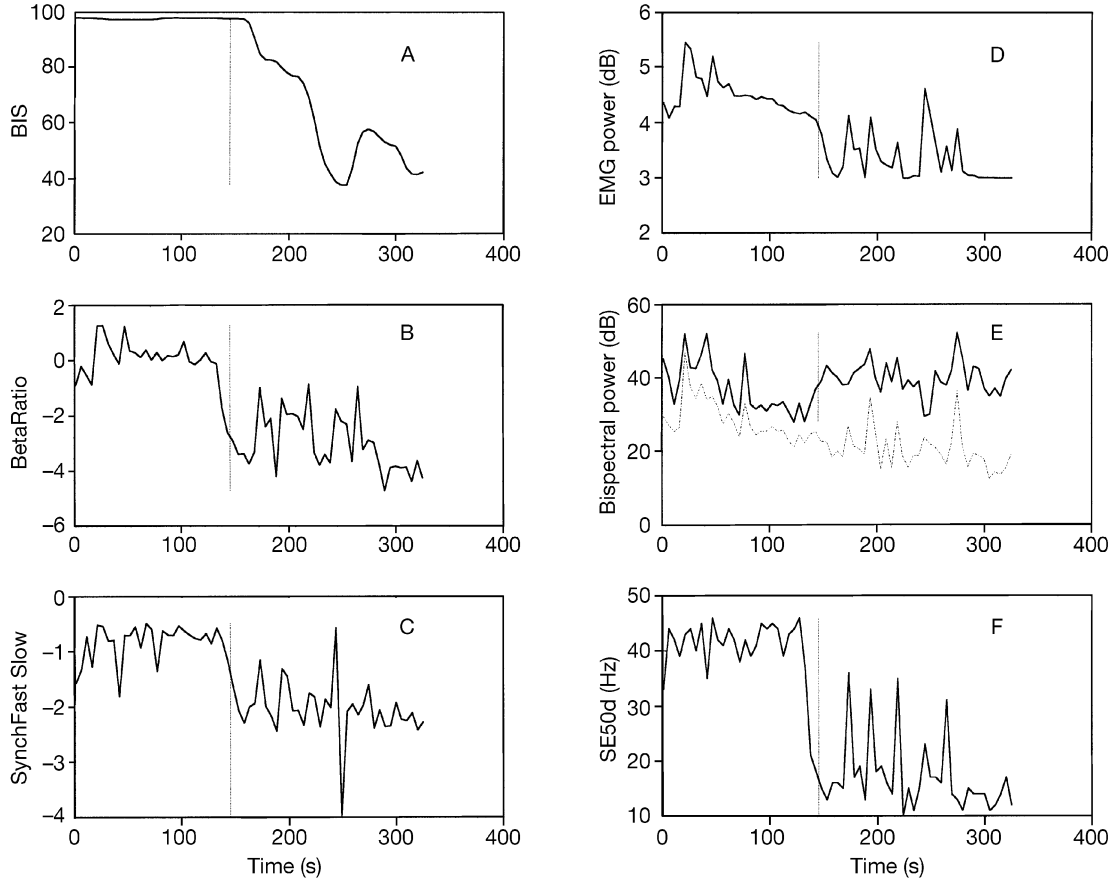

Fig 5 Typical changes in various EEG variables in a single patient during induction of anaesthesia. The vertical dotted line in each graph indicates the time of loss of consciousness. BIS, BetaRatio and SynchFastSlow are dimensionless ratios. The units of EMG power (D) are dB relative to $1(\mu V)^2\ Hz^{-1}$. The total power is the $\log_{10}$ of the volume under the bispectral surface from 0.5 to 47 Hz, and the high power is the logarithm of the volume under the bispectral surface from 40 to 47 Hz. See text for detailed description of the calculation of each variable.

Table 3 Comparison of the EEG variables at various stages of induction of anaesthesia. Values are median (25th to 75th centile). The units of the EMG power are dB relative to $1(\mu V)^2\ Hz^{-1}$. The units of both bispectral powers ('total' is 0.5–47 Hz; 'high' is 40–47 Hz) are dB; the others are unitless ratios. SEF = spectral edge frequency

Variable	Time point			
	AWAKE	LOC	LOC60	SURG
BIS	97 (95 to 98)	94 (87 to 97)	56 (39 to 75)	48 (39 to 67)
EMG_{power} (dB)	4.1 (3.8 to 4.5)	3.4 (3.0 to 3.7)	3.1 (3.0 to 3.3)	3.1 (3.0 to 3.2)
SEF (Hz)	12 (8 to 19)	21 (15 to 24)	13 (7 to 15)	12 (9 to 16)
SE50d (Hz)	40 (36 to 43)	18 (15 to 23)	15 (13 to 18)	15 (13 to 18)
$SE50d_{30Hz}$ (Hz)	20 (15 to 22)	14 (11 to 20)	14 (12 to 16)	14 (12 to 16)
BetaRatio	–0.11 (–0.53 to –0.62)	–2.21 (–2.83 to –1.45)	–2.86 (–3.43 to –2.06)	–2.92 (–3.51 to –2.38)
SynchFastSlow	–0.98 (–1.32 to –0.66)	–1.66 (–1.96 to –1.34)	–1.83 (–2.03 to –1.69)	–1.82 (–2.03 to –1.63)
Total bispectral (dB)	38 (31 to 43)	36 (29 to 42)	34 (27 to 44)	35 (26 to 44)
High bispectral (dB)	28 (20 to 33)	21 (12 to 26)	15 (07 to 25)	16 (9 to 24)

Table 4 Comparison of the predictive power of the three best EEG parameters (distinguishing patients at the start (AWAKE) versus the time of surgery (SURG)). Sensitivity is the proportion of those asleep who are correctly identified as being asleep. Specificity is the proportion of those awake who are correctly identified as awake. PPV is the proportion of patients with a value of the EEG variable less than the cutoff who are correctly diagnosed as being asleep. NPV is the proportion of patients with a value of the EEG parameter less than cutoff who are correctly diagnosed as being awake

Variable (cutoff value)	Sensitivity	Specificity	PPV	NPV
BIS (65)	0.61	0.98	0.97	0.75
SE50d (21)	0.89	0.97	0.97	0.90
BetaRatio (–0.09)	0.89	0.97	0.97	0.90

variables (i.e. other than the BIS), the most marked change occurred between the awake state at the start and the point of loss of consciousness. Using the area (SE) under the ROC curves, the SE50d (0.95 (0.12)), BIS (0.95 (0.12)) and BetaRatio (0.96 (0.12)) showed consistent and equivalent decreases when the values at the time of surgery were compared with those at the start. The SynchFastSlow was slightly less accurate (ROC area = 0.91 (0.12)). In contrast, the $SE50d_{30Hz}$ (0.80 (0.11)) and the 95% spectral edge frequency (0.52 (0.13)) were both significantly worse than the SE50d when comparing the area under ROC curve ($P<0.005$, *t*-test).

At arbitrary but reasonable cutoff points, the predictive power of the three variables was very similar (Table 4): the BIS was somewhat less able to predict the conscious state correctly, i.e. a significant number of patients with BIS>65 (who would be predicted to be awake) were actually asleep, indicating a greater overlap in awake versus asleep values by the BIS. If BIS of less than 57, a SE50d of less than 17 or a BetaRatio of less than –0.70 was used as the cutoff value, all three indices would achieve 100% positive predictive value.

EMG influence (n=30)

The interpretation of the EMG influence was not straightforward. During induction of anaesthesia, the spectral power of the $EMG_{submental}$ did not change significantly in the lower frequencies (1–20 Hz), but did decrease significantly ($P<0.001$) in the higher frequency range (20–47 Hz). As may be expected from this, the slope of the $EMG_{submental}$ power spectrum tended to increase with increasing depth of anaesthesia in a fashion that was similar to but less marked than that observed in the EEG (as estimated by the BetaRatio, for example).

When estimating the proportion of the EEG signal that was contaminated by the frontalis EMG signal, we used the 30–47 Hz frequency band, because that is the high-frequency component of the BetaRatio. Overall, the median (25th to 75th centile) of the ratio of $EEG_{scalp(30–47Hz)}$: $EMG_{frontalis(30–47hz)}$ was 12.6 (2.1–21) dB. This means that, on average, the EEG signal in the 30–47 Hz (i.e. low gamma) frequency band was more than eighteen ($=10^{1.26}$) times the magnitude of the EMG signal. However, the difference was more marked in the AWAKE state, for which the median ratio was 21.1 (14.7–27.5) dB. This corresponds to the EEG being over 100 times more powerful than the EMG in the gamma band. However, it must be noted that in the lowest decile of the patients the ratio was negative (i.e. the EMG power was greater than the EEG power). This indicates that, in some patients at least, there are inaccuracies in the assumptions used to derive the frontalis EMG amplitude.

Discussion

There are three main results from this study: (i) that there exist simpler (non-bispectral) derived EEG variables that

are similar in accuracy to the BIS in separating the awake from the surgically anaesthetized states; (ii) that, when detecting loss of consciousness, it is very important to avoid filtering out the frequencies above 30 Hz; and (iii) the changes in the power spectrum of EMG during induction are similar to the changes seen in the EEG, but are about ten times less in magnitude on average.

Compared with the BIS in our study, these alternative EEG indices are at an additional disadvantage because there was minimal artefact rejection in their preprocessing compared with the sophisticated artefact management used in the derivation of the BIS.[12] All predictive results need further prospective testing on an independent group before they can be recommended for routine clinical use. It must also be emphasized that the EEG parameters were evaluated during the induction of general anaesthesia. The changes that may occur during reawakening at the end of anaesthesia may differ.

It seems plausible that the improved performance of the SE50d (over the spectral edge frequency and the $SE50d_{30Hz}$) is due to: (i) the use of the first derivative, which has the effect of filtering out the fluctuating low-frequency artefact noise which, episodically, can dominate the true low-amplitude, high-frequency EEG power spectrum in the awake patient; and (ii) the fact that the SE50d emphasizes the importance of the desynchronized gamma rhythms, which are associated with the EEG of a subject in the attentive conscious state. The BetaRatio and the SE50d are similar in that they quantify the dominant EEG frequencies within a constrained frequency band. This includes the lower part of the gamma band and excludes the variable, dominant effects in the low frequencies (<10 Hz).

Schnider and colleagues, using the EEG as a monitor of propofol effect, have developed a variable called the semilinear canonical coefficient.[15] In simple terms this is a development of the statistical method of canonical regression, which, by an iterative method, automatically derives the best combination of weights for each frequency bin to describe the changes in the EEG signal during the transition from the alert state to anaesthesia. The non-linear link function is required to allow for the variable biphasic EEG response that occurs in the stage of light anaesthesia. In keeping with traditional practice, Schnider and colleagues used low-pass filtering of the EEG signal to exclude frequencies above 30 Hz. The diagrams of changes in the semilinear canonical coefficient during induction of anaesthesia in their paper (Fig. 3) are very similar to that of the $SE50d_{30\ Hz}$ in our paper (Fig. 4), showing a biphasic response. We suggest that this biphasic response may be attenuated or eliminated by the inclusion of higher frequencies in the analysed EEG signal.

There has been a number of studies using the auditory evoked steady-state response as a measure of depth of anaesthesia.[16 17] These studies have shown a good correlation between increasing anaesthetic concentrations and attenuation of the auditory evoked steady-state response.[18] Although the exact neurophysiological correlation between evoked (25 ms) 40 Hz activity and spontaneous EEG gamma-band activity is not entirely clear, there appears to be significant convergence: both are found to be relatively accurate indicators of the alert state.[19] It is of interest that, in a study by Schraag,[20] the area under the ROC curve (distinguishing the unconscious and conscious states) for the BIS (0.92) and their auditory evoked potential index (0.97) were very similar to the area under the ROC curves in our study. A simple estimator of the auditory response (the 'auditory evoked potential index') quantifies the response by summing the absolute magnitude of the first time-derivative of the signal, a procedure similar in some respects to the derivation of the SE50d.

The influence of changes in the frontalis EMG on the observed scalp EEG is problematical. Using our results, it would seem that, statistically, in about 90% of patients the EMG signal is a minor component of the observed scalp EEG signal. There is the important proviso that these conclusions are based on information obtained indirectly from the $EMG_{submental}$ and not directly from the (unmeasurable) $EMG_{frontalis}$. We have made the unproven assumption that, at least in the higher frequency ranges (>20 Hz), the slope of the power spectrum of the $EMG_{frontalis}$ was similar to that observed in $EEG_{submental}$. However, this problem is probably not clinically harmful, and is biased towards preventing intraoperative awareness in both possible scenarios. In most cases the effect of a high EMG spectral power is to flatten the BetaRatio, i.e. to make the patient appear more awake than he really is, and thus the anaesthetist would be tending to err towards increasing the amount of anaesthetic agent. Conversely, the $EMG_{frontalis}$ may have a very steep spectral slope (corresponding to an EMG BetaRatio of perhaps –3.00) caused by noise in the form of an excessive low-frequency EMG component of the scalp EEG signal, which would suggest that the patient is asleep when in fact he is awake. In this case, if the patient had that amount of muscle activity he would be able to forcefully indicate his conscious state to the surgeon! It is fortunate that all EEG indices tend to become more reliable in the presence of muscle relaxation (as long as this effect is taken into account when setting the thresholds of EEG parameters used for determining awareness).

One of the main criticisms of the BIS has been that it is derived empirically and not based on theory and neurophysiological facts. This study may go some way towards clarifying why the BIS is effective. As has been previously stated,[12] the BetaRatio is the important component of the BIS at light levels of anaesthesia. The success of this subcomponent in tracking the patient's level of consciousness during induction of anaesthesia seems to indicate that, if the goal is to decide if the patient is aware or not, then the dominant frequency of the 'desynchronized' oscillation is the important EEG feature. This phenomenon of blocking of the gamma rhythms is a feature of the commonly used

GABAergic general anaesthetic agents, and is much less marked with excitatory anaesthetic agents such as nitrous oxide or ketamine, which tend to maintain the gamma-band EEG activity.[21 22] This would explain why the BIS is not very sensitive when used during sedation with nitrous oxide.[23 24] The utility of the SE50d and BetaRatio with nitrous oxide is unknown.

Appendix 1

The two important subcomponents of the BIS—the BetaRatio and the SynchFastSlow—both estimate the importance of higher frequencies relative to the total signal. The BetaRatio is the logarithm of the ratio of the EEG spectral power in the 30–47 Hz band to the EEG spectral power in the 11–20 Hz band:

$$\text{BetaRatio} = \log_{10}[\text{spectral power}_{(30\text{–}47\ \text{Hz})} / \text{spectral power}_{(11\text{–}20\ \text{Hz})}].$$

The SynchFastSlow is the logarithm of the ratio of the bispectral power in the waveband 40–47 Hz to that in the band 0.5–47 Hz:

$$\text{SynchFastSlow} = \log_{10}[\text{bispectral power}_{(40\text{–}47\text{Hz})} / \text{bispectral power}_{(0.5\text{–}47\text{Hz})}].$$

It may be surmised that the success of the BIS may be due, in large part, to the emphasis on these higher frequencies extending into the gamma band. Although the bispectral index (BIS) is widely used as a monitor of the depth of anaesthesia, it has some disadvantages: (i) it is an empirically derived black box, with a complex non-linear algorithm that is difficult to relate to electrophysiological changes; (ii) the exact point at which individual patients lose consciousness occurs over a wide range of BIS values; (iii) it has a significant time lag, thus precluding individual titration to effect; and (iv) it does not reliably warn of impending arousal.

Almost all the published work on the higher-order spectra of the EEG signal in anaesthesia describes the changes in only the processed output of the Aspect Monitor: the BIS. Changes in the actual raw bicoherence and bispectrum of the EEG signal during natural sleep and epileptic seizures have been analysed by Bullock and colleagues.[25] Because the basis of the algorithm for calculating the BIS is not freely available, it is difficult to interpret the observed changes in terms of known neurophysiological processes. To understand the BIS fully, it is necessary to dissect it into its various subcomponents as far as possible. The theoretical basis of the bispectrum of the EEG signal is difficult to visualize intuitively. It has been claimed that a significant bispectral power is indicative of non-linear (quadratic) interfrequency phase coupling.[26] Strictly, this interpretation implies interactions among regular stationary cortical oscillators. It may be more realistic to consider the EEG as a stochastic (random) signal. In this case, the bispectral power may be better interpreted statistically as an estimate of the degree to which the signal is non-Gaussian, specifically its skewness.[27 28] Measurement noise and the EMG signal are both approximately Gaussian in distribution, and thus should not appear in the bispectrum. Therefore, it is conceivable that the bispectral techniques are effective because they are effectively reducing the influence of unwanted extra-EEG noise rather than revealing information about the degree of neurological integration. Unfortunately, the interpretation of the bispectrum is further complicated by the fact that even a truly Gaussian time series will have a non-zero bicoherence, because the bispectrum is a biased estimator, being distributed approximately as a χ^2 distribution.[29] Thus, it could be argued that the inclusion of complex bispectral measures is not important as long as the changes in high-frequency content are included in whatever EEG variable is chosen. If this is true, we could expect that similar information could be obtained without the necessity of using higher-order spectral techniques, by the use of a simpler, cut-down component of the BIS—the BetaRatio.

Appendix 2

There are two facts that make it possible to derive indirectly some (imperfect) information about the power spectrum of $EMG_{frontalis}$ and hence EEG_{true}. First, we can measure the $EMG_{submental}$ directly using a separate bipolar montage, giving an almost pure EMG signal. Secondly, the EEG content in the frontalis spectrum is negligible above 55 Hz. Thus, we can use the $EMG_{submental}$ to estimate the changes in the shape and slope of the EMG spectrum during induction of anaesthesia. We can then combine this information with the actual power of the EEG_{scalp} (equivalent to purely $EMG_{frontalis}$) in the frequency band 55–85 Hz to estimate what proportion of the total scalp 30–47 Hz power is attributable to $EMG_{frontalis.}$ This relies on the assumption that the slopes of the power spectra of $EMG_{frontalis}$ and $EMG_{submental}$ are similar (Fig. 3). The frontalis and submental EMG signals may both be affected independently by intermittent phenomena, such as voluntary local swallowing movements ($EMG_{submental}$), episodic brow wrinkling and eye movements ($EMG_{frontalis}$). Intuitively, it seems likely that the low-frequency components (<11 Hz) of the two EMG power spectra would often be uncorrelated, and we therefore ignored them. Conversely, the higher frequencies (gamma band) are more likely to reflect ongoing muscular tone and to be less sensitive to differences in voluntary movements between the forehead and the throat. The derivation of the mathematical formulae used to estimate the relative 30–47 Hz power is as follows. We assume that the $EMG_{submental}$ power spectrum behaves as an approximate scaled replica of the (unknown) $EMG_{frontalis}$ spectrum for frequencies higher than 30 Hz.

The ratio of submental to frontalis EMG power in the 30–47 Hz band equals the ratio in the 55–85 Hz band (using the symbols shown in Fig. 3):

$$A/C = D/E \quad (1)$$

where A is the 30–47 Hz submental power ($EMG_{submental(30–47Hz)}$), C is the 30–47 Hz frontalis power ($EMG_{frontalis(30–47Hz)}$) (unknown), D is the 55–85 Hz submental power ($EMG_{submental(55–85Hz)}$) and E is the 55–85 Hz frontalis power ($EMG_{frontalis(55–85Hz)}$). C is unknown but can be calculated from equation (1).

Actually we want to estimate the ratio B/C, where B is the 30–47 Hz total EEG power ($EEG_{scalp(30–47Hz)}$).

From equation (1),

$$B/C = (B \cdot D)/(A \cdot E) \quad (3)$$

Taking logs, and expressing in decibels,

$$10\log_{10}(B/C) = 10\log_{10}(B) + 10\log_{10}(D) - 10\log_{10}(A) - 10\log_{10}(E).$$

This will allow us to quantify the extent to which the total observed EEG power in the 30–47 Hz band ($EEG_{scalp(30–47Hz)}$) has been contaminated by frontalis EMG power. All the terms on the right-hand side of the equation are measurable experimentally.

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