

Dissociating the effects of nitrous oxide on brain electrical activity using fixed order time series modeling

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Abstract

A number of commonly used anesthetics, including nitrous oxide (N₂O), are poorly detected by current electroencephalography (EEG)-based measures of anesthetic depth such as the bispectral index. Based on a previously elaborated theory of electrocortical rhythmogenesis we developed a physiologically-inspired method of EEG analysis that was hypothesized to be more sensitive in detecting and characterising N₂O effect than the bispectral index, through its combined EEG estimates of cortical input and cortical state. By evaluating sevoflurane-induced loss of consciousness in the presence of low brain concentrations of N₂O in thirty eight elective surgical patients, N₂O was associated with a statistically significant reduction in the *input* the frontal cortex received from other cortical and subcortical areas. In contrast the bispectral index responded only to low, but not to high, concentrations of N₂O.

Keywords: electroencephalogram, anesthesia, nitrous oxide, sevoflurane, autoregressive moving-average model

1. Introduction

General anesthetic agents have a long history of successful use. Since the pioneering use of ether, chloroform and nitrous oxide (laughing gas, N_2O) as general anesthetic agents in the first half of the nineteenth century, the range of agents available to induce and maintain the anesthetized state has evolved to the point that anesthesia is among the safest of medical procedures. However, despite the significant advances in anesthetic practice, our understanding of the mechanisms of general anesthetic drugs remains incomplete. This lack of understanding has necessarily complicated attempts to monitor anesthetic depth such that levels of unconsciousness, immobility and analgesia are optimized. As a consequence of the uncertain and complex relationships between the molecular and cellular targets of anesthetic action, on the one hand, and the macroscopic or behavioral effects on the other, a range of heuristic monitoring approaches have been developed, the best known of which is a processed EEG measure called the bispectral index (BIS).

While the specific algorithms underpinning the monitoring approaches of the BIS and other proprietary EEG based depth of anesthesia monitoring approaches are not fully known, it is reasonably certain that most depend on the loss of high frequencies, and the shift to low frequencies, in order to quantify the level of anesthetic drug effect. While the BIS has been reported to correlate with anesthetic concentration and depth of hypnosis (1, 2) it and other quantitative EEG approaches suffer from two, possibly

interrelated, limitations. Firstly, as all currently available commercial monitoring approaches rely on a set of heuristic criteria obtained from the statistical phenomenology of the EEG in response to anesthetic drugs, there is necessarily no relationship between the indices so derived and the underlying physiological consequences of drug effect. This lack of physiological specificity is problematic as anesthetic agents have been shown to have multiple sites of action in the CNS, the relative actions of which determine clinically relevant levels of sedation, hypnosis, analgesia and immobility (3).

Secondly, some commonly-used anesthetics, such as N₂O (4-7) and the opioids (8-10), have little or no effect on EEG based measures of depth of anesthesia, thus limiting their usefulness and reliability. In the case of N₂O this has been attributed to its weak cortical action and the fact that it is believed to act mainly through the activation of descending inhibitory nor-adrenergic pathways in the brainstem and spinal cord (11). These sub-cortical actions of N₂O are completely undetectable by the algorithm that computes the BIS (12), but are associated with concentration dependent reductions in the amplitudes of a range of early- and mid- latency cortically recordable evoked potentials, indicating that N₂O principally attenuates afferent sensory input to cortex (13-18) .

A recently developed, physiologically inspired, method of EEG signal analysis may address these deficiencies of the BIS and other processed EEG measures of depth of anesthesia (19), by enabling the separation of the cortical and sub-cortical actions of anesthetics. This method, based on a theory developed by one of the authors (20), enables the empirical separation of changes in EEG activity that arise from modulations

in the *responsiveness (or state) of cortex*, from changes that arise due to changes in the magnitude of the *input to cortex*. The underlying theory has already been able to account for a number of EEG phenomena that are of relevance to better understanding and monitoring anesthesia, which include the benzodiazepine induced “beta buzz” (19), the pro-convulsant properties of some general anesthetic agents (21) and the biphasic surge in total EEG power that typically occurs during anesthetic induction (22, 23). While the full theory is mathematically elaborate (see for example Liley et al 2002), it does suggest that resting EEG can be meaningfully understood as arising from cortex acting as a linear filter on its input, and as such can be modeled as a fixed order autoregressive moving average (ARMA) process. In this manner the coefficients of the filter (theoretical and modeled) provide information regarding the *responsiveness (or state) of cortex*, whereas the amplitude of the random driving (theoretical or modeled) represents the magnitude of the *input to cortex*.

To evaluate the effectiveness and clinical relevance of this approach it was decided to quantify, and thereby attempt to dissociate, the EEG effects of anesthesia induced in the presence of N₂O. In particular N₂O is expected to result in a reduction in *input to cortex* for a fixed hypnotic state (loss of response to verbal command, LOR), but to leave the *responsiveness (or state) of cortex* unmodified. We therefore compared the ability of measures of cortical input and cortical state with the BIS to detect significant EEG changes at LOR during the induction of anesthesia with 4% inspired sevoflurane in the presence of either 0%, 33% or 66% inspired concentration of N₂O.

2. Methods

2.1 Patients and Anesthesia

With approval from the Human Research Ethics Committee of the Royal Melbourne Hospital and written informed consent, 69 patients aged >18 years and of American Society of Anesthesiologists' physical status I-II, presenting for surgery under general anesthesia, were recruited. Exclusion criteria included conditions or medications known to affect the EEG, a risk of gastro-esophageal reflux during inhaled induction, and inability to communicate in English, due to a language barrier, cognitive deficit or intellectual disability. Patients were randomised to receive sevoflurane 4% with 100% oxygen (O₂) (100% O₂ group), 33% N₂O in O₂ (33% N₂O group) or 66% N₂O in O₂ (66% N₂O group).

The study was conducted in a warm, quiet operating room. No premedication was administered. An intravenous cannula was inserted into a forearm vein and lactated Ringer's solution, 10 ml/kg, followed by an infusion at 10 ml/kg/hr, was administered and routine anesthetic monitoring and EEG data collection were commenced. Patients breathed the allocated gas mixture spontaneously from a circle circuit, *via* a close-fitting facemask that was held by the anesthesiologist. Flow rates were adjusted to 8 l/min and the airway and ventilation were supported if necessary. Assessment of consciousness was made every 15 s during the study in the following two ways: loss of response to command (LOR) was tested by asking the patient to open his or her eyes and loss of the eyelash reflex (LOER) was tested by lightly brushing the patient's eyelash with a cotton-wool tipped stick. After response to command and the eyelash reflex were lost,

the gas mixture was changed to 100% O₂ without sevoflurane. The study continued until the patient responded to command once more. At this time, anesthesia was induced with agents of the anesthesiologist's choice and surgery commenced.

Arterial blood pressure was measured non-invasively every minute. Heart rate, hemoglobin oxygen saturation, and inspired and expired gas concentrations were monitored continuously and recorded every minute (S/5 anesthesia monitor, Datex-Ohmeda, Helsinki, Finland). The raw EEG was acquired *via* an adhesive unilateral bipolar frontal electrode (BIS-Quattro, Aspect Medical Systems Inc., Newtown, MA, U.S.A.) connected to an A2000 EEG monitor (BIS-XP Version 4.0, Aspect Medical Systems Inc., Newtown, MA, U.S.A.). Bipolar electrode placements corresponded approximately to FpZ and Fp1 or Fp2 of the modified expanded '10-20' system for electrode placement. The raw EEG and other data computed by the A2000 monitor, including the BIS and electromyographic (EMG) power in the band 70-110 Hz, were downloaded onto a laptop computer for later analysis (as detailed below). The start of study drug administration, LOR, LOER, the change of the gas mixture to 100% O₂ without sevoflurane, the return of response to command and the commencement of the next induction were recorded digitally using event markers as each event occurred.

2.2 EEG Data Analysis

2.2.1 Motivation

Based on significant experimental evidence that the EEG recorded in the presence and absence of anesthesia can be modeled as a random linear process (19, 24-29) we used a

linearised version of a full non-linear theory of electrorhythmogenesis to motivate fixed order ARMA time series modeling to obtain measures of the *responsiveness (or state) of cortex* and the magnitude of the *input to cortex* (Figure 1). These measures will subsequently be referred to as *cortical state* (CS) and *cortical input* (CI) respectively.

Figure 1 about here

The full theory on which these measures are based considers the dynamics of the mean soma membrane potential (over a spatial scale of the order of 1 mm or so) of populations of excitatory (pyramidal) and inhibitory (stellate and other interneurons) cortical neurons. The EEG is, on the basis of extensive experimental evidence, assumed to be a linear function of the mean soma membrane potential of excitatory cortical neurons, h_e (30, 31). Specifically the theory was initially developed in an attempt to understand the genesis of alphoid (8 – 13 Hz) activity and its spread in cortex. It models cortex as an excitable spatial continuum of reciprocally connected populations of excitatory and inhibitory interneurons that interact synaptically by way of short-range (intracortical) and long-range (corticocortical) connections. The time course of “fast” excitatory (AMPA/kainate) and “fast” inhibitory (GABA_A) neurotransmitter kinetics, together with single compartment passive neuronal integration time constants, were used to define the respective dynamics of excitatory and inhibitory synaptic interactions (20).

The resulting theory is cast as a set of coupled non-linear partial differential equations, and as such do not possess explicit quantitative solution. However many important predictions of this theory can be obtained by studying the much simplified linear

equations that arise from linearising the original PDE formulation about one or more time-invariant steady states. In this manner the continuous time EEG signal in the frequency (Laplace) domain can be modeled as arising from the action of a transfer function

$$H_e(s) = \frac{\sum_{k=0}^{k=5} \bar{b}_k(q) s^{5-k}}{\sum_{k=0}^{k=8} \bar{a}_k(q) s^{8-k}} P(s) \quad (1)$$

$$= g(q') \frac{[s^5 + \sum_{k=1}^{k=5} \beta_k(q) s^{5-k}]}{[s^8 + \sum_{k=1}^{k=8} \alpha_k(q) s^{8-k}]} P(s) \quad (2)$$

$$= g(q') \frac{N(s;q)}{D(s;q)} P(s) \quad (3)$$

$$= g(q') G_e(s;q) P(s) \quad (4)$$

where $H_e(s)$ represents the EEG signal recorded from a single scalp electrode, \bar{a}_k and \bar{b}_k are coefficients that depend on a range of model physiological and anatomical parameters (represented by the vector q). These parameters include the time course and magnitude of “GABAergic” inhibition which, on the basis of extensive experimental evidence (32), is widely believed to be enhanced in a dose dependent manner by the majority of volatile and intravenous general anesthetic agents. $P(s)$ is the input a locally circumscribed region of cortex (underlying an electrode) receives from all sub-cortical sources. G_e is called the *electrocortical transfer function*, $g(q') \equiv \bar{b}_0 / \bar{a}_0$ is the factored out leading coefficients of the numerator and denominator which depend on a subset q' of the full model parameters q which are theoretically predicted not to be modified by anesthetic action, and $\alpha_k = \bar{a}_k / \bar{a}_0$, $\beta_k = \bar{b}_k / \bar{b}_0$. If it is reasonably assumed that cortical input is temporally so complicated as to be indistinguishable from band

limited white noise (i.e. $P(s) = P_0$), it is found that solutions to $D(s;q) = 0$ (i.e. the poles of electrocortical transfer function), for a range of physiologically and anatomically plausible parameter values q , give resonances corresponding theoretically to all the major EEG frequency bands.

Thus a linear model reveals somewhat surprisingly that spontaneous EEG may be understood as arising from a filtered random process. Numerical solutions of the full equations reveal that this linear approximation is sufficient for the prediction and modeling of a range of quantitative EEG phenomena (22). Further theoretical details can be found in Liley et al (19-22). Formally *cortical state* (CS) will be defined as corresponding to a scalar descriptor of the filter G_e (to be defined later), whereas *cortical input* (CI) will be defined as the magnitude of P_0 . Because the 8 poles and 5 zeros of the continuous time electrocortical transfer function are predicted to be of physiological significance the transformation of the electrocortical transfer function into the discrete domain for the purposes of estimating CI and CS needs to preserve their number. Therefore we require that poles and zeros in the continuous domain will be matched with poles and zeros in the discrete domain. Thus based on a matched pole-zero transformation (33) equation (2) is rewritten in the discrete domain as

$$H_e(z) = k_d g(q') \frac{[z^5 + \sum_{k=1}^{k=5} b_k(q) z^{5-k}]}{[z^8 + \sum_{k=1}^{k=8} a_k(q) z^{8-k}]} P(z) \quad (6)$$

$$= k_d g(q') \frac{[z^{-3} + \sum_{k=1}^{k=5} b_k(q) z^{-k-3}]}{[1 + \sum_{k=1}^{k=8} a_k(q) z^{-k}]} P(z) \quad (7)$$

where k_d is a constant required to match the gain in going from continuous to discrete time and $z = e^{s/f_s}$ with f_s being the sampling frequency. It follows that equation (7) can be rewritten as the following difference equation

$$h_e[n] = -\sum_{k=1}^{k=8} a_k h_e[n-k] + \sum_{k=0}^{k=5} b_k u[n-k-3] \quad (8)$$

where $u[n] \equiv k_d g(q') p[n]$, $b_0 = 1$ and where for clarity we have dropped any dependency on model parameters q . Because we have assumed that CI will be indistinguishable from band-limited white noise $p[n]$, and hence $u[n]$, will represent a sequence of uncorrelated random variables. Based on this and assuming that $u[n]$ is stationary with variance σ_u^2 , equation (8) can be seen to model h_e by the following fixed order ARMA process

$$h_e[n] = -\sum_{k=1}^{k=8} a_k h_e[n-k] + \sum_{k=0}^{k=5} b_k u[n-k] \quad (9) \quad \text{or}$$

$$A(z)h_e[n] = B(z)u[n] \quad (10)$$

where $A(z) = 1 + a_1 z^{-1} + \dots + a_8 z^{-8}$ and $B(z) = 1 + b_1 z^{-1} + \dots + b_5 z^{-5}$. These theoretically derived fixed AR and MA orders accord well with empirical determinations of optimal AR (range 3 – 14) and MA (range 2 – 5) orders obtained from resting awake eyes closed EEG using a range of information theoretic criteria (26, 29). The poles and zeros of this discrete time linear filter are the respective solutions to $A(z) = 0$ and $B(z) = 0$.

As the poles and zeros of the estimated electrocortical filter $B(z)/A(z)$ are predicted to be of physiological significance tracking their motion would seem to provide the best

means of characterizing variations in the state of the electrocortical filter. However the robust tracking of individual poles or zeros is usually not reliable. Therefore to quantify the state of the electrocortical filter, and thus cortical state (CS), we choose instead to quantify mean pole location \bar{z}_p . We choose not to use other available scalar measures of the derived filter such as Itakura distance (34), pole distance, weighted pole distance or ARMA spectral distance (35, 36) because of the computational complexity in evaluating them and their uncertain specificity in detecting anesthetic related EEG changes. Because poles which possess a non-zero imaginary component always exist in conjugate pairs \bar{z}_p will be real. It follows that $\bar{z}_p = -a_1/8$, as it is easily seen that the sum of the 8 roots of $A(z) = 0$ is $-a_1$. For a given sequence of $\bar{h}_e[n]$ from which the coefficients $\{a_k\}$ and $\{b_k\}$ are estimated the square root of the variance of

$\frac{A(z)\bar{h}_e[n]}{B(z)k_d g(q')}$ will provide a root mean square estimate of the cortical input $p[n]$. From a

practical point of view no attempt will be made to evaluate the factor $k_d g(q')$ as it is predicted to remain invariant to all anesthetic interventions (22).

In summary a theory of the genesis of EEG enables the specification of a relatively simple method by which variations in CS and CI can be estimated from actual EEG recordings.

2.2.2 Implementation

The A2000 monitor output raw EEG at 128 samples per second and other derived parameters, such as BIS and EMG (spectral power between 70 and 110 Hz), at 1 sample per second. According to the A2000 operating manual (37) the monitor applies either a

2-70Hz band-pass filter with a notch filter at 50/60Hz or a 0.25-100Hz band-pass filter to the displayed raw EEG, depending on a user setting. However, spectral analysis of the recorded data, as in Figure 2, revealed that the downloaded raw EEG was low pass filtered at approximately 47 Hz and high pass filtered at about 0.1 Hz.

Because of the sharp roll-off of the low pass filter, ARMA estimated poles and zeros from the raw EEG will be unnecessarily fitted to the filter's band edge thus impairing the physiological relevance of the fixed ARMA order. Therefore the raw EEG was resampled to 80Hz, limiting the bandwidth to be modelled to 0.1-40Hz. Resampling to a subband in which the low pass filter is assumed to have a relatively flat pass band and therefore minimal effect, allows more meaningful, and therefore accurate, models of the underlying EEG to be estimated using the physiologically significant AR and MA orders of 8 and 5 respectively. The band edge of 40Hz was chosen as i) it is well clear of the cut off of the low pass filter, ii) all major oscillatory features of the EEG occur well below this value and iii) 50/60 Hz power line interference is eliminated and EMG interference is minimised. The effect of high pass filtering raw EEG over the range 0.1 – 0.5 Hz revealed a minimal effect on estimated ARMA models and was therefore not specifically dealt with.

Figure 2 about here

The resampling was performed in Matlab (Mathworks, Natick, MA, USA) using a process of interpolation, anti-aliasing filtering and downsampling. The anti-alias filter used was an FIR filter with a sharp cut off at 40Hz. Whilst setting the cut-off of the filter to the Nyquist frequency can result in aliasing, it is necessary to minimise its

effect on subsequently derived models (38). The transition band of the FIR filter was made sufficiently sharp to minimise any aliasing. The effects of resampling the EEG can be seen in Figure 2.

Figure 3 about here

ARMA models of order (8,5) were fitted to 50% overlapping 2 s epochs using the ARMASA Matlab Toolbox (39). Two second epochs were chosen as a compromise between the duration of EEG signal stationarity (typically < 10 s – Niedermeyer and Lopes da Silva 2005) and the accuracy of the estimated model when compared to those obtained using epoch lengths of 5 and 10 s (Figure 3). ARMASA removes the mean of the epoch then estimates an invertible and stationary ARMA model using a variant of Durbin's method with optimal intermediate AR order (39). For each resampled EEG epoch $\bar{h}_e^{rs}[n]$ CS was calculated as $-a_1/8$ and CI as the square root of the variance of $\frac{A(z)\bar{h}_e^{rs}[n]}{B(z)}$ (variance of $\bar{h}_e^{rs}[n]$ divided by the power gain of the derived filter for a unit variance white noise innovation) as detailed previously.

2.3 Statistical Analysis

Normally distributed data were summarised as mean \pm standard deviation, skewed data as median (range) and counts as number (%). Omnibus tests were performed using analysis of variance (ANOVA) or the Kruskal-Wallis test where appropriate based on the results of Levene's test for homogeneity of variance. Post-hoc multiple comparisons were made using Tukey's HSD or the Mann-Whitney U test with Bonferroni correction

where appropriate. All statistical analyses were performed using SPSS for Windows v16 (SPSS Inc, Chicago, IL, USA). A value of $p < 0.05$ was considered statistically significant.

3. Results

Of the original 69 patients recruited for the study only the EEG data recorded from 48 was used, due to technical failures in data collection. Because the remaining 48 EEG recordings were of variable quality it was decided to only analyze a subset that were free of any obvious artifacts (spikes or broadband noise). This left a total of 38 recordings distributed among the 100% O₂ (n = 10), 33% N₂O (n = 11) and 66% N₂O (n = 17) treatment groups. Demographic variables were similar in all treatment groups. No significant differences between treatment groups existed for end-tidal sevoflurane gas concentration, or any of the measured physiological variables, at LOR (Table 1).

Figure 4 shows an example of the variation in CI and CS during the anesthetic procedure relative to average pre-induction values. This example reveals a number of features that were common to the recordings i) the “U” shaped variation in CS and CI with anesthetic induction and recovery ii) the decline of CI with increasing anesthetic effect iii) the return of CI and CS to pre-induction levels following the gas mixture being changed to 100% O₂ and iv) the changes in CI and CS generally occur sooner and more gradually than those of the BIS. Thus the measures of CI and CS are sensitive to anesthetic effect. To subsequently determine whether the measures of CS and CI were able to detect treatment group differences comparisons were made at a known anesthetic endpoint (LOR) in order to control for patient state. For CI and CS relative

values were used for subsequent comparisons between treatment groups in order to control for individual variation. Because the BIS index implicitly controls for individual variation no similar normalization was performed.

Figure 5 shows box and whisker plots of relative CS, relative CI, relative EMG, relative RMS EEG amplitude and the BIS averaged over a 30 s window centered on the recorded LOR in order to take into account the uncertainty in the determination of LOR (see 2.1 *Patients and Anesthesia*). Except for relative CI in the 100% O₂ treatment group, the median value of all EEG derived measures were changed from their pre-induction levels. Omnibus tests indicated that variations in relative CI and BIS between treatment groups were significant. The results of the statistical tests are summarized in Table 2. Subsequent multiple comparison *post-hoc* pair-wise comparison tests revealed that relative CI was significantly different between 100% O₂ and 33% N₂O, and 100% O₂ and 66% N₂O groups. In contrast the BIS was significantly different between 100% O₂ and 33% N₂O, and 33% N₂O and 66% N₂O treatment groups but not between the 100% O₂ and 66% N₂O groups.

Tables 1 & 2 about here

Figure 4 & 5 about here

4. Discussion

In assessing the state of the brain during anesthesia it is important to distinguish changes in brain state that occur as a result of altered cortical function (hypnosis) from

those that occur as a result of altered sensory input (analgesia) to cerebral cortex. While an analysis of cortically recordable event related potentials can provide information about the integrity of input pathways to cortex, the technique is limited because not all cortical areas are the direct recipients of peripherally derived sensory information. Furthermore, current quantitative EEG methods involving time or frequency domain analyses are unable to distinguish between changes in *cortical input* and the changes in *cortical responsiveness* that are occasioned with anesthetic drug action, because the corresponding heuristic algorithms are unable to make assumptions regarding the physiological sources of changes in the recorded EEG signal. In contrast we have shown here that a physiologically inspired processed EEG method is able to electroencephalographically distinguish between the effects that N₂O has on *cortical input* and the effects it has on *cortical responsiveness*, at LOR in the presence of sevoflurane.

Quantitatively the magnitude of the N₂O induced effect was an approximately two-fold reduction in the median CI (Figure 5b) at LOR. In contrast, no difference in CS was detectable. That N₂O did not affect CS does not necessarily mean it has no direct cortical effect, as it may be that our simple scalar determinant (mean pole location) did not adequately characterize the estimated linear filters. The result that the BIS at LOR showed a non-linear dose response relationship with N₂O concentration (Figure 5c) is consistent with studies involving its sole administration. Concentrations of N₂O less than 50% appear to increase high frequency EEG activity (5, 40), whereas concentrations greater than 50% seem to attenuate high frequencies while promoting low frequency activity (41). As one of the measures underpinning the BIS algorithm involves calculating the relative power in the gamma band (defined to be 40 – 47

Hz)(42) it seems reasonable to conclude that the BIS is detecting these dose dependent effects. This N₂O induced variation in BIS value for a fixed hypnotic level emphasizes the need for physiological measures that meaningfully reflect brain state.

Our conclusion that changes in cortical input may be important determinants of N₂O action is supported by studies investigating its effect on somato-sensory, auditory and visual evoked potentials. Sole administration of N₂O is associated with both reductions in amplitude and increases in latency of a range of middle latency evoked potential components that include the middle latency auditory evoked potential (13, 14, 16-18). The neurogenic source of the middle latency auditory evoked potential is probably a combination of activity arising from the temporal/auditory cortex and a number of sub-cortical structures such as the inferior colliculus and thalamus (43). Thus changes in the shape and amplitude of the middle latency auditory evoked potential during N₂O administration, while reflecting changes in cortical input, nevertheless also reflect changes in cortical state. This lack of specificity is largely overcome by our present approach in which we have used theoretical intuitions regarding the genesis of resting EEG activity to differentiate the cortical and subcortical effects and targets of anesthetic action.

A recurring criticism leveled against the use of the EEG to monitor brain function is that it is difficult or even impossible to eliminate EMG activity (44, 45) and thus impossible to know whether changes in recorded activity are due to brain, muscle or a combination. This issue is of particular relevance in the context of N₂O, as N₂O is commonly believed to increase tonic skeletal muscle activity and hence EMG (44, 45). In the present study it is possible that N₂O induced EMG activity may have masked

changes in the BIS and CS. However this seems unlikely given that no significant differences could be discerned in estimated EMG activity (as determined by total power in the 70 – 110 Hz band) and total EEG power between the various treatment groups at LOR. In contrast the effect of any EMG activity, N₂O induced or otherwise, would be to increase CI and thus to underestimate the attenuating sub-cortical effects of N₂O.

Clinically N₂O is used for its anesthetic-sparing properties. Nitrous oxide when combined with more potent volatile anesthetic agents, such as sevoflurane, reduces the concentration of the potent volatile agent necessary to induce unconsciousness, immobility and surgical levels of anesthesia (46, 47). Therefore it is possible that the treatment group differences we observed in CI were due to variations in brain sevoflurane concentration at LOR induced by the anesthetic sparing properties of N₂O. In the absence of detailed effect site (brain) pharmacokinetic modeling this possibility cannot be definitively eliminated, however it does seem unlikely given that no significant treatment group differences were detected in end-tidal sevoflurane concentrations at LOR (see Table 1).

Because of the short duration of the anesthetic induction it is almost certain that alveolar and brain gas concentrations would not have had time to equilibrate. Therefore the absence of any significant difference between relative CI at LOR in the 33% N₂O and 66% N₂O groups might have been due to end-tidal (alveolar) gas concentrations not accurately reflecting effect site (brain) concentrations, rather than as a consequence of limitations in the actual electroencephalographic measure. Therefore subsequent studies involving N₂O may need to involve some form of pharmacokinetic modeling in order to determine dose-response relationships for the measures of CI and CS.

In conclusion, we have shown that a theoretically constrained method for the analysis of EEG time series was able to detect differences in the EEG state at loss of consciousness induced by sevoflurane for differing concentrations of adjuvant N₂O. This method may therefore provide a physiologically more specific method for monitoring brain function during anesthesia. All currently available depth of anesthesia monitoring methods, BISTM (5, 6, 48), Spectral Entropy (5, 49, 50), SNAPTM II (7), PSITM (5) and AAITM indices (13), rely on a range of statistical criteria that have no clear connection with the underlying physiological processes of electrorhythmogenesis or anesthetic action, thus limiting their clinical utility. Because our method has a physiological specificity that these other methods do not possess, it may find utility not only in evaluating the efficacy of a range of cognitively acting pharmaceutical agents, but may also help in evaluating their central targets of action.

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Table Legends

Table 1: *Anesthetic variables at loss of response.* Anesthetic variables at loss of response to verbal command (LOR) for all patients from which artifact free EEG was recorded (n = 38). All data are expressed as mean \pm standard deviation (normally distributed) or median (range) (skewed data).

Table 2: *Groupwise comparisons.* Results of Omnibus tests (ANOVA or Kruskal-Wallis) and post-hoc pairwise comparisons. * indicates significance at the $p < 0.05$ level.

Figure Legends

Figure 1: *Schematic outline of the theoretically motivated time series modeling.*

Schematic outline of the derivation of the physiologically-based fixed order electroencephalographic time series modeling. Because we have specified the fixed order ARMA model from a theoretical linear transfer function we are able to infer *cortical state* and *cortical input* from an analysis of suitably segmented electroencephalogram. PDE = partial differential equation; ARMA = autoregressive moving average. For full details of the derivation see Liley et al (2002).

Figure 2: *Spectrum of resampled EEG.* In order to avoid poles and zeros being fitted to the band edge of the low pass filter, raw EEG was resampled to 80 Hz. (a) Spectrogram (2 s 50% overlapping Hamming windowed segments) of raw EEG recorded during a representative anaesthetic induction illustrating the clear filter edge at approximately 47 Hz (b) Spectrogram of resampled EEG (c) averaged power spectral density obtained over the whole procedure illustrating i) the absence of a low pass filter edge in resampled EEG and (ii) that the distribution of spectral power has been preserved following resampling. SI = start of induction, LOR = loss of vocal response, LOER = loss of eyelash reflex, O₂ = 100% O₂ given, SNI = start next induction.

Figure 3: *Effect of window size on ARMA estimation.* Effect of variations in the window length used to estimate the ARMA(8,5) model of resampled data recorded during a representative anaesthetic procedure. Models were calculated from segments of 2, 5 and 10 s with overlapping set to produce a result every 1 s. Displayed results were smoothed with a 30 s moving average window. All other symbols as per Figure 2.

Figure 4: *Representative anesthetic induction.* Variation in relative CS, relative CI and BIS over the duration of a representative anesthetic procedure. Relative CS (CS/CS_0) and CI (CI/CI_0) were defined with respect to average, artifact free, pre-induction values. Displayed data has been smoothed with a 30 s moving average window. The negative relative CS has been plotted to facilitate comparison with the BIS. The absence of a BIS value means that the A2000 monitor was unable to generate an index. All other symbols as per Figure 2. For further details refer to text.

Figure 5: *Summary of group statistics.* Box and whisker plots of relative CS, relative CI, relative EMG, relative RMS EEG amplitude and BIS averaged over a 30 s window centered on the recorded LOR in order to take into account the uncertainty in the determination of LOR. Red lines indicate median values, blue boxes the inter-quartile range, whiskers the largest (smallest) non-outlier and red crosses outliers (defined as values extending outside 1.5 times the inter-quartile range).

Table 1

	100% O₂ (n = 10)	33% N₂O (n = 11)	66% N₂O (n = 17)	Omnibus test p value
Oxygen saturation (%)	99 (91-100)	99 (99-100)	99 (99-100)	0.245
Heart rate (beats per min)	70.90 ± 15.55	76.55 ± 12.80	71.65 ± 13.78	0.586
Systolic blood pressure (mmHg)	123.20±13.68	127.36 ± 9.01	120.41±14.88	0.397
Inspired oxygen (%)	95.50 (90-96)	62.00 (32-69)	33.00 (24-46)	0.000
End-tidal nitrous oxide (%)	0	26 (14-33)	45 (20-67)	0.000
End-tidal sevoflurane (%)	3.6 (1.8-4.2)	3.00 (2.1-4.1)	2.9 (1.9-3.8)	0.413

Table 2

Measure	Omnibus Test p value	Post-hoc comparison (2 tailed)	
		Pair-wise Condition	p value
Relative CS	0.196	100% O ₂ – 33% N ₂ O	-
		100% O ₂ – 66% N ₂ O	-
		33% N ₂ O – 66% N ₂ O	-
Relative CI	0.002*	100% O ₂ – 33% N ₂ O	0.01*
		100% O ₂ – 66% N ₂ O	0.003*
		33% N ₂ O – 66% N ₂ O	0.989
BIS	0.02*	100% O ₂ – 33% N ₂ O	0.05*
		100% O ₂ – 66% N ₂ O	1.00
		33% N ₂ O – 66% N ₂ O	0.027*
Relative RMS	0.262	100% O ₂ – 33% N ₂ O	-
		100% O ₂ – 66% N ₂ O	-
		33% N ₂ O – 66% N ₂ O	-
Relative EMG	0.204	100% O ₂ – 33% N ₂ O	-
		100% O ₂ – 66% N ₂ O	-
		33% N ₂ O – 66% N ₂ O	-

Figure 1

full non-linear theory
(PDEs)



linear approximation
(transfer function)



(8,5)-ARMA time
series model

- cortical state (CS)
- cortical input (CI)

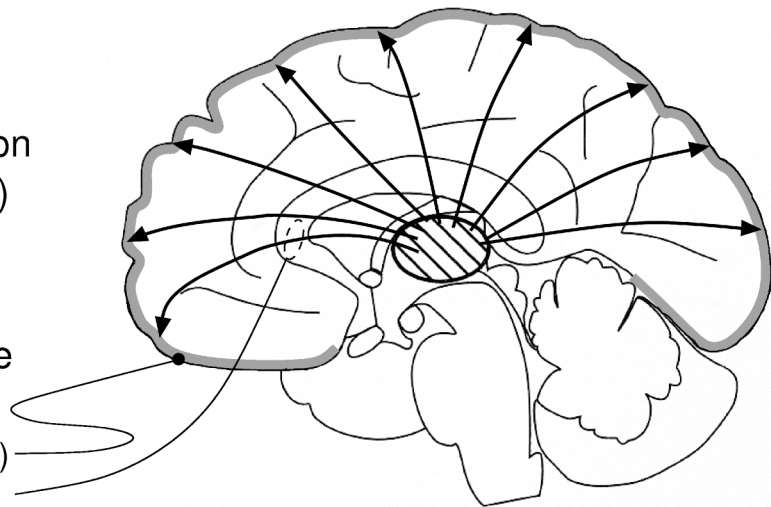


Figure 2

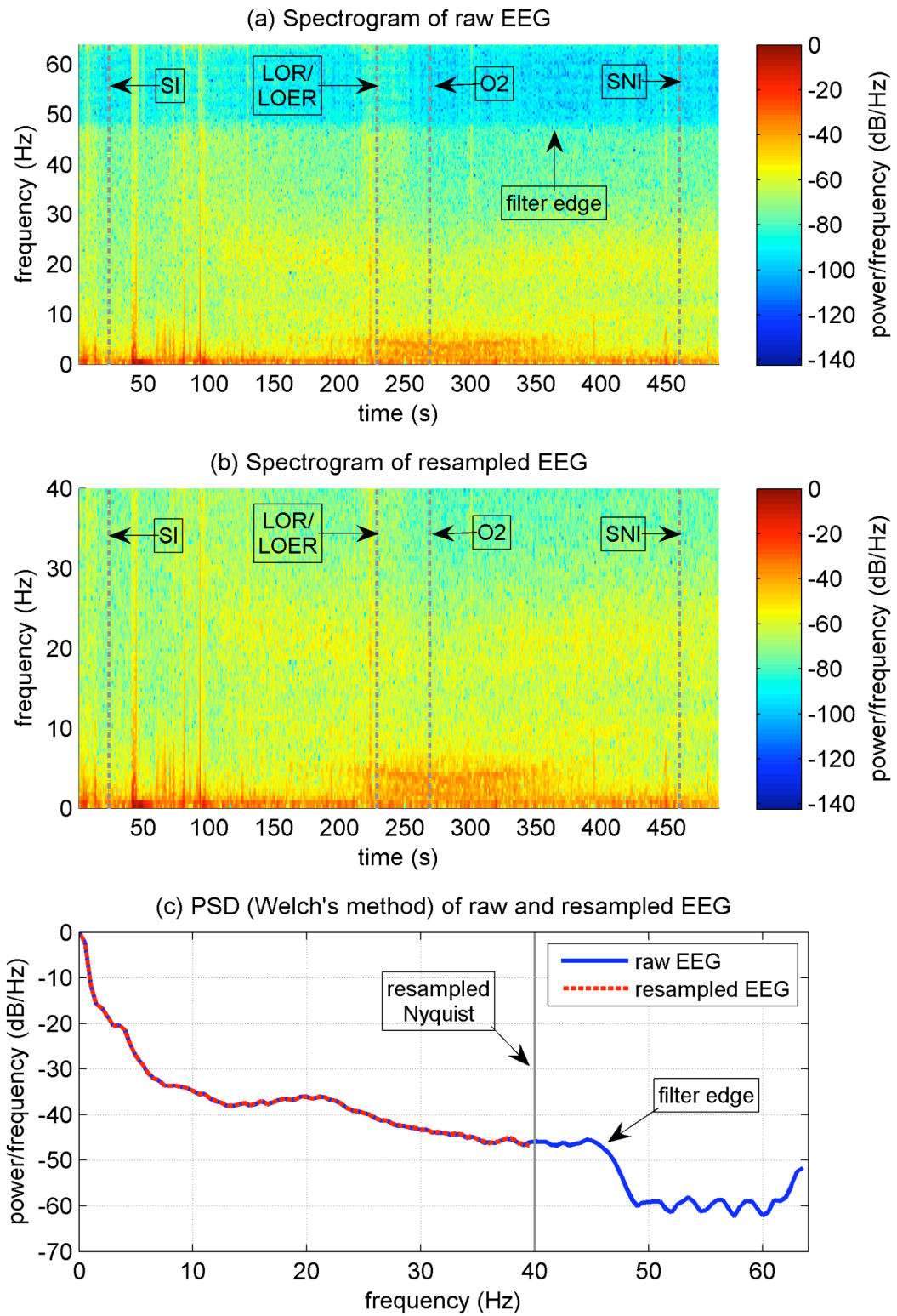


Figure 3

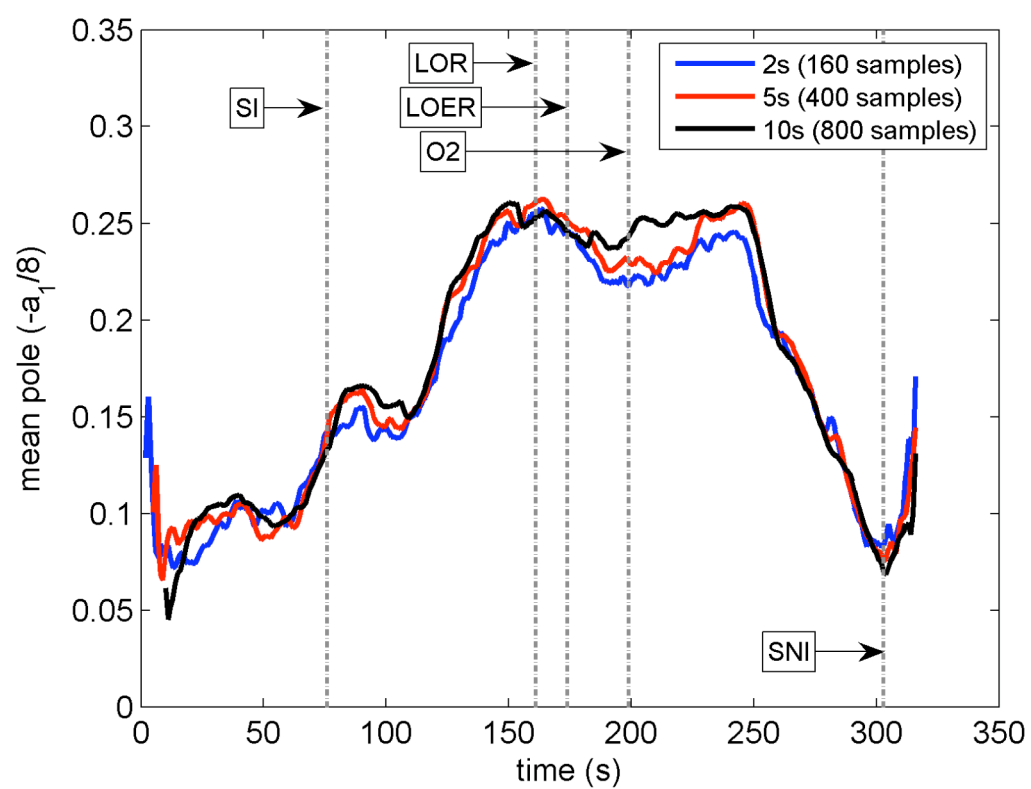


Figure 4

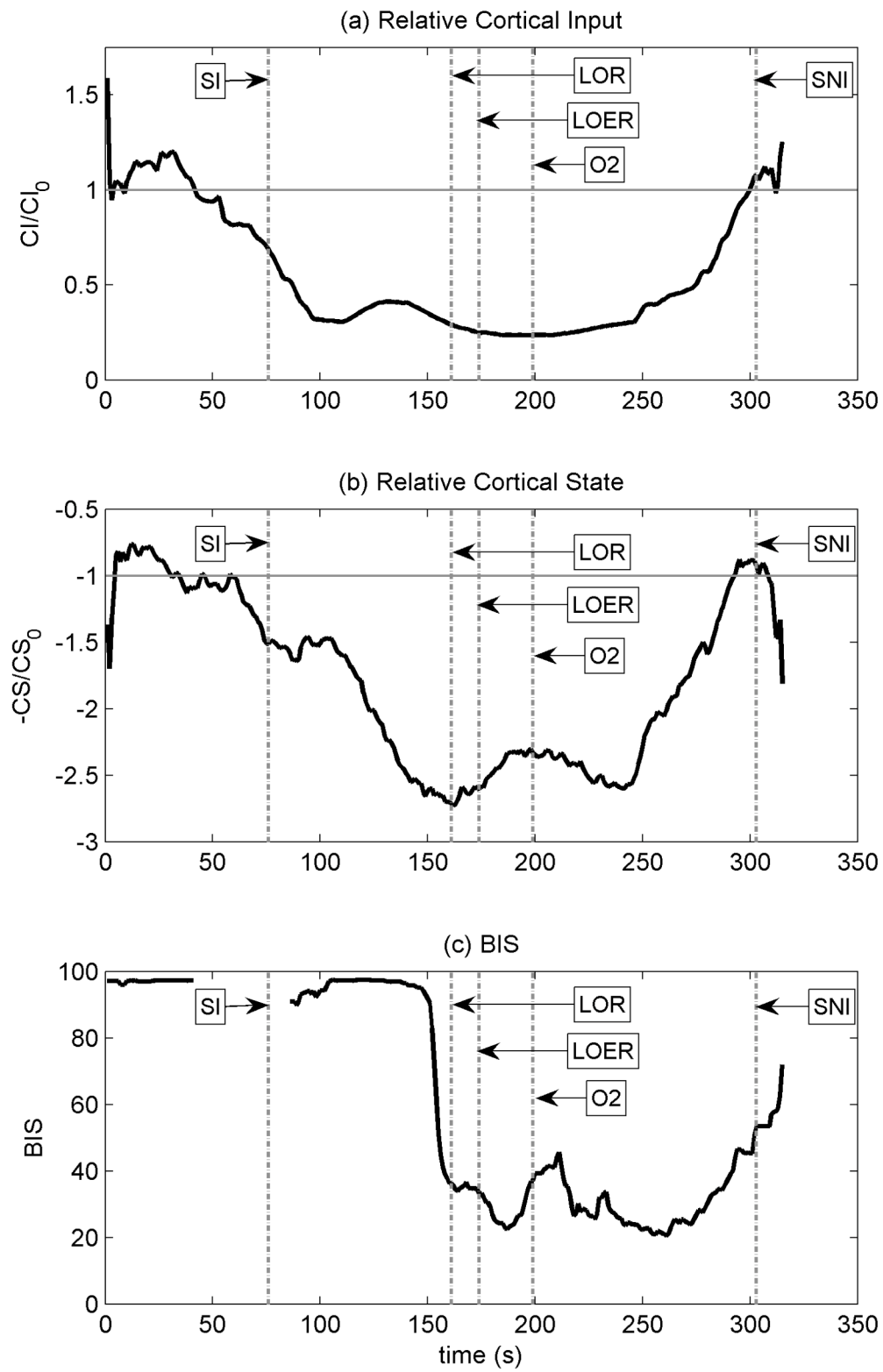
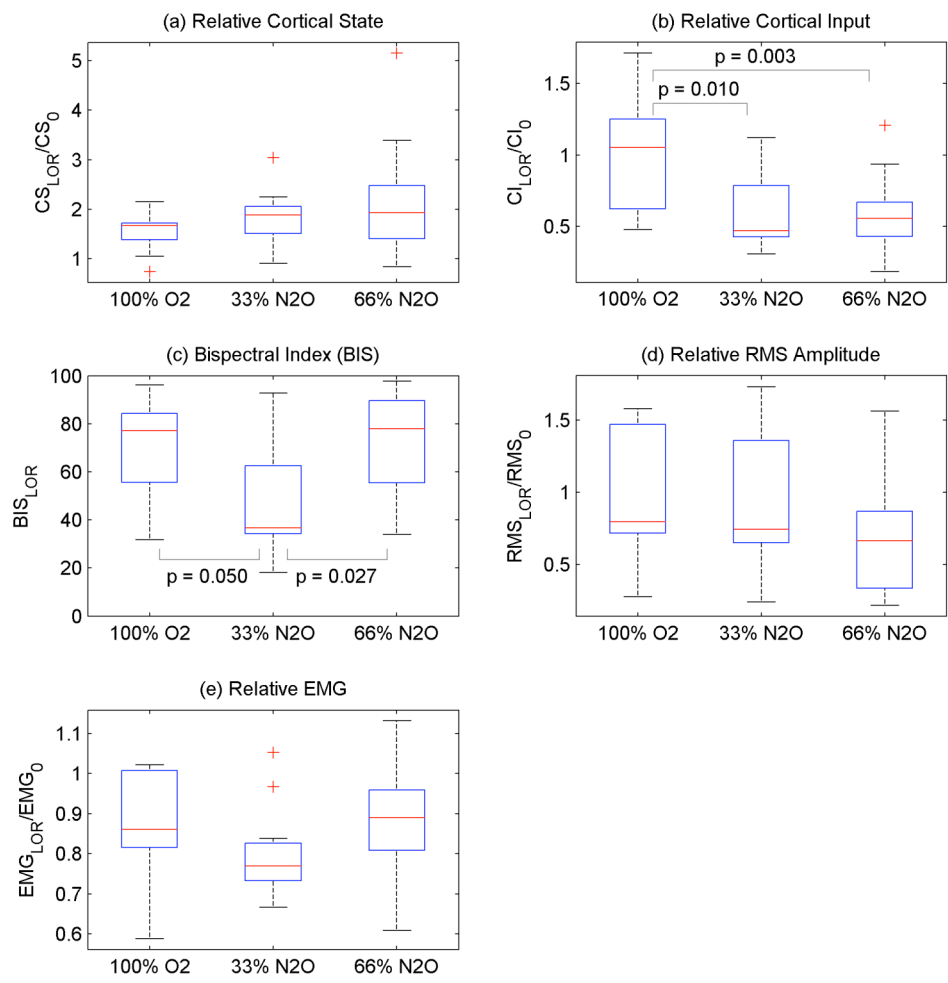


Figure 5



Summary

Objective: A number of commonly used anesthetics, including nitrous oxide (N_2O), are poorly detected by current electroencephalography (EEG)-based measures of anesthetic depth. We therefore developed a physiologically-inspired method of EEG analysis that was hypothesized to be sensitive in detecting and characterising N_2O effect through its combined EEG estimates of cortical input and cortical state.

Methods: Sixty nine elective surgery patients were randomized to one of three treatment groups: sevoflurane 4% + 100% oxygen; sevoflurane 4% + 33% N_2O in oxygen; sevoflurane 4% + 66% N_2O in oxygen. Following loss of response to verbal command and eyelash reflex, participants breathed 100% oxygen until response to command returned. Raw EEG and bispectral index, together with event markers corresponding to the assessed levels of consciousness, were digitally recorded for later analysis. EEG was analysed using a physiologically-constrained time series modelling approach

Results: Sevoflurane induced loss of consciousness in the presence of N_2O was associated with a statistically significant reduction in the *input* the frontal cortex received from other cortical and subcortical areas. In contrast the bispectral index responded only to low, but not to high, concentrations of N_2O .

Conclusions: This new method of EEG data analysis enables a physiologically more specific analysis of anesthetic effect by simultaneously evaluating both cortical state and cortical input.

Significance: Evaluation of cortical state and cortical input may provide a new approach to quantifying the central effects of a range of pharmaceutical agents.