Bispectral Analysis of the Electroencephalogram Predicts Conscious Processing of Information during Propofol Sedation and Hypnosis

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Background: The bispectral index (BIS) measures changes in the interfrequency coupling of the electroencephalogram (EEG). The purposes of this study were (1) to determine whether BIS correlates with responses to command during sedation and hypnosis induced by propofol or propofol and nitrous oxide, and (2) to compare BIS to targeted and measured concentrations of propofol in predicting participants' responses to commands.

Methods: Twenty volunteers (15 men and 5 women, aged 22–50 yr) were given propofol by computer-controlled infusion, and EEG was recorded for off-line analysis of BIS. Responses to randomly ordered verbal commands or voice plus touch were measured with two categorical scales (CS1 and CS2, respectively). All subjects received a propofol infusion targeted to achieve effect site concentrations of 1, 2, 4, 2, 1, and 0 μg/ml. Ten participants had repeated infusion, whereas 10 others breathed 30% nitrous oxide and oxygen and received a propofol infusion targeted for 0.5, 1, 2, 4, 2, 1, 0.5, and 0 μg/ml. Five minutes after each targeted concentration had been reached, CS1, CS2, and arterial propofol concentra-

tion were determined. The area under the receiver operating characteristic curve was used to compare the accuracy of (1) BIS, (2) targeted propofol concentration, (3) measured concentration, and (4) treatment history as predictors of response.

Results: Bispectral index was a strong predictor of CS1 and CS2 ($P < 0.0001$) and significantly more accurate than targeted or measured propofol concentrations ($P < 0.0003$ and $P < 0.003$, respectively). It also provided additional predictive power when combined with treatment history ($P < 0.02$). Nitrous oxide slightly decreased the probability of response at a given value of BIS ($P < 0.05$), but accuracy was unaffected.

Conclusions: Bispectral index accurately predicts response to verbal commands during sedation and hypnosis with propofol or propofol plus nitrous oxide. Accuracy is maintained in situations likely to be encountered during clinical use: when propofol concentrations are increasing or decreasing and when repeated measurements are made over time. (Key words: Brain; intravenous anesthetics; monitoring; nitrous oxide.)

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SEVERAL investigators have studied the sensitivity of the electroencephalogram (EEG) as a measure of sedation or anesthesia in persons receiving propofol infusions.[1-8] In attempting to establish a correlation between the changes in the EEG and changes in consciousness, the EEG parameter must be able to indicate in real time when participants retain or lose their capacity to actively, consciously process information. It has generally been accepted that the EEG scalp-recorded rhythmic activity associated with consciousness is generated from pacemakers within the brain stem reticular activating formation and is mediated and modulated through thalamic connections.[9-14] Bispectral analysis of the EEG determines the interfrequency coupling or coherence among all the component waves of the EEG.[15-18] The bispectral index (BIS) is a univariate parameter computed from the bispectrum.[19-21] The rhythmic activity observed at the scalp is strongly influenced (if not controlled) by subcortical generators mediating consciousness.[9-14] Given that bispectral analysis measures scalp-recorded phase locking or harmonic relations among

EEG frequencies, our hypothesis is that BIS reflects the relations of EEG pacemakers and is, therefore, closely associated with the presence or absence of conscious thinking.

The BIS has already been shown to be useful as a monitor of sedation during surgical procedures performed under regional anesthesia.[5] A recent multicenter trial showed that the BIS correlates with sedation in volunteers given either propofol, midazolam, or isoflurane.[22] These studies did not directly investigate the relation between BIS and conscious processing, defined as the ability to respond appropriately to a complex command. This prospective study had four purposes: (1) to determine whether changes in BIS correlate with healthy volunteers' responses to commands during propofol-induced sedation and hypnosis; (2) to evaluate the effect of adding low concentrations of inhaled nitrous oxide in oxygen on that correlation; (3) to compare BIS to both targeted effect site and measured plasma concentrations of propofol in predicting participants' responses to commands; and (4) to assess whether BIS increases prediction accuracy when the targeted drug concentrations and the presence or absence of inhaled nitrous oxide are known.

Methods

Participants and Monitors

The study was approved by the Subcommittee on Human Studies. Twenty paid volunteers classified as American Society of Anesthesiologists' physical status I and II were recruited and enrolled after giving informed written consent. Individuals were excluded from the study if they had a history of neurologic or psychiatric disorders; were taking anticonvulsant, antidepressant, or other psychoactive medications; had a history of smoking more than one-half pack of cigarettes a day; or had a known allergy to propofol. An intravenous catheter for propofol infusions and a radial artery catheter for blood pressure monitoring and blood samples were placed in supine participants. In addition to the arterial blood pressure, each person was monitored with an electrocardiograph, capnograph, oxygen analyzer, and pulse oximeter. A semiclosed anesthesia cir-

cuit was used to deliver oxygen or nitrous oxide and oxygen by face mask. Propofol was infused into an antecubital vein using a Harvard 22 electronic syringe pump (Harvard Apparatus, South Natick, MA) controlled by a laptop computer running the software program STANPUMP (S. Shafer, M.D., Palo Alto, CA, October 1993). The apparatus was used to deliver propofol infusions targeted to achieve specific effect site concentrations. The pharmacokinetic and pharmacodynamic data used to predict effect site concentration were those of Shafer *et al.*[23] and were based on changes in the scalp-recorded EEG in response to propofol.** Two anesthesiologists were present at all times to monitor respiratory and cardiovascular function and to determine the need for interventions such as jaw support to maintain an adequate airway.

Electroencephalography

Four channels of EEG referenced to Cz or Fp2 were recorded, using Grass E5 gold cup electrodes (Quincy, MA) secured with collodion in a frontotemporal montage according to the diagram shown in figure 1. Impedances were kept at less than 2,000 φ, the time constant was set at 0.3 s, and low- and high-frequency filters were set at 0.5 and 100 Hz, respectively. Using an electroencephalograph (model A 1000 spectral EEG monitor; Aspect Medical Systems, Natick, MA), baseline awake EEG recordings were conducted with the participants' eyes closed for 5 min before infusion of propofol, and then throughout the study, until they were fully awake and appropriately responsive to commands. The quality of the EEG recordings was monitored by a registered EEG technologist to determine artifact. The investigators were blinded to the EEG recordings.

Bispectral Index

Details of bispectral analysis of the EEG and the BIS have been reported before.[22] In this study, the digitized EEG was recorded in real time, using a commercially available software program (Datalogger; Aspect Medical Systems). The digital recordings and computer-processed EEG variables, including BIS, were stored in time-synchronized computer files for subsequent statistical analysis. We used BIS version 2.5 in this study. The information used to create BIS 2.5 was derived from data obtained during previous clinical trials. These data consisted of recorded 100-s segments of EEG that were correlated with the state of wakefulness and states of drug-induced sedation, as defined by clinical criteria. The observation points were divided into a learning set

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** This data set incorporates adjustments for body weight and assumes the following kinetic parameters for a 70-kg person: $V_c = 24.5$ l; $K_{12} = 0.0621$ min^{-1}, $K_{21} = 0.0108$ min^{-1}, $K_{10} = 0.0889$ min^{-1}, $K_c o = 0.2500$ min^{-1} (Data set included with STANPUMP program).

Fig. 1. The frontotemporal electroencephalographic recording montage. The bispectral index was derived from each of the four leads, but only data from Fp1 and Fp2 are reported here.

Ch1 (Fp1)
Ch2 (Fp2)
Ch3
Ch4
Ref - Fpz
Gnd - above nasion
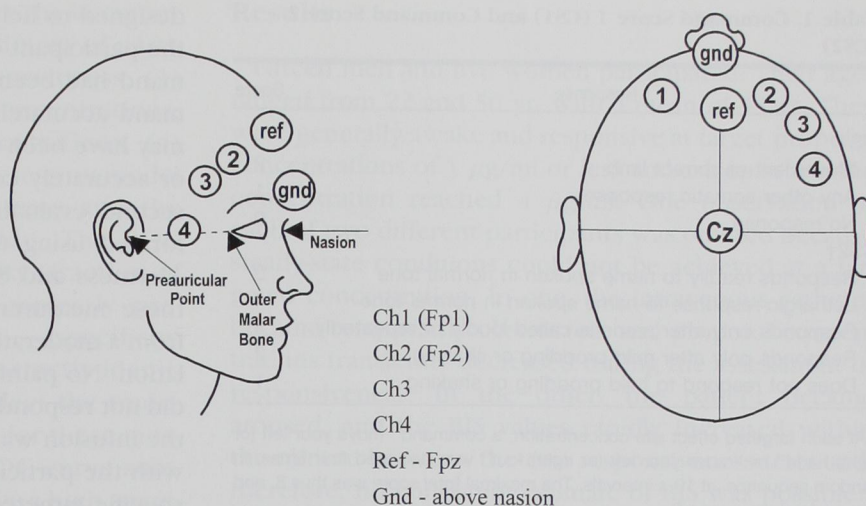
(n = 208) and a test set (n = 840). The EEG profiles, including the statistical properties of frequency and power observed in the power spectrum and harmonic and phase information derived from the bispectrum, were extracted at each observation point from a series of 2-s epochs of EEG. A multivariate regression analysis of those EEG characteristics that demonstrated the strongest statistical correlations with sedation and hypnosis was used to develop a nonlinear statistical model for sedation/hypnosis scores. This model was used to create an "index" (BIS), which is a number without dimension, scaled from 0 to 100, and designed to correlate in real time with the hypnotic effects of commonly used anesthetic drugs. The performance of this nonlinear model was confirmed using the test set. The EEG recordings from the present study were not used in the development of BIS 2.5.

Propofol Infusions

The infusion protocol is represented schematically in figure 2. While breathing 100% oxygen by face mask, each participant underwent two programmed propofol infusions (labeled A and B) consisting of stepped increases in the targeted effect site concentrations until the participant was no longer responsive to commands, followed by stepped decreases until he or she was fully awake and responsive and STANPUMP predicted that the targeted concentration was < 0.5 µg/ml. Each participant rested for approximately 20–30 min between the two infusions. During the second infusion, one half of the participants were randomized to receive 30% nitrous oxide in oxygen by face mask. The targeted

concentrations selected were 0, 1, 2, and 4 µg/ml during infusion A, and this was repeated in participants receiving oxygen alone. Those receiving nitrous oxide had target concentrations of 0, 0.5, 1, 2, and 4 µg/ml during infusion B.

This protocol was designed (1) to assess the stability of repeated BIS measurements over time and (2) to determine changes in BIS in response to increases and decreases in drug concentrations. With this design, each measurement could be assigned a unique sequence number (see fig. 2). For example, sequence
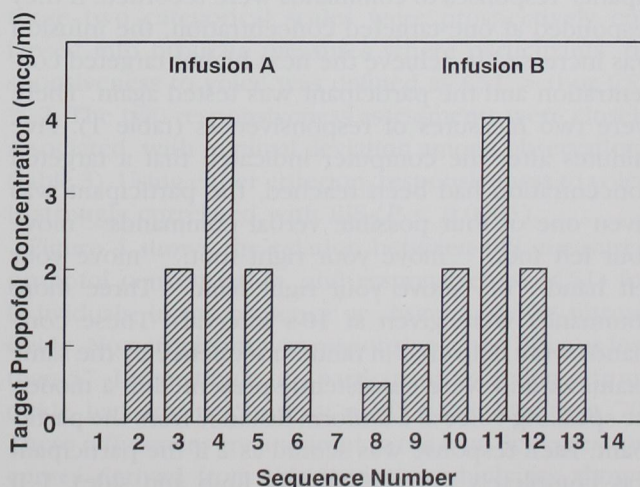

Fig. 2. Two infusions were given to each participant, targeting specific propofol effect-site concentrations in sequence. Infusion A was repeated in the 10 persons receiving propofol alone. The 10 persons who received 30% nitrous oxide during infusion B had the infusion sequence shown.

Table 1. Command Score 1 (CS1) and Command Score 2 (CS2)

Response	Score
CS1*	
Movement of correct limb	2
Any other somatic response	1
No response	0
CS2†	
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1

* At each targeted effect site concentration, a command "move your left (or right) hand" or "move your left (or right) foot" was delivered four times, in random sequence, at 10-s intervals. The maximal total score was thus 8, and the minimal score was 0.

† This is the Modified Observer's Assessment of Alertness/Sedation Scale (MOAAS). No painful stimuli (score = 0) were used.

number 12 always represented a targeted concentration of 2 μg/ml on the descending portion of infusion B. In this way, each sequence number represents a specific "history" of drug treatment. This history identifies the targeted concentration and indicates whether the concentration is increasing or decreasing, and whether nitrous oxide has been administered.

Assessment of Responsiveness

At each steady-state targeted concentration, the participants' responses to commands were recorded. If they responded at one targeted concentration, the infusion was increased to achieve the next higher targeted concentration and the participant was tested again. There were two measures of responsiveness (table 1): Five minutes after the computer indicated that a targeted concentration had been reached, the participant was given one of four possible verbal commands: "move your left foot," "move your right foot," "move your left hand," or "move your right hand." Three more commands were given at 10-s intervals. These commands were delivered in random sequence by the same examiner and were consistently presented in a moderate speaking voice at a uniform distance from the participant. Each response was scored as 2 if the participant was completely correct (correct limb and side), 1 if any other movement response occurred, and 0 for no response. The total command score (CS1) therefore ranged from 0 to 8. This score (CS1) was instituted to determine participants' responses to voice alone. It was

designed to help differentiate sedation states in which the participant clearly recognized that a complex command had been given and then carried out that command accurately, from states in which the command may have been heard, but the action could not be fully or accurately completed. One minute after the CS1, a second evaluation of responsiveness (CS2) was performed using the Modified Observers Assessment of Alertness and Sedation rating scale.[24] The stimuli for these measurements are graded and varied, ranging from a moderate speaking voice to mild physical stimulation. No painful stimuli were used. Once the subject did not respond to commands and physical stimulation, the infusion was then decreased in a stepwise manner, with the participants tested for responsiveness at each specific targeted concentration until the targeted concentration was <0.5 and the participant was awake.

Propofol Analysis

Two samples of arterial blood were drawn for analysis at each targeted concentration: The first was drawn when the computer indicated that the targeted propofol concentration had been achieved, and the second was taken 5 min later. During infusion B, only the later sample was taken after each stepped change in concentration. The samples were collected, frozen, and later analyzed for propofol concentrations using high-performance liquid chromatography analysis at the Anesthesia Research Laboratory at Duke University Medical Center. The separation and quantification procedures were conducted with a C-18, 15 cm × 4.6 mm column (Supelcosil LC-18, Supelco, Bellefonte, PA), and detection was fluorometric. Spiked standards (0.5 and 5 μg/ml) were required to be within ± 20% of the true value with an interassay variability of ± 12%. The duplicate assays of the participants' samples were required to be within ± 20% of each other.

Statistical Analysis

Each of the two categorical responsiveness scores, CS1 and CS2, was dichotomized to define responsiveness and unresponsiveness to voice command. Using CS1, responsiveness to voice was defined as CS1 > 0; using CS2, responsiveness was defined as CS2 > 2. Mean BIS values at all steady-state targeted propofol concentrations when participants were responsive were compared with the mean BIS values at all steady-state targeted concentration when they were unresponsive.

The area under the receiver operating characteris-

tic (ROC) curve was used to summarize the accuracy of the following five variables as predictors of participants' responsiveness and unresponsiveness: (1) BIS, (2) targeted propofol effect site concentrations, (3) measured arterial propofol concentrations, (4) treatment history, and (5) a logistic regression model using measured propofol concentrations and the presence or absence of nitrous oxide. The ROC curve for each variable plots sensitivity (fraction of unresponsive participants who are correctly predicted to be unresponsive) against 1 − specificity (fraction of responsive participants correctly identified). The ROC curves, therefore, reflect the trade-off between sensitivity and specificity for these measurements, and the area under the ROC curve summarizes the predictive power to achieve a high specificity at any given sensitivity.[25] An area > 0.5 indicates that the measurement is predictive, and a measurement with 100% accuracy would have an area of 1. The trapezoid rule was used to calculate the areas under the ROC curves, and paired jackknife t tests were used to test for significant differences among the five diagnostic measurements. The jackknife method calculates standard errors appropriate to study designs that incorporate repeated measures in individual subjects.[26] Paired, two-sided t tests were performed to compare the areas, with significance defined as $P < 0.05$.

The effect of three other factors on BIS' prediction of responsiveness (CS1 and CS2) was investigated using jackknife t tests:

1. During a programmed infusion, each targeted concentration is sought twice, once as drug concentrations increase and once as they decrease. The first analysis compared the BIS prediction of responsiveness when these concentrations were increasing and decreasing. (Data for the highest propofol concentration could not be included in this analysis because this target was sought only once during each infusion.)
2. The stability and reproducibility of the BIS predictions over time were assessed in the ten participants who received two identical infusions (i.e., those persons who did not receive nitrous oxide). This analysis compared the BIS prediction of responsiveness during the first with the second propofol infusion.
3. The effect of nitrous oxide was studied by comparing responses and BIS during propofol with propofol and nitrous oxide administrations.

Results

Fifteen men and five women participated. Their ages ranged from 22 and 50 yr, with a mean of 33 yr. They were generally awake and responsive at target propofol concentrations of 1 μg/ml or less and asleep when the concentration reached 4 μg/ml. One observation in each of two different participants was omitted because steady-state conditions could not be achieved at a targeted concentration. In one, the intravenous catheter became temporarily obstructed, and propofol concentrations transiently decreased during the assessment of responsiveness. In the other, the patient became aroused, and the BIS values rapidly increased within the minute between the two responsiveness tests and, therefore, no consistent estimate of BIS was possible.

The top panel of figure 3 shows the relation between targeted and measured propofol concentrations when propofol was administered alone. The model-driven infusion produced the desired effect of an orderly increase and decrease in drug concentration. Concentrations were not quite at steady state, but they did not change markedly during the 5-min sampling period at each step. The bottom panel of figure 3 shows that the individual values for BIS decreased and increased in inverse relation with propofol concentration.

Table 2 reveals that most CS1 scores were either 0 or 8 (completely unresponsive or completely responsive) with relatively few observations between 1 and 7. The same distribution was seen for the sedation score, CS2: Most scores were either 1 or 5. As indicated in Methods, these two categorical scales were prospectively collapsed into bivariate measures where participants' responsiveness to voice was defined as CS1 > 0 or CS2 > 2. The two responsiveness assessments were closely associated, with minimal deviation among observations (table 3). Using either criterion, responsiveness to voice is strongly correlated with BIS ($P < 0.0001$).

Figure 4 shows the relation between BIS, measured propofol concentration, and responsiveness (CS1) for individuals, in the presence or absence of 30% nitrous oxide. No participant was responsive when BIS was less than 57. Interestingly, no participant receiving nitrous oxide had any response at a BIS value less than 70. These differences are apparent in the logistic regression curves derived from this data set, which are shown in figure 5. The curves describe the probability that a participant will respond to voice as a function of BIS. The slopes of the curves are not different, but there is a significant rightward shift with nitrous oxide: BIS_{50}
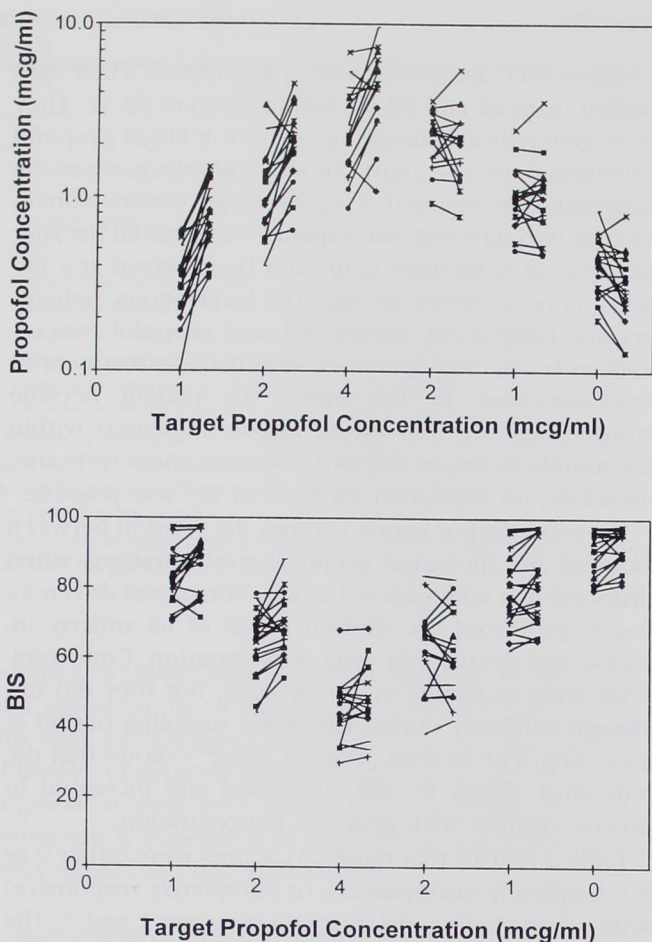
Fig. 3. Raw data from this study during the course of infusion A. The upper panel depicts targeted and measured arterial propofol concentrations. The connected points are the two samples collected at each target concentration. The infusions had not reached steady state, although the logarithmic ordinate magnifies these changes. The lower panel shows the simultaneous measurements of the bispectral index. (See text for details.)

(the BIS predicting 50% response; 95% CI in parentheses) is 65.2 (62.9–67.6) for propofol alone, but it is 75.7 (71.2–80.1) for propofol plus nitrous oxide. The BIS_5 (the BIS predicting 5% response) is a more clinically relevant number, and it is 53.8 (48.7–59.0) for propofol alone and 68.3 (60.5–76.2) for propofol plus nitrous oxide.

Figure 6 shows the ROC curve for the prediction of responsiveness (CS1) using BIS. Similar curves were constructed for several other measured variables, and the ability of each variable to predict responsiveness is summarized by the areas under the ROC curves, shown in table 4. In all cases the ROC curves have an area

Table 2. Distribution of Responses for Command Score 1 and Command Score 2

Score	No. of Responses
Command Score 1*	
8	245
7	3
6	12
5	1
2	11
1	4
0	108
Command Score 2†	
5	245
4	19
3	23
2	16
1	81

* Score > 0 = any response to voice command; 0 = unresponsive.

† Score > 2 = responsive to voice command; ≤2 = unresponsive to voice.

Table 3. Relationship between Command Score 1 (CS1) and Command Score 2 (CS2)

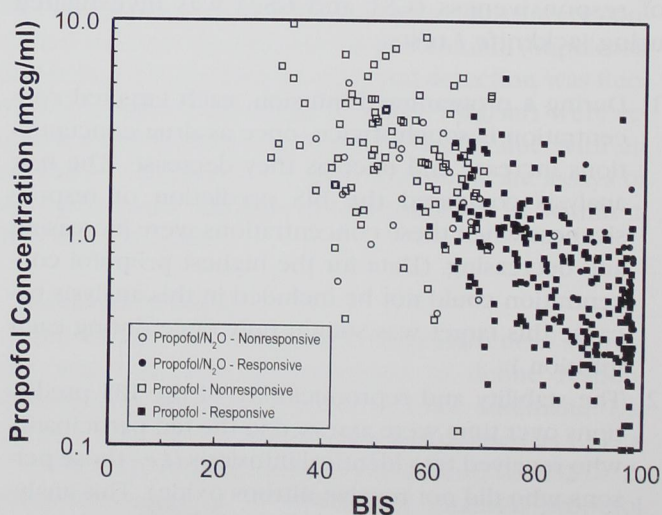|	CS2 ≤ 2	CS2 > 2
CS1 = 0	63	10
CS1 > 0	3	193

Fig. 4. The relation among the bispectral index, simultaneously measured arterial propofol concentration, and responsiveness as determined by CS1. Response to voice is denoted by a filled symbol, whereas an open symbol denotes lack of response. Circles and squares indicate nitrous oxide and no nitrous oxide, respectively.
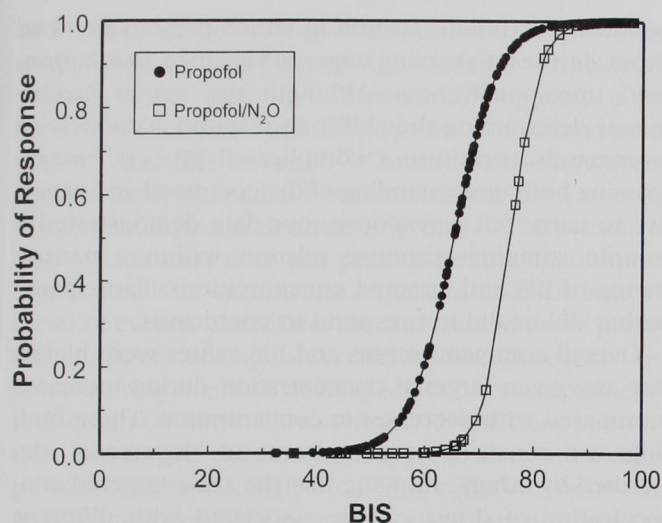
Fig. 5. Logistic regression curves derived from the data in figure 4. The probability of response was lower for a given value of the bispectral index when nitrous oxide was used (see text for details).

Table 4. Areas under Receiver Operating Characteristic Curve (ROC) for Prediction of Responsiveness

Measured Variable	Command Score 1	Command Score 2	P Value (vs. BIS)
BIS	0.9787	0.9763	
Treatment history*	0.9523	0.9678	NS
Targeted concentration	0.9179	0.9230	<0.0003
Logistic regression model†	0.8974	0.9076	<0.04
Measured concentration	0.8787	0.8820	<0.003

BIS = bispectral index; NS = not significant.

* Sequence number that identifies the target propofol concentration and incorporates information on whether the propofol concentration is increasing or decreasing and whether nitrous oxide has been administered.

† Logistic regression model that uses measured propofol concentration and the presence or absence of nitrous oxide.

greater than 0.5, indicating that each measure does predict responsiveness. However, BIS is a significantly better predictor than targeted concentration ($P < 0.0003$), measured propofol concentrations ($P < 0.003$), and a logistic regression model that combines measured propofol concentrations and the presence (or absence) of nitrous oxide ($P < 0.04$). The BIS was not a significantly better predictor than treatment "history," the sequence number that incorporates information about the history of drug administration. However, when BIS was combined with the information in treatment "history," using a logistic regression model, it provided additional predictive power for CS1 ($P < 0.02$).

CS1 and CS2 were higher for a given target concentration during the periods when concentrations were increasing compared with periods when concentrations were decreasing ($P < 0.001$). This means, for example, that some participants were awake when the target of 2 µg/ml was achieved initially, asleep when it was increased to 4 µg/ml, and still asleep when it was reduced to 2 µg/ml. These differences in responsiveness were reflected in the values for BIS ($P < 0.001$). Neither BIS, CS1, nor CS2 were significantly different when a given target was reached during infusion A compared with B, indicating that the measurement was stable over time.

Discussion

Our purpose in this study was to determine whether BIS correlated with volunteers' responsiveness to commands during computer-controlled infusions of propofol with and without nitrous oxide. Our findings indicate the following. (1) There is a strong association between BIS and command scores, whether the command consists simply of a uniform voice asking the volunteer to move a hand or foot, or incorporates graded and then varied stimuli, ranging from a normal
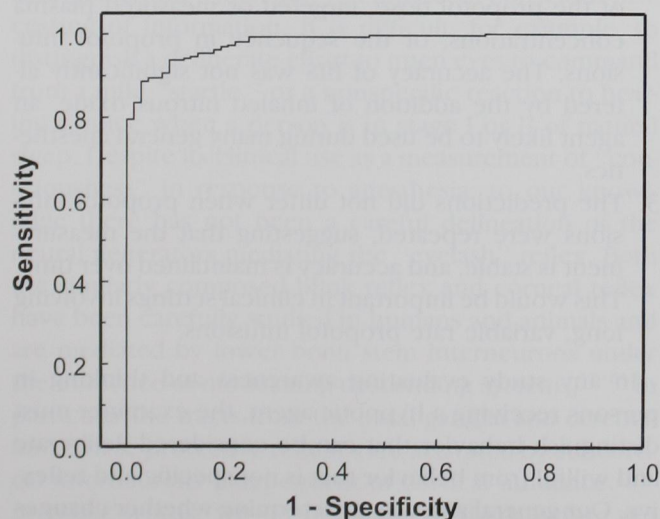

Fig. 6. The receiver operating characteristic curve for the bispectral index showing the trade-off between sensitivity (fraction of unresponsive participants correctly identified) and specificity (fraction of responsive participants correctly identified). The area under this curve is 0.9787 (see table 4), indicating high sensitivity and specificity.

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voice to a loud voice, to gentle touch and, finally, to shaking. (2) The relation between BIS and responsiveness scores remains consistent not only over time but also when propofol concentrations are increasing or decreasing. (3) Although both BIS and propofol concentrations show a significant correlation with sedation scores, BIS is a better predictor of responsiveness than either targeted or measured concentrations. (4) The BIS is as accurate in predicting participants' responsiveness as knowing the "treatment history," the sequence number that identifies the targeted concentration, and indicates whether the concentration is increasing or decreasing and whether nitrous oxide has been administered. The clinician administering anesthesia has some of this information with which to work, but most anesthetics would not follow such a uniform pattern. Given that the prediction from the sequence numbers uses many parameters specifically fitted to this data set, it is not unexpected that it would be a strong predictor of participants' responses to command. Especially noteworthy is the fact that BIS can be combined with knowledge of the participants' treatment history to provide additional predictive accuracy beyond that determined by the history alone.

An unexpected finding was the small shift in the relation between responsiveness and BIS when nitrous oxide was used. Clinical studies suggest that the value of BIS should be less than 55–60 to ensure adequate hypnosis, and data from the multicenter volunteer trial do not demonstrate any differences in this value when different hypnotic agents are used or when hypnotics are combined with alfentanil.[22] The difference we found was small (a 5% probability of response was associated with a BIS value of 65–70), and it is based on a relatively small data set. Unless these data are confirmed in a much larger trial, it seems prudent to use the more conservative lower numbers.

A small change in BIS substantially altered the probability that a participant would carry out complex commands. This very narrow range in BIS separating those who did and did not follow commands suggests either that the incremental increases in propofol concentrations were too large to produce graded responses or that there was an abrupt loss of conscious processing at a measured BIS threshold of approximately 65–70. Our data support the argument of Prys-Roberts[27] that loss of consciousness under anesthesia occurs at a threshold separating wakefulness from unresponsiveness. Our data do not support the view that BIS and conscious processing of information are related in a

gradual, continuous fashion in which persons descend from alertness to varying stages of vigilance, inattention, and unresponsiveness. Although the neural mechanisms determining the ability to respond accurately to commands constitute a complicated process encompassing both understanding of the command and capacity to carry out a response, our data demonstrated a simple stimulus–response relation within a narrow range of BIS and targeted concentrations. Participants either did or did not respond to commands.

Overall command scores and BIS values were higher for any given targeted concentration during increases compared with decreases in concentration. These findings are consistent with patterns of "hysteresis" described by others, showing that the same targeted concentration of drugs can be associated with different behavioral and electroencephalographic effects.[28,29] Hysteresis may partially explain why measured arterial and predicted effect-site concentrations of propofol did not predict responses and BIS did.

Our findings suggest that a randomly obtained value of BIS, by itself, may be sufficiently accurate to predict sedation, hypnosis, and impairment of conscious thinking:

1. Our estimates of accuracy were based on absolute values of BIS, without reference to baseline measurements.
2. Accurate predictions were made without knowledge of the propofol dose, targeted or measured plasma concentrations, or the sequence in propofol infusions. The accuracy of BIS was not significantly altered by the addition of inhaled nitrous oxide, an agent likely to be used during many general anesthetics.
3. The predictions did not differ when propofol infusions were repeated, suggesting that the measurement is stable, and accuracy is maintained over time. This would be important in clinical settings involving long, variable rate propofol infusions.

In any study evaluating awareness and thinking in persons receiving a hypnotic agent, the examiner must distinguish behavior that can be considered deliberate and willful from behavior that is nonspecific and reflexive. Our general aim was to determine whether changes in BIS reflected the participants' ability to perceive sensory information. Our arguments rest on the strength of the relation between the participants' response and the specific measurable properties of the EEG, and the strength of the association between these responses

and conscious processing of information. In previous studies, loss of consciousness was defined variously as absence of eye opening to command,[8] suppression of the eyelash reflex,[8,22] uninhibited release of a hand-held object,[22] and lack of recall.[21] Consciousness, however, is customarily defined as a state consisting of awareness of surroundings and alertness to events.[30] The presence of consciousness does not preclude either inattention to the details of specifically requested tasks or lack of recall of events. Therefore, the test used in these previous studies to distinguish conscious from unconscious behavior may not have been specific for consciousness. It is common, after all, to witness distraction, inattention, and forgetfulness even in normal, alert and awake persons. The test designed to define conscious behavior must elicit a response requiring discrimination among choices.

Our paradigm required that the participant be aware of the command, persist in the effort to follow the command, and then carry out the command accurately, distinguishing between the right and left side and two anatomic structures, the hand and the foot. The information from this paradigm differs from that obtained from eye opening to command, the eyelash reflex, and the uninhibited release of an object. To perform the task accurately under our protocol, the participant must choose the correct response consistently. Eye opening to command may elicit nonspecific responses that are ambiguous and which may not represent conscious processing of information. It is difficult, for example, to distinguish a deliberate effort to open eyes to command from a mild "startle," or a nonspecific reaction to hearing a voice when a person is in stage I or II of natural sleep. Despite its clinical use as a measurement of "consciousness" in response to anesthesia, to our knowledge there has not been a careful delineation of the neural generators mediating the "eyelash" reflex. Both the similarly composed blink reflex and corneal reflex have been carefully studied in humans and animals and are mediated by lower brain stem interneurons under the influence of modulating descending systems,[31-33] in particular the tracts from the basal ganglia and cerebellum. These protective reflexes are activated by subcortical interneurons independent of cortical influence.[31,32] In other words, we do not have to think before we blink! The blink reflex is suppressed by dopamine receptor antagonists such as haloperidol and other agents while participants are awake and alert.[34] Even smoking a cigarette suppresses the complicated blink reflex in awake persons.[35] Such findings challenge the notion that suppression of these reflexes by hypnotic agents is a specific marker for loss of consciousness. We are uncertain what precise information may be derived from observing a person release an object in response to an infusion of propofol.

Our study consisted exclusively of healthy volunteers who were not being prepared for surgery, who were not subjected to any painful stimuli, and who were given only one or two drugs. A second large multicenter trial has now established that titration of propofol with BIS is useful during clinical anesthesia and surgery.[36] Thus BIS is an empirically derived measurement that appears to reflect an important component of the anesthetic state. Further study of this technology under other clinical conditions may prove helpful, not only in outlining the value of its application in clinical practice but also in understanding the electrical mechanisms of drug-induced loss of consciousness.

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