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Propofol and Remifentanil Differentially Modulate Frontal Electroencephalographic Activity

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ABSTRACT

Background: The purpose of this study was to evaluate a new, physiologically inspired method for the analysis of the electroencephalogram during propofol–remifentanil anesthesia. Based on fixed-order autoregressive moving-average modeling, this method was hypothesized to be capable of dissociating the effects that hypnotic and analgesic agents have on brain electrical activity.

Methods: Raw electroencephalographic waves from a previously published study were reanalyzed. In this study, 45 American Society of Anesthesiologists status I patients were randomly allocated to one of three groups according to a specific target effect-site remifentanil concentration (0, 2, and 4 ng/ml). All patients received stepwise-increased targeted effect-site concentrations of propofol (Ce_{PROP}). At each step change in target Ce_{PROP}, the Observer's Assessment of Alertness/Sedation score was evaluated. Raw electroencephalograph was continuously acquired from frontal electrodes. Electroencephalography traces were analyzed using a fixed-order autoregressive moving average model to give derived measures of Cortical State and Cortical Input. Response surfaces were visualized and modeled using Hierarchical Linear Modeling.

Results: Cortical State (a measure of cortical responsiveness) and Cortical Input (a measure of the magnitude of cortical input) were shown to respond differently to Ce_{PROP} and effect-site remifentanil concentration. Cortical Input decreased significantly with increasing effect-site remifentanil concentration, whereas Cortical State remained unchanged with increasing effect-site remifentanil concentration but decreased with increasing Ce_{PROP}.

Conclusion: Because Cortical State responds principally to variations in Ce_{PROP}, it is a potential measure of hypnosis, whereas the dependence of Cortical Input on effect-site remifentanil concentration suggests that it may be useful as a measure of analgesic efficacy and the nociceptive–antinociceptive balance.

What We Already Know about This Topic

- Assessing depth of anesthesia by spontaneous electroencephalographic activity is limited
- Neurophysiology-based processed electroencephalographic monitoring in response to an arbitrary stimulus might improve performance

What This Article Tells Us That Is New

- In 45 patients undergoing surgery, fixed-order time-series modeling of electroencephalographic activity differentiated effects of the hypnotic propofol from those of the analgesic remifentanil
- This approach might enable independent monitoring of hypnotic and analgesic drug actions

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TO date depth of anesthesia monitoring has relied on a range of heuristic measures to objectively assess depth of anesthesia. The most successful existing methods are arguably those derived from the analysis of spontaneous or time-locked electroencephalographic activity.[1] In particular, the Bispectral Index® (BIS®; Aspect Medical Systems, Norwood, MA) has achieved a substantial level of routine clinical use because of its reported efficacy in defining optimal levels of hypnosis such that intraoperative awareness is minimized.[2] Although reportedly enabling anesthesia to be more optimally administered, it does so in the context of a number of well-documented limitations: not all hypnotic agents are reliably detected or monitored (nitrous oxide[3–6] and the short-acting synthetic opioids[7–9] being quintessential examples), and the index admits of no clear physiologic interpretation because it has been constructed to act as a quantitative surrogate for an ostensibly subjective state. Although a range of other processed electroencephalographic monitoring approaches have been developed in an attempt to circumvent such limitations or to improve on the predictive ability of the BIS in quantifying anesthesia, none has shown any clear advantage.[1] Such approaches include those based on spontaneous electroencephalographic activity, such as the Narcotrend index (Narcotrend®; Schiller AG, Baar, Switzerland) and the State Entropy and Response Entropy indices (M-entropy® module; GE Healthcare Finland Oy, Helsinki, Finland), and those based on analyzing the morphology of the middle latency auditory-evoked potential such as the A-Line ARX index (AAI®; formerly Danmeter A/S, Odense, Denmark, no longer trading). These indices, and a range of other empirical measures that are based on assumed changes in the complexity of the electroencephalogram signal with increasing depth of anesthesia, are all heuristic constructs. Because these measures are not derived from an understanding of the mechanisms responsible for the genesis of dynamical activity in the electroencephalogram, any anesthetic-induced electroencephalographic changes detected using such measures must necessarily be of suboptimal sensitivity and specificity and consequently will be of limited physiologic relevance. Therefore, the development of physiologically more specifically motivated processed electroencephalographic approaches would be expected to result in improved performance compared with existing methods. We outline one such approach and show that it is able to differentiate the effects of propofol and remifentanil on frontally recorded electroencephalograms. This has the potential to pave the way for monitoring the hypnotic effect of propofol independent of the analgesic effect of remifentanil, a feature absent in all existing processed clinical electroencephalogram-based monitoring approaches.[10]

The approach we will consider is based on a detailed theory of mammalian cortical electrorhythmogenesis.[11–13] In brief, it speculates that the rhythmic activity observed in the electroencephalogram arises from the reverberant activity of spatially distributed networks of excitatory and inhibitory cortical neurons. This theory is able to account for a number of electroencephalographic phenomena that are of relevance to better understand and monitor anesthesia—the benzodiazepine-induced "β buzz,"[13] the proconvulsant effects of the volatile general anesthetic agent enflurane,[14] and the biphasic surge in total electroencephalographic power that typically accompanies anesthetic induction and emergence.[11,15] Although the full theory is mathematically elaborate, it does suggest, to first approximation, that resting electroencephalography may be regarded as a filtered pseudorandom linear process. In particular, it posits that the electroencephalogram can be regarded as arising from cortex linearly filtering subcortical (thalamic) input. The direct empirical consequence is that the electroencephalogram can be modeled as a fixed-order autoregressive moving average (ARMA) process.[13] In this manner, the estimated ARMA coefficients characterize the properties of the "cortical" filter, whereas the estimated amplitude of the white noise driving corresponds to the assumed magnitude of the subcortical (thalamic) input. In subsequent analyses, a single scalar measure of the filter characteristics is referred to as Cortical State (CS), whereas the amplitude of the innovating noise is defined as the Cortical Input (CI). From a functional point of view, CS can be understood as characterizing the response of cortex to an arbitrary stimulus or input. Because of this increase in physiologic specificity, it was speculated that this fixed-order ARMA analysis would be able to detect the effects of agents not readily detected using other methods. Initial application of this method to sevoflurane in the presence of varying levels of adjuvant nitrous oxide[16] revealed that nitrous oxide, consistent with its antinociceptive properties, reduced CI but left CS unaffected.

To further investigate the relevance of fixed-order ARMA modeling for monitoring depth of anesthesia, we sought to determine whether the ultra–short-acting synthetic opioid remifentanil, like nitrous oxide, exerted its principle cortical effect by reducing CI. Even in the absence of specific noxious stimuli, we would expect there to be a "background" of subcortical input arising from ambient sensory stimulation that will be ablated by opioid action. In the study reported here, it is found that during propofol–remifentanil anesthesia CS responds principally to variations in propofol effect-site concentration (Ce_{PROP}) and is therefore a likely measure of hypnotic state, whereas CI responds dominantly to changes in remifentanil effect-site concentrations (Ce_{REMI}) and therefore might represent a measure of analgesic state (nociceptive–antinociceptive balance).

Materials and Methods

Patient Recruitment and Study Design

Raw electroencephalographic waves from a previously published study were reanalyzed.[17] The original study was approved by the institutional ethics committee (Ghent University Hospital, Ghent, Belgium) and written informed consent was obtained from 45 patients of American Society of Anesthesiologists status I, aged 18–60 yr, and scheduled

Table 1. Responsiveness Scores of the Modified Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

to undergo orthopedic surgery. Exclusion criteria were as follows: weight less than 70% or more than 130%, of ideal body weight (per table of Desirable Weights, Metropolitan Life Insurance, 1983), neurologic disorder, recent use of psychoactive medication or alcohol. Per study by Ferenets *et al.*[17], patients were randomly allocated to one of three groups: remi0, in which no remifentanil was given, and groups remi2 and remi4, in which effect compartment-controlled infusions of remifentanil were targeted at 2 and 4 ng/ml, respectively. Four minutes after the start of the remifentanil infusion, a "stair-case" computer-controlled infusion of propofol was commenced and initially targeted to an effect-site concentration of 0.75 μg/ml, which was subsequently increased every 4 min in steps of 0.25–0.3 μg/ml until the loss of response to all clinically relevant measurements of alertness and sedation was observed. Ten seconds before each increase in target propofol concentration, clinical assessment of the level of alertness and sedation was made using the Modified Observer's Assessment of Alertness/Sedation (OAA/S) (table 1). This scale is assessed by applying progressively more intense stimulation ranging from a moderate speaking voice to physical shaking or moderate noxious stimulus (trapezius squeeze) until a response is observed. Patients were considered responsive to vocal stimulus at OAA/S levels 5, 4, or 3 and scored as unresponsive to vocal stimulus at OAA/S levels 2, 1, or 0.

Propofol and remifentanil were administered *via* a computer-assisted continuous infusion device to a target effect-site concentration (RUGLOOP II; Demed, Temse, Belgium) using a three-compartment model enlarged with an effect-site compartment. For propofol, the pharmacokinetic-dynamic model previously published by Schnider *et al.*[18,19] was used. For remifentanil, the corresponding model used was that previously published by Minto *et al.*[20,21] Predicted effect-site propofol concentration (Ce_{PROP}) was computed to yield a time to peak effect of 1.6 min after bolus injection (also as published by Minto *et al.*,[22]) and pharmacokinetically confirmed in a clinical population by Struys *et al.*[23] For remifentanil, an age-dependent k_{e0} (effect-site elimination rate constant) value of $0.595 - 0.007 \times (\text{age} - 40)$ min^{-1} was applied as described by Minto *et al.*[20,21] Propofol and remifentanil infusions were administered using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base (Fresenius Vial Infusion Systems, Bresin, France). RUGLOOP II controls the pump at infusion rates between 0 and 1,200 ml/h *via* an RS232 interface. This infusion technique enables titration to a steady state defined as the equilibration between the calculated plasma and effect-site concentrations of the drug. To minimize the prediction error of the steady-state drug concentration at the time of clinical observation, an equilibration time of 4 min was allowed after every change of drug concentration before response to stimuli was tested. Remifentanil and propofol were infused *via* a large left forearm vein. Each patient received approximately 200 ml of crystalloid fluid during the study period. No fluid load was given before induction. None of the patients received any preanesthetic medication, and no other were drugs given. During the study period, all patients maintained spontaneous ventilation *via* a facemask delivering 6 l/min O_2.

Data Acquisition

Heart rate, noninvasive blood pressure, oxygen saturation measured by pulse oximetry, and capnography were monitored continuously using an S/5 Anesthesia Monitor (GE Healthcare, Helsinki, Finland) and recorded electronically using RUGLOOP II data management software. The raw electroencephalogram was recorded with the M-Entropy module of the S/5 Anesthesia Monitor and was sampled at 400 Hz, and written to disk, by using the S5-collect software. The standard entropy sensor was used with a slightly modified positioning: the two recording electrodes of the sensor were located bilaterally on the forehead approximately 5 cm above the eyebrows and 4 cm from the midline in either direction. The ground electrode was located between the two recording electrodes. This alternative montage was chosen to minimize electromyographic activity that normally contributes to the calculation of the State Entropy and Response Entropy measures, but for our purposes it is considered artifactual. This bifrontal montage gives rise to approximately the same mean electroencephalographic amplitudes as a unilaterally placed sensor.

Offline Signal Processing and Artifact Rejection

Both sampled raw and resampled raw electroencephalograms were used in subsequent analyses. Time series models (see Eqs.1 and 2 below) were fitted to resampled (from 400 to 80 Hz) raw electroencephalogram as per Liley *et al.*[16] As discussed therein, this was performed to avoid spurious fitting to 50-Hz spectral peaks or any low-pass filter band edges. Resampling was performed in MATLAB (Mathworks, Natick, MA) using a process of antialiasing filtering and downsampling. The antialias filter used was a finite impulse response filter with sharp cutoff at 40 Hz with the transition band made sufficiently sharp to minimize any aliasing.

Both the original and resampled electroencephalogram time series were segmented into 2-s 50% overlapping epochs and aligned with the respective measurements of estimated steady-state propofol concentration and OAA/S. For the original electroencephalogram time series, the electromyograph (defined as the total power between 70 and 110 Hz

excluding a notch at 98–102 Hz due to 50 Hz electric power harmonic at 100 Hz) was calculated. The root mean square (RMS) amplitude was calculated from the resampled electroencephalogram time series. Subsequently, an automated artifact rejection method was used to classify all epochs based on the original and resampled electroencephalogram time series. Epochs were excluded from further analysis if any of the following occurred: total electromyographic power greater than approximately 400 μV^2 or less than approximately 0.004 μV^2, RMS amplitude less than 5 μV or greater than 150 μV, amplitude distributions were not normal (based on Lilliefors[24] test at $P = 0.01$) or epochs to either side, of the epoch in question, were rejected. For each event (targeted propofol concentration or OAA/S observation), average CS, CI, RMS, and electromyogram were calculated for the 30 s preceding the event. If more than 50% of the corresponding epochs were corrupted then this event was not subsequently used.

CS and CI were calculated using the resampled electroencephalogram as described previously by Liley *et al.*[16] We now briefly summarize the salient details of this method. Based on significant experimental evidence that electroencephalogram recorded in the presence and absence of anesthesia can be modeled as a random linear process,[13,25–30] a linearized version of a fully nonlinear theory of electrorhythmogenesis was used to motivate fixed-order (ARMA) time series modeling. Specifically, the sampled electroencephalogram signal $s[n]$ was modeled using an (8,5) ARMA model

$$s[n] = -\sum_{k=1}^{k=8} a_k\, s[n-k] + \sum_{k=0}^{k=5} b_k\, u[n-k] \qquad (1)$$

or

$$A(z)S(z) = B(z)U(z) \qquad (2)$$

where $u[n]$ represents a stationary sequence of uncorrelated random variables of variance σ_u^2, a_k and b_k are the respective estimated autoregressive and moving average parameters. $S[z]$ and $U[z]$ are the respective Z-transforms of $s[n]$ and $u[n]$ (*i.e.*, $S[z] = Z\{s[n]\}$, $U[z] = Z\{u[n]\}$), $A(z) = 1 + a_1 z^{-1} + \ldots + a_8 z^{-8}$ and $B(z) = 1 + b_1 z^{-1} + \ldots + a_5 z^{-5}$. $\dfrac{B(z)}{A(z)}$ represents the electrocortical filter and describes how subcortical input (assumed to be so complicated as to be indistinguishable from an uncorrelated random process) is filtered to give rise to the surface recordable electroencephalogram. The theoretically derived autoregressive and moving average orders of 8 and 5 accord well with empirical determinations of optimal autoregressive (range, 3–14) and moving average (range, 2–5) orders obtained from resting awake eyes closed electroencephalogram using a range of information theoretic criteria.[27,30] The poles and zeros of the electrocortical filter are the respective solutions to $A(z) = 0$ and $B(z) = 0$. The poles and zeros of the estimated electrocortical filter are predicted to be of physiologic significance. For example, weakly damped poles will be seen as dominant oscillatory processes in the electroencephalogram (for example, the 8–13 Hz α rhythm). Therefore, tracking how the poles and zeros of the electrocortical filter change would seem to provide the best means of characterizing variations in the state of the electrocortical filter. One easily calculated scalar measure of the state of the electrocortical filter is the mean pole location. Therefore, for each resampled epoch $s[n]$, CS was calculated as the scaled mean pole location a_1. CI was calculated as the square root of the variance of $Z^{-1}\left\{\dfrac{A(z)S(z)}{B(z)}\right\}$ (*i.e.*, the variance of $s[n]$ divided by the power gain of the derived filter). Thus, CI represents the RMS amplitude of the noise innovating the electrocortical filter. The (8,5) ARMA model parameters were robustly determined with well-established methods,[31] using the ARMASA MATLAB Toolbox.[32] In brief, ARMASA removes the mean of the epoch then estimates an invertible and stationary ARMA model using a variant of Durbin methods with optimal intermediate autoregressive order.

Statistical Analysis

Normally distributed data were summarized as mean ± SD, and skewed data were given as median (range) and counts as number (%). Omnibus tests were performed using analysis of variance or the Kruskal–Wallis test appropriately based on the results of the Levene test for homogeneity of variance. *Post hoc* multiple comparisons were made using Tukey Honestly Significant Difference or the Mann–Whitney U test with Bonferroni correction wherever appropriate. All statistical analyses, except for the hierarchical linear modeling (see Eqs. 3 and 4 below), were performed using SPSS for Windows (version 16; SPSS Inc., Chicago, IL). A value of p less than 0.05 was considered statistically significant.

To assess the ability of CS and CI to indicate the subjects level of sedation, both prediction probability (P_k) and Spearman ρ were calculated. P_k is an asymmetric measure of ordinal association and is a rescaled version of the more familiar statistics Somers' d_{XY} and Kim's $d_{Y \cdot X}$.[33,34] In particular, $P_k \cong \dfrac{d_{XY} + 1}{2} = \dfrac{d_{Y \cdot X} + 1}{2}$, where X is the dependent variable (OAA/S level) and Y is the independent regressor variable (CI or CS). We chose to calculate P_k using Somers' D statistic in SPSS, which also provides an estimate of the Goodman and Kruskal approximate SE,[34] $\sigma_{SOMERS\ D}$. As a consequence, we define the SE of P_k, σ_{PK}, to be $\dfrac{\sigma_{SOMERS\ D}}{2}$. The P_k, and its SE, calculated in this way is reported to be associated with no significant bias compared with the corresponding jackknife estimates calculated using the PKMACRO of Smith *et al.*[34] P_k has a value of 1 when the indicator variable (CI or CS) predicts observed anesthetic depth perfectly and a value of 0.5 when the indicator predicts no better than a 50:50 chance. Because it is often reported, we also chose to calculate the Spearman rank correlation coefficient with correction for tied ranks. Although it has the advantage of avoiding distributional assumptions of other correlational measures, it has the disadvantage of lacking an

Table 2. Patient Demographics for No Remifentanil (Remi0), 2 ng/ml Remifentanil (Remi2), and 4 ng/ml Remifentanil (Remi4) Treatment Groups

Group	Age, yr (SD)	Height, cm (SD)	Weight, kg (SD)	M/F
Remi0	36 (10)	171 (10)	70 (8)	6/8
Remi2	33 (5)	168 (13)	67 (15)	5/9
Remi4	39 (8)	172 (9)	71 (16)	7/7

intrinsic meaning, in that its units depend very much on the ordinal scales used. This makes subsequent comparisons with other depth of anesthesia measures difficult. For this reason, P_k is typically preferred.

The relationship between Ce_{PROP} and Ce_{REMI} and the derived electroencephalographic measures of CI and CS was analyzed using hierarchical linear modeling (also known as multilevel analysis). This multilevel analysis is a more advanced form of simple multivariate linear regression.[35] This regression strategy was preferred because (1) we had no *a priori* reason to believe that CI and CS would follow a bivariate sigmoidal E_{max} model and (2) the data were nested, such that each participant will have had CI and CS measured at one target remifentanil concentration but multiple target propofol concentrations; that is, data are first grouped with respect to Ce_{REMI} and with respect to Ce_{PROP}. Specifically, the following two-level mixed effects model was posed

$$y = \sum_{n=0}^{n=N} \beta_n(R) P^n + \varepsilon \quad (3)$$

$$\beta_n(R) = \sum_{m=0}^{m=M_n} \gamma_{nm} R^m + u_n \quad (4)$$

where y is either CI or CS, P and R are Ce_{PROP} and Ce_{REMI}, respectively, and ϵ and u_n are error terms (assumed to be normally distributed). Default regressor orders were set to cubic (*i.e.*, $N = 3$, $M_n = 3$) for initial exploratory analyses. Fitting was performed using HLM 6.08 (Scientific Software International, Lincoln, IL). Optimal regressor orders were subsequently determined based on the residual variance, the structural simplicity of the model, the homogeneity of the level 1 residuals of regression, and the collinearity of the level 2 Mahalanobis distance (test of normality/outliers) and chi-square measures. A linear relationship between the Mahalanobis distance and chi-square supports the assumption of normality in the data and ensures that no outliers have biased any of the estimated regression coefficients. All possible residual covariance terms were used for the level 2 modeling.

Results

All changes in hemodynamic and capnography were within clinical limits (data not presented). The demographic data for all patients are given in table 2.

Relationship between Electroencephalographic Measures and Clinical Assessments of Patient State

Approximately 23% of all 2-s electroencephalogram epochs were rejected because of artifact. This resulted in elimination of 9% of all OAA/S measurements as a result of the absence of sufficient artifact-free electroencephalogram (see Materials and Methods for further details). Figure 1 shows box and whisker plots for CS, CI, RMS, and electromyographic activity *versus* OAA/S levels for each remifentanil treatment group. CS and electromyogram clearly decrease with decreas-

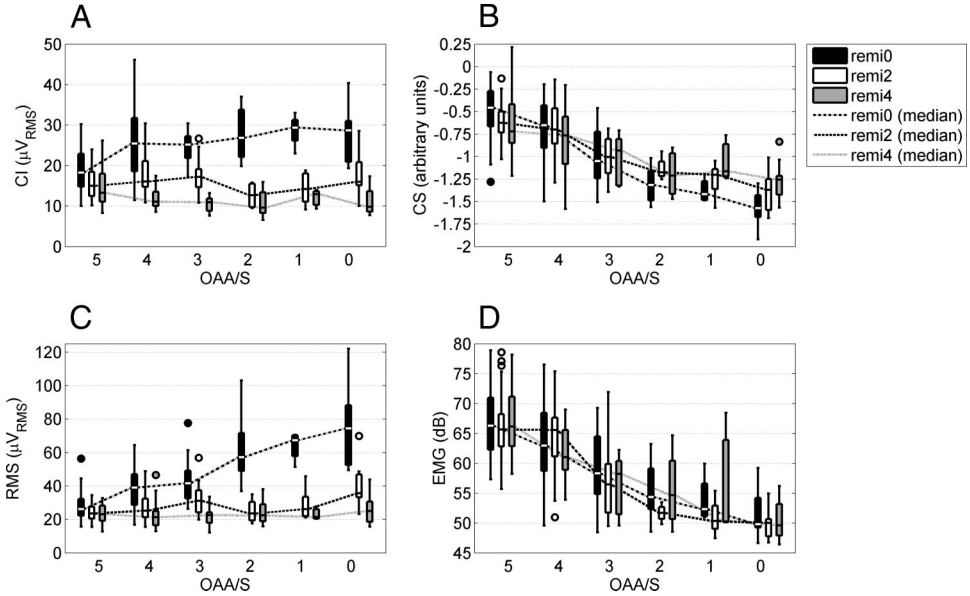

Fig. 1. Box-and-whisker plots for derived electroencephalographic measures as a function of the Observer's Assessment of Alertness/Sedation (OAA/S) level for no remifentanil (remi0), 2 ng/ml remifentanil (remi2), and 4 ng/ml remifentanil (remi4) treatment groups. *Boxes* represent interquartile ranges, *lines enclosed within boxes* (and *connected lines*) median values, *whiskers* represent the largest (smallest) nonoutlier, and *circles* represent outliers (defined as values extending further than 1.5 times the interquartile range—equivalent to approximately 3 SDs for normally distributed data). (*A*) Cortical Input (CI), (*B*) Cortical State (CS), (*C*) root mean square (RMS) electroencephalogram amplitude, and (*D*) electromyogram (EMG).

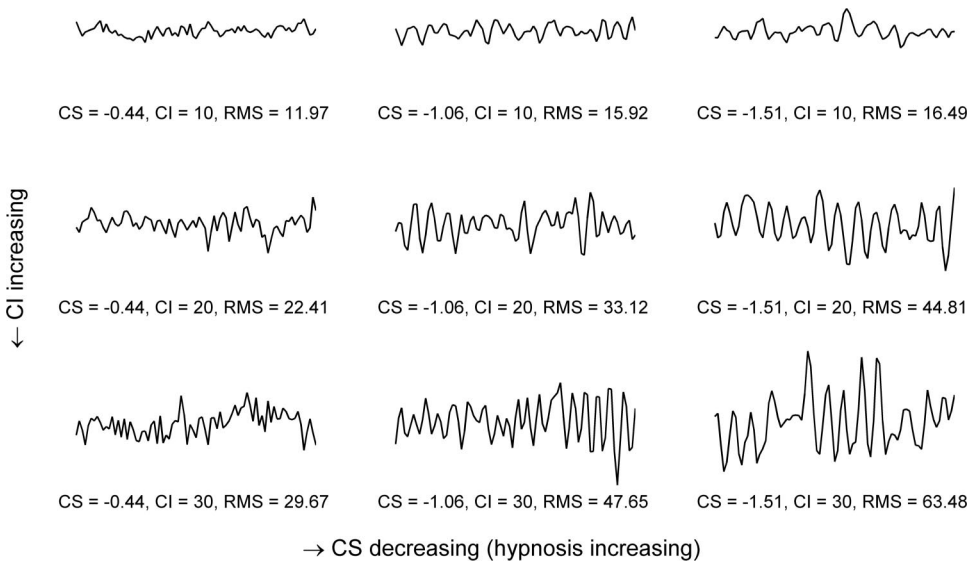

Fig. 2. Examples of synthetic 2-s epochs of electroencephalogram data illustrating the independence of Cortical Input (CI) and root mean square (RMS) electroencephalogram amplitude. Each column of this figure represents a realization of a fixed autoregressive moving average process, estimated from an artifact-free 2-s epoch of electroencephalogram to which a Gaussian white-noise innovation of differing amplitudes was applied. The 2-s electroencephalogram epochs were chosen at random from the recorded electroencephalogram of a patient in the treatment group that received no remifentanil (remi0) at various levels of estimated hypnosis (Cortical State [CS]). Note that for a fixed CS (column-wise), CI and RMS covary, whereas for varying CS (row-wise), CI remains fixed while RMS varies.

ing levels of consciousness, whereas CI and RMS are seen to be largely independent of the clinically assessed patient state. However, as confirmed subsequently by hierarchical linear modeling (see Relationship between Electroencephalographic Measures and Effect-site Remifentanil and Propofol Concentrations below), significant differences in these latter measures were observed as a function of predicted effect-site remifentanil concentration and were increasingly marked at

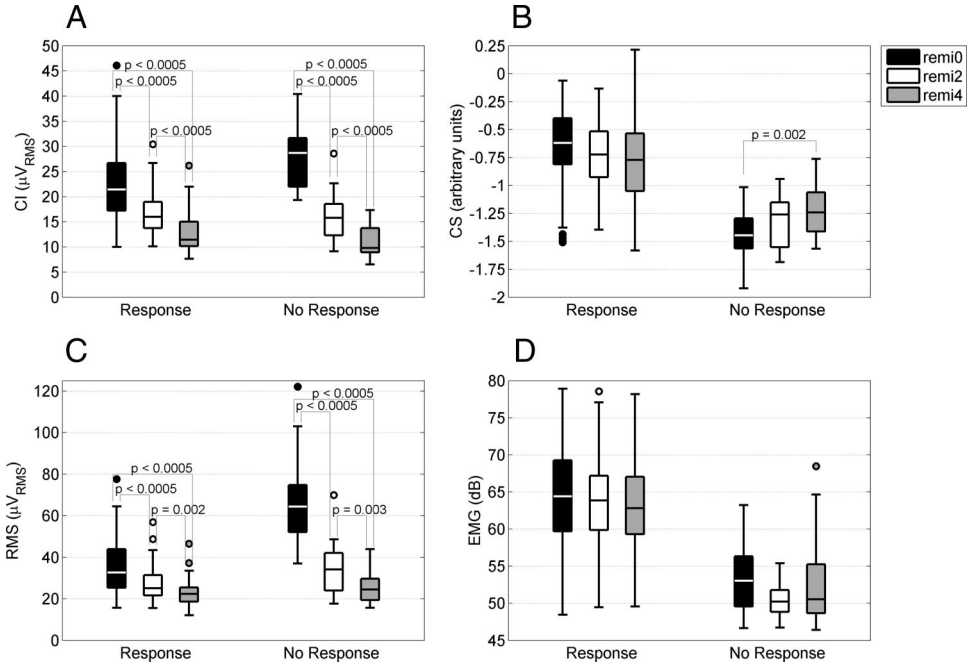

Fig. 3. Box-and-whisker plots for derived electroencephalographic measures for loss of vocal response for no remifentanil (remi0), 2 ng/ml remifentanil (remi2), and 4 ng/ml remifentanil (remi4) treatment groups. *Boxes* represent interquartile ranges, *lines enclosed within boxes* (and *connected lines*) median values, *whiskers* represent the largest (smallest) nonoutlier, and *circles* represent outliers (defined as values extending an additional 1.5 times the interquartile range—approximately equivalent to 3 SDs for normally distributed data). (*A*) Cortical Input (CI), (*B*) Cortical State (CS), (*C*) root mean square (RMS) electroencephalogram amplitude, and (*D*) electromyogram (EMG).

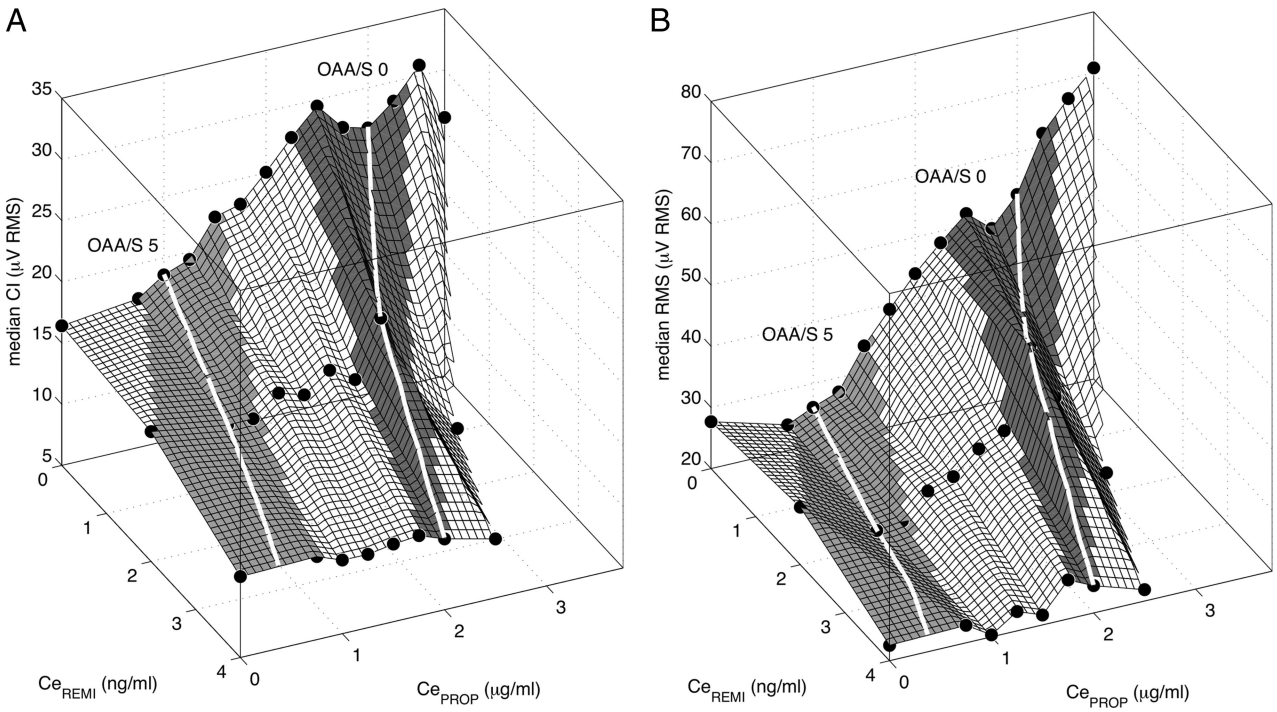

Fig. 4. (*A*) Median Cortical Input (CI) *versus* target remifentanil (Ce_{REMI}) and propofol (Ce_{PROP}) concentrations. Mesh represents the linearly interpolated surface through data (*filled circles*). Interquartile (25th–75th percentile) ranges of target propofol concentration for a given Observer's Assessment of Alertness/Sedation (OAA/S) level and remifentanil level are shown as shaded (OAA/S 5 = *light gray*, OAA/S 0 = *dark gray*) patches on the interpolated surface. Median values correspond to the respective *solid white line*. This surface together with the shaded interquartile ranges indicates that for a fixed OAA/S level and target propofol concentration, CI decreases with increasing Ce_{REMI}. (*B*) Median root mean square (RMS) electroencephalogram amplitude *versus* Ce_{REMI} and Ce_{PROP}. All other details as for *A*.

deeper levels of clinically assessed sedation. In particular, at OAA/S level 0 (unresponsive to painful stimulus), CI displayed significant reductions with increasing predicted effect-site remifentanil concentration. The similarity between the changes in CI and RMS as a function of OAA/S levels is a reflection of the fact that the former measure depends on the latter for its calculation. Nevertheless, as illustrated in figure 2 CI can remain fixed whereas RMS changes depending on variations in CS. Therefore, despite its simpler calculation, RMS cannot be used as a proxy for CI. In contrast, the similarity between CS and the estimated electromyogram cannot be a consequence of the method of their calculation because the latter is calculated only on recorded scalp electrical activity between 70 and 110 Hz, whereas the former is calculated on the range of 0–40 Hz. On this basis, we can reasonably speculate that CS and the estimated electromyogram are related at a deeper physiologic level.

Relationship between Electroencephalographic Measures and Loss of Response to Vocal Stimulus

Because CI and CS are being assessed with respect to their ability to characterize the level of sedation in the presence of remifentanil, it is important to determine their ability to predict loss of response. On this basis, the above OAA/S data were dichotomously aggregated into either the presence or absence of response to vocal stimulus. Loss of response to a vocal stimulus corresponds to the transition from OAA/S level 3 (responds only after name is called loudly or repeatedly) to OAA/S level 2 (responds only after mild prodding or shaking). Therefore, OAA/S levels 5–3 are treated as responsive to verbal command, whereas OAA/S levels 2–0 are defined as unresponsive to verbal command. Figure 3 shows the box and whisker plots for this aggregated data. As expected from figure 1, CS and the electromyogram are particularly sensitive to the loss of response to vocal stimulus.

Relationship between Electroencephalographic Measures and Effect-site Remifentanil and Propofol Concentrations

Figures 4 and 5 show interpolated surface plots of median CI, CS, RMS, and electromyogram as a function of predicted effect-site remifentanil and propofol concentrations. In general, it is observed that median CI and RMS (fig. 4) vary with propofol and remifentanil concentration, whereas CS and the electromyogram (fig. 5) principally depend on variations in target propofol levels. The results of the hierarchical linear modeling (tables 3 and 4) confirm that significant reductions in CI occur with increasing effect-site remifentanil concentration as for fixed propofol levels CI is negatively correlated (γ_{11} is less than 0) with remifentanil level. It is notable that none of the level 2 random effects for CI are significant, implying that individual level differences were not important contributors to CI

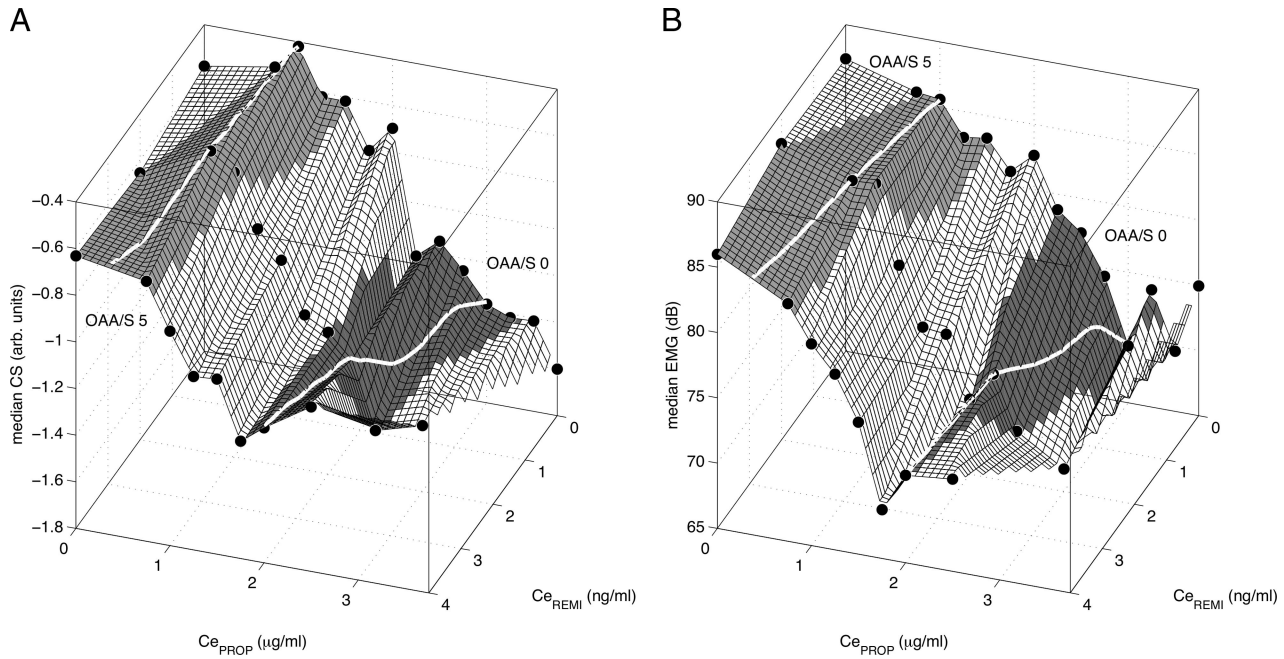

Fig. 5. (*A*) Median Cortical State (CS) *versus* target remifentanil (Ce_{REMI}) and propofol (Ce_{PROP}) effect-site concentrations. Mesh represents the linearly interpolated surface through data (*filled circles*). Interquartile (25th–75th percentile) ranges of target propofol concentration for a given Observer's Assessment of Alertness/Sedation (OAA/S) level and remifentanil level are shown as shaded (OAA/S 5 = *light gray*, OAA/S 0 = *dark gray*) patches on the interpolated surface. Median values correspond to the respective *solid white line*. This surface together with the shaded interquartile ranges indicates that for a fixed OAA/S level and target propofol concentration, CS remains unchanged with increasing Ce_{REMI}. (*B*) Median electromyographic (EMG) activity *versus* Ce_{REMI} and Ce_{PROP}. All other details as for *A*.

variability. In contrast, CS is found to be independent of remifentanil level, because the optimum hierarchical linear model does not depend on target remifentanil concentration. In further contrast to CI, some of the level 2 random effects for CS were significant, allowing us to infer that individual level differences were making some contribution to CS variability.

Prediction Probability (P_k) and Spearman ρ for Clinically Assessed Levels of Sedation

Prediction probability (P_k) and Spearman ρ are measures of ordinal association and provide information regarding how well quantitative measures of sedative state correlate with clinically relevant endpoints. Tables 5–7 show P_k and ρ.

Table 3. Results of Hierarchical Linear Modeling of the Effects of Target Remifentanil and Propofol Effect-site Concentration on Cortical Input (CI)

Fixed Effect	Coefficient	SE (Robust)	*t* Ratio	*P* Value
β_0				
γ_{00}	162.569	8.065	20.079	<0.0005
β_1				
γ_{11}	−17.500	2.080	−9.641	<0.0005
β_2				
γ_{20}	40.091	5.673	6.981	<0.0005
β_3				
γ_{30}	−8.941	1.588	−5.758	<0.0005
Random Effect	**Variance Component**	***df***	**Chi-square**	
u_0	2461.937	35	141.125	<0.0005
u_1	1902.514	35	40.351	0.245
u_2	965.518	35	37.101	0.372
u_3	23.420	35	38.072	0.331
ϵ	548.473			

Estimated effects of target remifentanil (Ce_{REMI}) and propofol (Ce_{PROP}) effect-site concentrations on CI for the model $CI = \gamma_{00} + \gamma_{11}R \times P + \gamma_{20}P^2 + \gamma_{30}P^3 + u_0 + u_1P + u_2P^2 + u_3P^3 + \epsilon$, where P and R are Ce_{PROP} and Ce_{REMI}, respectively, and ϵ and u_n are normally distributed error terms. Because $\gamma_{11} < 0$ and the associated $p < 0.0005$, we conclude that CI is significantly negatively correlated with the product of Ce_{REMI} and Ce_{PROP}. All possible residual covariance terms were used for the level 2 modeling (data not shown).
df = degress of freedom.

Table 4. Results of Hierarchical Linear Modeling of the Effects of Target Remifentanil and Propofol Effect-site Concentration on Cortical State (CS)

Fixed Effect	Coefficient	SE (Robust)	*t* Ratio	*P* Value
β_0				
γ_{00}	−0.588	0.050	−11.754	<0.0005
β_1				
γ_{10}	0.381	0.102	3.737	0.001
β_2				
γ_{20}	−0.559	0.078	−7.162	<0.0005
β_3				
γ_{30}	0.106	0.016	6.648	<0.0005
Random Effect	**Variance Component**	***df***	**Chi-square**	
u_0	0.241	35	105.646	<0.0005
u_1	0.445	35	48.715	0.061
u_2	0.363	35	62.983	0.003
u_3	0.078	35	73.039	<0.0005
ϵ	0.026			

Estimated effects of target remifentanil (Ce_{REMI}) and propofol (Ce_{PROP}) effect-site concentrations on CS for the model $CS = \gamma_{00} + \gamma_{10}P + \gamma_{20}P^2 + \gamma_{30}P^3 + u_0 + u_1P + u_2P^2 + u_3P^3 + \epsilon$, where P and R are Ce_{PROP} and Ce_{REMI}, respectively, and ϵ and u_n are normally distributed error terms. This optimal model allows us to conclude that CS depends significantly on Ce_{PROP} but is independent of Ce_{REMI}. All possible residual covariance terms were used for the level 2 modeling (data not shown).

df = degress of freedom.

These tables show measures of ordinal association calculated at all OAA/S levels, OAA/S levels 0 and 5, and dichotomized levels, respectively. These tables reveal that CI, and to a lesser extent RMS, are not predictive of the level of sedation, whereas CS and the electromyogram are highly predictive of sedative state. Therefore, we can conclude that CS represents a meaningful measure of the hypnotic state, whereas CI is essentially uncorrelated with the level of sedation. It is worth noting that the P_k values obtained for CS and the electromyogram are in the same range as those obtained in previous studies using other indices of depth of anesthesia, such as the BIS and State Entropy and Response Entropy indices.

Discussion

The electroencephalographic monitoring of anesthetic depth has well and truly become a part of standard anesthetic practice; it may become an important component of standard-of-care patient monitoring during surgery in a manner similar to that of pulse oximetry.[36] However, unlike pulse oximetry, the physiologic underpinnings of electroencephalographic monitoring remain somewhat obscure. For example, doubts remain about whether processed electroencephalographic measures are characterizing the response of brain electrical activity to anesthetic effect or are merely measuring the effects of these agents in ameliorating tonic electromyographic activity.[37] This is arguably due in large part to the fact that the physiologic mechanisms responsible for the generation of rhythmic activity in the electroencephalogram remain unresolved. As a consequence, all processed electroencephalographic measures of depth of anesthesia have had to depend on the application of a range of heuristic, and thus physiologically arbitrary, criteria. This physiologically nonspecific "black-box" analysis can be argued to underlie the current inability of the BIS and other processed measures to detect, and thus monitor, a range of anesthetic agents that include the opioids and nitrous oxide. Therefore, the development of better physiologically motivated methods for the analysis and characterization of electroencephalographic activity can be reasonably speculated to result in more sensitive and specific methods for monitoring brain state during anesthesia. In this article, we have evaluated this proposition using a physiologically motivated linear time series analysis method[13,16] and

Table 5. Prediction Probability (P_k) and Spearman ρ, plus the Respective SE, Calculated over All OAA/S Levels

	CI		CS		RMS		EMG	
	P_k (SE)	ρ (SE)	P_k (SE)	ρ (SE)	P_k (SE)	ρ (SE)	P_k (SE)	ρ (SE)
Remi0	0.709 (0.029)	−0.489 (0.060)	0.838 (0.022)	0.724 (0.045)	0.835 (0.022)	−0.726 (0.044)	0.785 (0.025)	0.636 (0.052)
Remi2	0.533 (0.045)	−0.077 (0.108)	0.826 (0.024)	0.744 (0.045)	0.686 (0.038)	−0.441 (0.086)	0.836 (0.026)	0.758 (0.050)
Remi4	0.649 (0.048)	0.356 (0.109)	0.763 (0.030)	0.625 (0.061)	0.518 (0.050)	−0.041 (0.119)	0.850 (0.031)	0.772 (0.056)
All	0.527 (0.025)	−0.063 (0.059)	0.814 (0.014)	0.707 (0.028)	0.651 (0.023)	−0.351 (0.053)	0.819 (0.015)	0.712 (0.031)

CI = Cortical Input; CS = Cortical State; EMG = electromyogram; OAA/S = Observer's Assessment of Alterness/Sedation; Remi0 = patient group receiving no remifentanil; Remi2 = patient group receiving 2 ng/ml remifentanil; Remi4 = patient group receiving 4 ng/ml remifentanil; RMS = root mean square electroencephalogram amplitude.

Table 6. Prediction Probability (P_k) and Spearman ρ, plus the Respective SE, Calculated over OAA/S Levels 5 (Responds Readily) and 0 (No Response to Painful Stimulus)

	CI		CS		RMS		EMG	
	P_k (SE)	ρ (SE)	P_k (SE)	ρ (SE)	P_k (SE)	ρ (SE)	P_k (SE)	ρ (SE)
Remi0	0.858 (0.053)	−0.517 (0.088)	1.000 (0.000)	0.722 (0.063)	0.992 (0.009)	−0.710 (0.063)	0.995 (0.006)	0.715 (0.063)
Remi2	0.642 (0.097)	−0.232 (0.158)	0.997 (0.004)	0.812 (0.046)	0.914 (0.054)	−0.677 (0.096)	1.000 (0.000)	0.817 (0.046)
Remi4	0.765 (0.085)	0.439 (0.142)	0.962 (0.029)	0.765 (0.063)	0.542 (0.110)	−0.069 (0.182)	1.000 (0.000)	0.828 (0.044)
All	0.550 (0.063)	−0.078 (0.099)	0.991 (0.006)	0.771 (0.032)	0.787 (0.053)	−0.451 (0.085)	0.998 (0.002)	0.782 (0.032)

CI = Cortical Input; CS = Cortical State; EMG = electromyogram; OAA/S = Observer's Assessment of Alertness/Sedation; Remi0 = patient group receiving no remifentanil; Remi2 = patient group receiving 2 ng/ml remifentanil; Remi4 = patient group receiving 4 ng/ml remifentanil; RMS = root mean square electroencephalogram amplitude.

have shown, in contrast to existing processed measures, that the effect of remifentanil on frontally recorded spontaneous electroencephalograms can be dissociated from that of propofol. The existing literature paints a complex picture of the effects of opioids on the electroencephalogram. For example, the sole administration of remifentanil is often reported to cause a dose-dependent slowing of the electroencephalogram, but typically only for levels much higher than those used in the current study.[20,38–40] In contrast, remifentanil, when administered with propofol, is generally reported to have no effect on derived electroencephalographic parameters such as the BIS[41–48] but is occasionally found to result in an increase[49,50] or a decrease[51–56] in such derived measures of hypnosis. The contention that opioids such as remifentanil produce a predictable dose-dependent slowing of the electroencephalogram is not borne out by our own results, because CS remains unchanged to variations in the level of remifentanil. Although CS was unaffected by remifentanil, it nevertheless remains a possibility that CI and RMS were affected indirectly due to increased arterial carbon dioxide levels. In experimentally induced hypercapnia in animals, increased arterial carbon dioxide levels are correlated with reductions in resting amplitude of the electroencephalogram.[57,58] Although end-tidal carbon dioxide levels were within clinical limits in our study, future studies involving CS and CI should have these levels percutaneously measured to ensure that increased carbon dioxide levels are not acting as a confounding influence.

In contrast to the BIS[59] and State Entropy and Response Entropy[60] indices, our method does not depend on quantifying the changes in either the nonlinearity or complexity of brain activity that are hypothesized to attend anesthetic action. We have found, somewhat surprisingly, that putative measures of hypnosis and analgesic drug action can be defined based on a relatively standard but physiologically constrained linear signal analysis technique. The constrained use of this linear technique has emerged from a detailed theory for the rhythmogenesis of the electroencephalogram[12] that has been successfully applied to modeling the effects of anesthetics on brain electrical activity.[11,14] Therefore, the possibility exists that estimated ARMA parameters (see Eq. 1) may be theoretically more specifically linked to the central modes and sites of drug action, thus suggesting additional methods by which anesthetic action may be better monitored. Because the computational demands of the fixed-order ARMA method are relatively modest, it can easily be calculated in real time using dedicated hardware similar to that used in BIS® monitoring.

The derived electroencephalogram measures of CS (a measure of the responsiveness of cortex) and CI (a measure of the magnitude of cortical input) were shown to respond differentially to target propofol and remifentanil effect-site concentrations. In particular, it was found, on the basis of hierarchical linear modeling, that CI decreased significantly with increasing target remifentanil concentration, whereas CS was found to be statistically independent of variations in effect-site remifentanil level. Both CS and CI responded to effect-site propofol levels: CS monotonically decreased, whereas CI responded nonuniformly depending on remifentanil level; propofol was agonistic at low remifentanil levels but antagonistic at high remifentanil levels. The reduction in CI is consistent with the reported effects of remifentanil in atten-

Table 7. Prediction Probability (P_k) and Spearman ρ, plus the Respective SE, Calculated over Aggregated OAA/S Levels 5–3 (Responsive) and Levels 2–0 (Nonresponsive)

	CI		CS		RMS		EMG	
	P_k (SE)	ρ (SE)	P_k (SE)	ρ (SE)	P_k (SE)	ρ (SE)	P_k (SE)	ρ (SE)
Remi0	0.725 (0.047)	−0.320 (0.069)	0.951 (0.017)	0.641 (0.045)	0.939 (0.021)	−0.625 (0.048)	0.911 (0.027)	0.585 (0.051)
Remi2	0.550 (0.073)	0.075 (0.111)	0.928 (0.026)	0.654 (0.054)	0.691 (0.069)	−0.292 (0.106)	0.960 (0.018)	0.703 (0.049)
Remi4	0.653 (0.073)	0.246 (0.117)	0.836 (0.046)	0.540 (0.078)	0.578 (0.074)	−0.125 (0.118)	0.883 (0.049)	0.616 (0.084)
All	0.508 (0.043)	0.012 (0.065)	0.916 (0.016)	0.628 (0.031)	0.676 (0.040)	−0.265 (0.061)	0.919 (0.019)	0.632 (0.035)

CI = Cortical Input; CS = Cortical State; EMG = electromyogram; OAA/S = Observer's Assessment of Alertness/Sedation; Remi0 = patient group receiving no remifentanil; Remi2 = patient group receiving 2 ng/ml remifentanil; Remi4 = patient group receiving 4 ng/ml remifentanil; RMS = root mean square electroencephalogram amplitude.

uating a range of somatosensory and auditory-evoked potentials,[10,61] thus providing further weight to the notion that this derived measure is indeed quantifying some aspect of input to cortex. At present, we do not know why propofol alone increases CI, but we can speculate that it is due to its differential effects on a range of subcortical structures that contribute to cortical input. Because propofol enhances inhibitory activity through the potentiation of γ-aminobutyric acid receptor subtype A activity, it can result in the inhibition or disinhibition of activity depending on how it differentially modulates inhibitory activity terminating on excitatory and inhibitory neurons. Indeed, there is good evidence to suggest that such differential binding is responsible for the characteristic increase in β (13–30 Hz) band electroencephalogram activity seen with most sedatives and anesthetics.[13]

We chose to model drug effect using hierarchical linear modeling,[35] rather than the more familiar bivariate sigmoidal E_{max} models,[51,62–64] principally because a bivariate sigmoidal E_{max} model contains insufficient degrees of freedom to account for the dependency of CI and CS on target drug concentrations. Although a great deal of pharmacodynamic effects and interactions are plausibly based on the paradigm of molecular mass action, there is no *a priori* reason to believe that our processed measures of CS and CI will adhere to such a principle. CS and CI characterize the collective activity of many thousands of neurons, interacting over many temporal and spatial scales, and thus the steps between the microscopic details of drug binding and the consequent macroscopic physiologic effect are simply too complicated to be accounted for by a uni- or bivariate monotonic dose–response relationship. Indeed, even in the study of much simpler pharmacologic processes, sigmoid dose–response relationships, although common, are not universal—linear, linear–quadratic, log–linear, and exponential best–fit relationships are also found.[63] Although our use of hierarchical linear modeling is not fully general, it is nevertheless more flexible in that it is able to statistically account for the nonuniform dose–response relationship (propofol agonistic at low remifentanil levels but antagonistic at high remifentanil levels; see fig. 4A) that we have observed between CI and remifentanil and propofol concentrations. A further reason for choosing hierarchical linear modeling over sigmoid-based curve-fitting strategies is the issue of the nesting of patient data. The nesting of these data arises because variance and covariance cannot be expected to be distributed uniformly across repeated observations and patients. As far as we are aware, such heteroscedasticity cannot be dealt with by NONMEM.

At this point in time, the optimal response surface models relating CI and CS to drug levels admit of no obvious physiologic interpretation. Nevertheless, they provide clear statistical evidence for the contention that increases in remifentanil levels are associated with a significant reduction in CI, whereas CS remains unaffected. The significance of our finding of a correlation of CI with remifentanil level is underscored by the development of the surgical stress index.** The surgical stress index, developed to provide a measure of analgesic efficacy during surgery, is based on a sum of the normalized pulse beat interval and the pulse wave amplitude time series of the photoplethysomogram. A number of studies have shown it to correlate well with target-controlled remifentanil levels[65] and the probability of response to a noxious stimulus.[66] Therefore, given its clear dependence on target remifentanil level, CI should be compared prospectively with the surgical stress index, under conditions involving noxious surgical stimuli, as a potential additional measure of the nociception–antinociception balance. CI may have a number of specific advantages in that it may reflect both the central and autonomic responses to noxious stimuli. Being able to differentiate the effects of a hypnotic agent and an analgesic agent, as is done here, is a necessary first step toward the development of such an index of analgesic state.

On the basis of our results, we speculate that CS and CI provide "orthogonal" measures of hypnosis and analgesia. In particular, as per our hypothesis, we found CI had a P_k of approximately 0.5, meaning it was no better than chance in predicting sedative state. In contrast, CS had a much higher P_k of approximately 0.8, meaning that it was a meaningfully predictive method of the level of hypnosis as quantified by OAA/S assessment. The values of P_k obtained for CS are in the same range as those seen in similar studies involving other quantitative depth of anesthesia measures such as BIS and State Entropy and Response Entropy indices. Although CI and RMS seemed to be correlated, the P_k of the latter (~0.65) was intermediate between that of CI and CS and thus would be neither a good measure of sedative state nor a potential measure of analgesia.[48,50,55] Because of the lack of any significant correlation between the measures of CS and CI, they may subsequently be found to have utility in guiding clinical decision support during the control and administration of balanced anesthesia.[67]

Denny Myer, Ph.D., Senior Lecturer in Biostatistics, Faculty of Life and Social Sciences, Swinburne University of Technology, Hawthorn, Victoria, Australia, advised on the use of hierarchical linear modeling.

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** Expected to be renamed the Surgical Pleth Index (SPI) by the manufacturer (GE Healthcare, Helsinki, Finland).[64]

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