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Quantitative EEG Correlations with Brain Glucose Metabolic Rate during Anesthesia in Volunteers

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Background: **To help elucidate the relationship between anesthetic-induced changes in the electroencephalogram (EEG) and the concurrent cerebral metabolic changes caused by anesthesia, positron emission tomography data of cerebral metabolism obtained in volunteers during anesthesia were correlated retrospectively with various concurrently measured EEG descriptors.**

Methods: **Volunteers underwent functional brain imaging using the ^{18}fluorodeoxyglucose technique; one scan always assessed awake-baseline cerebral metabolism (n = 7), and the other scans assessed metabolism during propofol sedation (n = 4), propofol anesthesia (n = 4), or isoflurane anesthesia (n = 5). The EEG was recorded continuously during metabolism assessment using a frontal-mastoid montage. Power spectrum variables, median frequency, 95% spectral edge, and bispectral index (BIS) values subsequently were correlated with the percentage of absolute cerebral metabolic reduction (PACMR) of glucose utilization caused by anesthesia.**

Results: **The percentage of absolute cerebral metabolic reduction, evident during anesthesia, trended median frequency ($r = -0.46$, $P = 0.11$), and the spectral edge ($r = -0.52$, $P = 0.07$), and correlated with anesthetic type ($r = -0.70$, $P < 0.05$), relative β power ($r = -0.60$, $P < 0.05$), total power ($r = 0.71$, $P < 0.01$), and bispectral index ($r = -0.81$, $P < 0.001$). After controlling for anesthetic type, only bispectral index ($r = 0.40$, $P = 0.08$) and α power ($r = 0.37$, $P = 0.10$) approached significance for explaining residual percentage of absolute cerebral metabolic reduction prediction error.**

Conclusions: **Some EEG descriptors correlated linearly with the magnitude of the cerebral metabolic reduction caused by propofol and isoflurane anesthesia. These data suggest that a physiologic link exists between the EEG and cerebral metabolism during anesthesia that is mathematically quantifiable. (Key words: Deoxyglucose; humans; radionuclide imaging.)**

THE existence of a physiologic relation between electroencephalographic (EEG) activity and cerebral metabolism during anesthesia seems well established.[1] It has been known for some time that several anesthetics can cause EEG burst suppression, coincident with a cerebral metabolic reduction of approximately 50%, and that an isoelectric EEG can be produced by some anesthetic agents, coincident with greater levels of cerebral metabolic reduction.[1] However, although the EEG changes in predictable ways with increasing doses of various anesthetic agents[2–6] and cerebral metabolism also changes in predictable ways (*i.e.*, generally decreases) with increasing doses of various anesthetic agents,[7] relatively few data exist that directly quantify the nature of the relation between cerebral metabolism during anesthesia and the EEG.

To help to elucidate the nature of this fundamental physiologic relation, positron emission tomography (PET) data of cerebral glucose metabolic rates evident in volunteers during either propofol sedation,[8] propofol anesthesia,[9] or isoflurane anesthesia[10] were correlated retrospectively with previously and simultaneously obtained measurements of various EEG descriptors. The EEG descriptors evaluated included those historically used to quantify the spectral parameters of the EEG signal, including relative α, β, δ, and θ, power bands, along with total power. Also evaluated were those EEG descriptors thought to correlate in some way with increasing anesthetic dose, including 95% spectral edge frequency, median power frequency, and the bispectral index (BIS). Median power frequency and 95% spectral edge frequency are suggested frequently to monitor some component of anesthetic depth or anesthetic ef-

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fectiveness,[11-14] although the clinical usefulness of these simple EEG descriptors as monitors of anesthetic depth appears limited.[15] The BIS is an empirically developed complex descriptor of the EEG that has been shown to have some clinical usefulness for titrating the hypnotic effects of anesthetic agents, such as propofol and isoflurane.[16]

Materials and Methods

This was a retrospective analysis of EEG data gathered during studies of the regional cerebral metabolic effects of propofol and isoflurane anesthesia in paid volunteers. Institutional review board approval was obtained, and all volunteers gave written informed consent. Volunteers underwent functional brain imaging using the ^{18}fluorodeoxyglucose technique (^{18}FDG); one scan always assessed awake-baseline cerebral metabolism (n = 7), and the other scans assessed metabolism during propofol sedation (n = 4), propofol anesthesia (n = 4), or isoflurane anesthesia (n = 5). Data from seven right-handed men with recorded EEG and PET data and 22 individual PET scans served as the basis for the current analyses.[8-10] Cerebral metabolism data from one volunteer's propofol anesthetic were obtained after the initial propofol report was published, and, thus, they have not been reported before. At least 1 week separated scanning sessions between anesthetic conditions and baseline. A minimum of 1 yr separated scanning sessions for two volunteers who participated in both the propofol and isoflurane studies.

Volunteers

Volunteers were healthy men who do not smoke (mean age, 24 ± 3 yr). Each was classified as American Society of Anesthesiologists physical status 1, and all had no evidence of psychiatric illness. The men avoided caffeine and other medications for at least 48 h before each scan. They fasted for at least 8 h before each scanning session and received oral antacid (30 ml sodium citrate taken orally) before scans involving anesthesia. Each volunteer had two or three intravenous catheters inserted, one to administer the ^{18}FDG PET tracer, one for blood sampling, and one for the propofol infusion, when necessary. Monitoring devices included a three-lead electrocardiograph, an automated noninvasive blood pressure monitor, a pulse oximeter, a tight-fitting face mask for end-tidal carbon dioxide monitoring, a temperature monitor, and a precordial stethoscope.

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

Response	Score Level
Responds readily to name spoken in normal tone	5 (alert)
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 skaking	1
Does not respond to noxious stimulus	0

Anesthetic Procedures

The details of the anesthetic administration procedures have been reported.[9,10] Anesthetic doses were incrementally and slowly adjusted upward to achieve the desired clinical endpoints. The endpoint for the "anesthesia"-related scans was a score of 1 or less on the modified Observer Assessment of Alertness and Sedation (table 1) rating scale.[16]

Isoflurane Anesthesia. Isoflurane was administered *via* a tight-fitting face mask using a calibrated vaporizer through a semiclosed non-rebreathing circuit. End-tidal isoflurane concentration was monitored using a Poet II agent analyzer (Criticare Systems Inc., Milwaukee, WI). Isoflurane was administered incrementally in 0.1% expired steps to achieve loss of consciousness with no response to mild prodding. After loss of consciousness was achieved, the end-tidal isoflurane concentration was fixed for the rest of the experiment.

Propofol Anesthesia. Volunteers were administered propofol as a 0.4 mg/kg bolus followed by a continuous infusion of 2 $mg \cdot kg^{-1} \cdot h^{-1}$. This infusion was adjusted upward in increments of 2 $mg \cdot kg^{-1} \cdot h^{-1}$ every 15–20 min until volunteers lost consciousness and had no response to mild prodding. After the volunteer was unresponsive, the first of four propofol blood level samples was taken, and the propofol infusion rate was fixed. Propofol blood sample 2 was obtained at the start of the ^{18}FDG uptake period, sample 3 was obtained 15 min into the uptake period, and sample 4 was taken at the end of the uptake period just before the infusion was stopped.

Propofol Sedation. Propofol sedation infusions

were titrated to achieve a targeted sedation score not less than 3. Volunteers in the sedate condition were quite drowsy but remained aware and responsive during the study period. Before metabolism was assessed, all volunteers were in a cognitive state in which each failed to recall at least one of three common objects presented and verbally repeated 3 min before questioning. Responsiveness was assessed intermittently (every 3–15 min, depending on clinical signs) throughout the measurement of cerebral metabolism by noting responsiveness to loud verbal stimulation. The volunteers were instructed, before the experiment, to raise and quickly lower their right index finger if, and when, the investigator asked "Are you doing okay?". Sometimes, when the volunteers were not responsive to this verbal stimulation, they were further stimulated by mild prodding or shaking. In all such cases, the additional tactile stimulation returned each volunteer to a verbally responsive state. None spent more than 3 min in a verbally unresponsive state during the 32-min uptake period. Three propofol blood samples were obtained during the sedation scans: one at the start of the ^{18}FDG uptake period, one at the midpoint of the uptake period, and one at the end.

Awake-baseline Conditions

For the awake control scans, the volunteers lay quietly on a gurney with their eyes closed. Again responsiveness was assessed intermittently (every 3–15 min, depending on clinical signs) throughout the measurement of cerebral metabolism according to their responsiveness to verbal stimulation. All volunteers remained responsive to verbal stimulation throughout the 32-min uptake period and, after the experiment, no volunteer reported any subjective episodes of spontaneous sleep during metabolism assessment.

Procedural Overview

The volunteers were administered anesthesia, as described before, while in a small, darkened, sound-shielded room. Measurement of cerebral metabolism during each anesthetic condition did not begin until volunteers clinically approached a steady-state level of anesthesia (*i.e.*, no changes in heart rate, breathing pattern, or blood pressure for 12 min). Once stable in the desired conditions, 5 mC ^{18}FDG was injected intravenously. The volunteers remained at the targeted level of anesthesia for the next 32 min. After labeling of the brain with the positron emitting tracer, the anesthetic was discontinued. The volunteers were allowed to emerge from the anesthetic and regain awareness before being taken to the PET scanner. They continued to recover from the anesthetic while in the PET scanner.

For the baseline condition, a similar labeling and scanning sequence was followed as outlined before. Scanning of all volunteers began within 20 min from the end of each uptake period for each condition. The time between injection of the ^{18}FDG and the start of each scan was standardized across conditions to ensure that it was similar in duration for all volunteers.

Electroencephalography. An EEG signal was obtained using gold cup electrodes applied to the scalp with cream and located according to the international 10–20 system. Skin impedance was maintained at $< 5\ k\Omega$. The following leads were recorded: left and right frontal-mastoid (Fp1-A1, Fp2-A2, channels 1 and 2), left and right frontal-CZ (Fp1-CZ, Fp2-CZ, channels 3 and 4), plus a ground electrode placed at the center of the forehead. The EEG was recorded using an Aspect A-1000 EEG monitor (Aspect Medical Systems, Natick, MA). Data averaged from the combined frontal-mastoid leads (channels 1 and 2) are presented in this article.

Conventional frequency bands were used to describe power spectrum variables. Raw EEG, power bands, spectral determinants, and the BIS were recorded continuously, along with time-locked clinical event markers, as needed, and were stored in a computer database with tape backup for subsequent off-line analysis. The sampling rate was 128 samples/s. Spectral variables were recorded in 2-s epochs with an update rate of 10 s. Spectral and BIS smoothing were set to 30 s. Low- and high-pass filters were set to 0.25 Hz and 30 Hz. For those scans not obtained using the current version of the BIS, the recorded EEG data were subsequently reanalyzed using the BIS software algorithm version 3.2. Electromyographic activity was defined as the absolute power in the range of 70–110 Hz, reported in decibels ($n = 11$; two early propofol anesthesia volunteers did not have electromyographic values recorded). For each volunteer, the EEG descriptor values that were recorded while cerebral metabolic activity was being assessed were averaged to form a single number representative of that volunteer's average EEG descriptor value associated with that particular type and dose of anesthesia being studied.

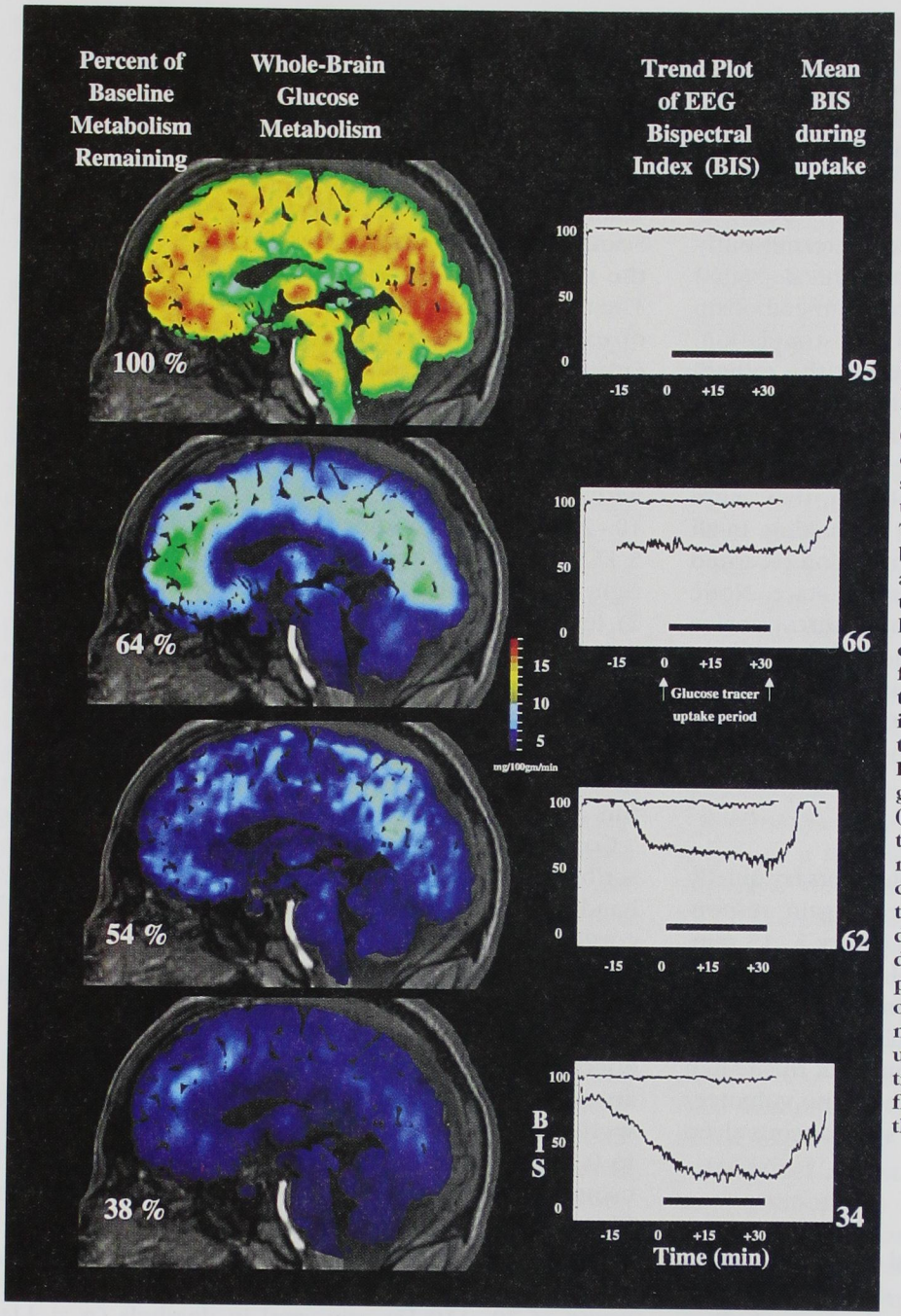

Fig. 1. Brain metabolic reduction during anesthesia compared with concurrent measurements of one electroencephalogram (EEG) descriptor, the bispectral index (BIS). The data show the whole-brain positron emission tomography glucose metabolic results (mg · 100 g^{-1} · min^{-1}) on color-coded brain images, along with the concurrent trend plots of the BIS data obtained from one representative volunteer (S2) across the different depths and types of anesthesia studied. Each of the EEG descriptors evaluated showed a similar trending pattern, as illustrated by the BIS. The upper row of data show the awake-baseline conditions for brain metabolism and BIS. Data in the second row are from the propofol sedation condition (the baseline BIS plot, from the first row, is replicated in the plots of the other conditions for purposes of comparison). Data in the third and bottom rows are from the isoflurane and propofol anesthesia conditions, respectively. In each row, the mean BIS (last column) recorded while cerebral glucose utilization was being determined (black bar) is shown and compared with the percentage of baseline metabolism remaining at each depth of anesthesia (first column). The figure shows that the relation identified between the percentage reduction of brain metabolism caused by different doses, and types, of anesthesia parallels concurrent changes in the EEG of similar magnitude. The underlying magnetic resonance image was obtained using a SPGR sequence with repetition time of 24 ms, echo time of 5 ms, and a flip angle of 40° for contiguous 1.2-mm-thick axial slices.

Positron Emission Tomography Procedures. The regional cerebral metabolic rate of glucose utilization was measured with two different PET cameras. For the isoflurane data, a GE2048 head-dedicated scanner was used (GE/Scanditronix, Stockholm, Sweden). This scanner replaced an older NeuroEcat scanner that was used to collect the propofol data. In each case, a volunteer's baseline was obtained on the same scanner that was used for that volunteer's anesthesia-related scan. The GE PET scanner has eight rings with 256 detectors per ring to achieve a resolution of 4.5 mm at full-width-half-maximum in plane and 6 mm axially. The NeuroEcat PET scanner had a single ring with shadow shields and septa to achieve 7.6-mm

Table 2. Effects of Different Anesthetic Levels on Cerebral Metabolic Rate (CMR), EEG Descriptors, and EMG Activity

Variable	Anesthetic Level			Significance	
	(1) Sedate Propofol	(2) Unresponsive Isoflurane	(3) Unresponsive Propofol	Overall ANOVA (*P* Value)	Pairwise Post-hoc
CMR (% reduction)	34 ± 16	46 ± 11	60 ± 9	0.05	1 *vs.* 3
Bispectral index	66 ± 3	54 ± 9	37 ± 6	0.001	1 *vs.* 3, 2 *vs.* 3
Total power (mV^2)	63 ± 2	67 ± 4	71 ± 4	0.01	1 *vs.* 3
Relative β power (%)	26 ± 6	11 ± 8	2 ± 1	0.001	1 *vs.* 2, 1 *vs.* 3
95% spectral edge frequency (Hz)	19 ± 2	14 ± 3	11 ± 2	0.01	1 *vs.* 2, 1 *vs.* 3
Median power frequency (Hz)	6.2 ± 3.0	3.1 ± 1.7	1.0 ± 0.4	0.05	1 *vs.* 3
Relative δ power (%)	46 ± 10	65 ± 15	79 ± 11	0.05	1 *vs.* 3
Relative θ power (%)	7.2 ± 5	6.4 ± 2.9	4.1 ± 2.0	NS	
Relative α power (%)	20 ± 8	17 ± 10	15 ± 9	NS	
EMG activity (dB)	37 ± 1	33 ± 3	29 ± 1	0.05	1 *vs.* 3

NS = not significant.

resolution (full-width-half-maximum) in plane and 9.9 mm axially. For the GE2048 scanner, two sets of 15 image planes, resulting in 30 PET images across the whole brain, were obtained for each volunteer. With the NeuroEcat scanner, 13 image slices across the whole brain were obtained that started at the level of 85% of head height (vertex to canthomeatal line, usually 12–14 cm) and stepped downward in steps of 10 mm. All scans were obtained relative to the canthomeatal line. Volunteers were positioned using laser guidance, and a thermosetting plastic face mask was used to hold each volunteer's head stationary during image acquisition for both the awake-baseline and anesthesia conditions.

Table 3. Correlations of Various EEG Determinates and Anesthetic Level with Percent Absolute Cerebral Metabolic Reduction

Variable	r Value	*P* Value	Controlled for Anesthetic Type	
			r Value	*P* Value
Anesthetic type	0.70	<0.05		
Bispectral index	−0.81	<0.001	−0.40	0.08
Total power (mV^2)	0.71	<0.01	0.26	0.27
Relative β power (%)	−0.60	<0.05	−0.01	0.98
95% spectral edge frequency (Hz)	−0.52	0.07	−0.09	0.71
Median power frequency (Hz)	−0.46	0.11	−0.09	0.70
Relative δ power (%)	0.36	0.23	0.27	0.25
Relative θ power (%)	−0.34	0.25	−0.03	0.92
Relative α power (%)	0.17	0.57	0.37	0.10
EMG activity (dB)	−0.58	0.06	−0.22	0.48

Whole-brain and regional metabolic rates of glucose utilization were calculated using established PET methods and the well-established models of deoxyglucose kinetics.[17–20] The sagittal image reconstruction (fig. 1) was rendered using "BrainImage" software.[21]

Statistical Analyses

Data are presented as mean ± SD. Cerebral metabolism data were analyzed as the percentage change from baseline values or, alternatively, as the percentage of absolute cerebral metabolic reduction (PACMR) of whole-brain glucose utilization caused by anesthesia. This allowed the PET data from the separate studies, which were gathered from different PET scanners, to be directly comparable.[22] Significant changes in EEG descriptor values, PACMR values, and electromyographic values at the various anesthetic levels were assessed using a one-way analysis of variance, with *post hoc t* testing and Bonferroni–Dunn correction for multiple comparisons, with $P < 0.05$ considered significant. Pearson's correlation coefficient with Fisher's r to z conversion was used to evaluate relations between the various EEG descriptors and the PACMR evident during anesthesia, with $P < 0.05$ considered significant. To control for the effects of the different anesthetic levels on the resulting simple linear correlations, a partial correlation approach was also used. The partial correlations help to determine the effectiveness of using EEG-derived variable x to approximate PACMR values after they have been adjusted for anesthetic type. An alternative explanation is possible: If changes in global cerebral metabolism are changing the anesthetic level, then par-

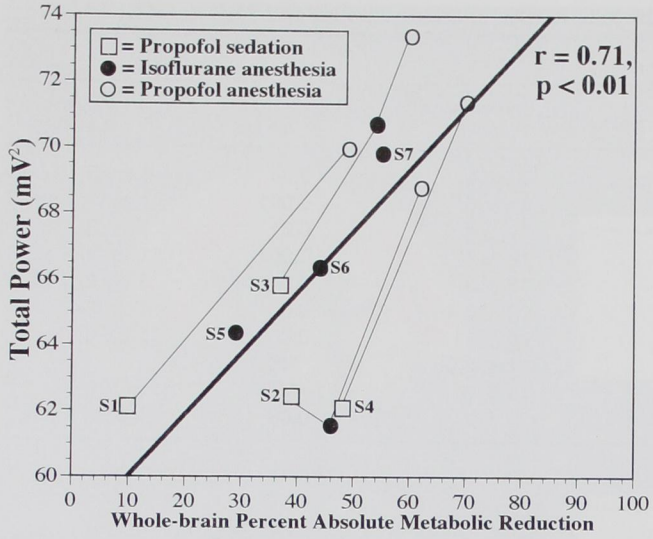

Fig. 2. A linear regression analysis for total power. The dark black line is the regression line through the data that results when the data points are treated as independent (n = 13). The correlation coefficient and the probability values of this linear regression are given. A significant linear relation is found, such that the increases in total power that occur with the different anesthetic levels correlate with the magnitude of the cerebral metabolic reduction caused by the anesthetics. Individual volunteers are labeled with "S numbers" for comparison among the various EEG descriptors. Some volunteers participated in all phases of the study (*e.g.*, S2 and S3) and are shown on the graph as more than one data point. The nonindependent data points are joined together with lighter black lines. Because the data points are not completely independent, the correlation analysis should be interpreted with caution when the lighter lines do not approximately parallel the regression line.

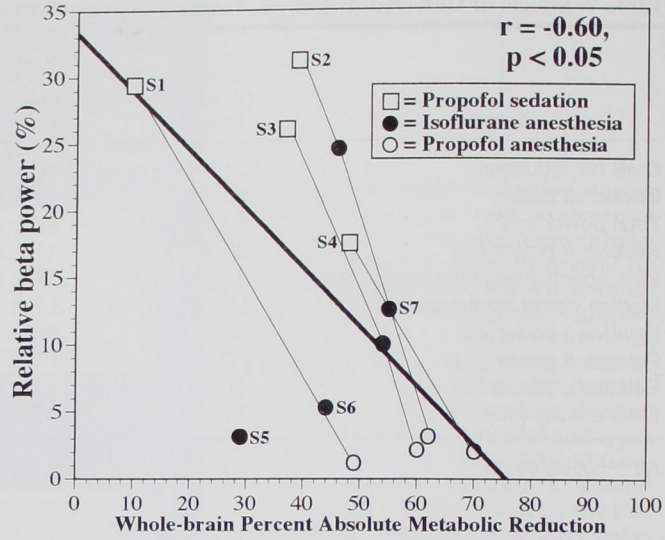

Fig. 3. A linear regression analysis for relative β power. A significant linear relation is found, such that the decreases in relative β power that occur with the different anesthetic levels correlate with the magnitude of the cerebral metabolic reduction caused by the anesthetics. The lines and labels are as shown in figure 2.

tial correlation analysis will determine whether EEG variable x offers any more information about cerebral metabolic reduction than does simply knowing the anesthetic level.

Results

The mean (± SD) propofol infusion rate was 4.5 ± 1.0 $mg \cdot kg^{-1} \cdot h^{-1}$ during sedation and 9 ± 2 $mg \cdot kg^{-1} \cdot h^{-1}$ while volunteers were unresponsive. Resultant blood levels were 1.0 ± 0.2 and 3.5 ± 0.6 $\mu g/ml$ plasma, respectively. The mean expired end-tidal isoflurane concentration at unresponsiveness was 0.5 ± 0.1%. The magnitude of the metabolic reduction that occurred during each level and type of anesthesia can be qualitatively appreciated by referring to figure 1. The figure (showing the data from a single volunteer [S2] who participated in all phases of the study) reveals how brain metabolism decreases with increasing doses, and the different types, of anesthesia studied. The figure also shows how one of the EEG descriptors, the BIS, changed with the changing level of anesthesia in this particular person.

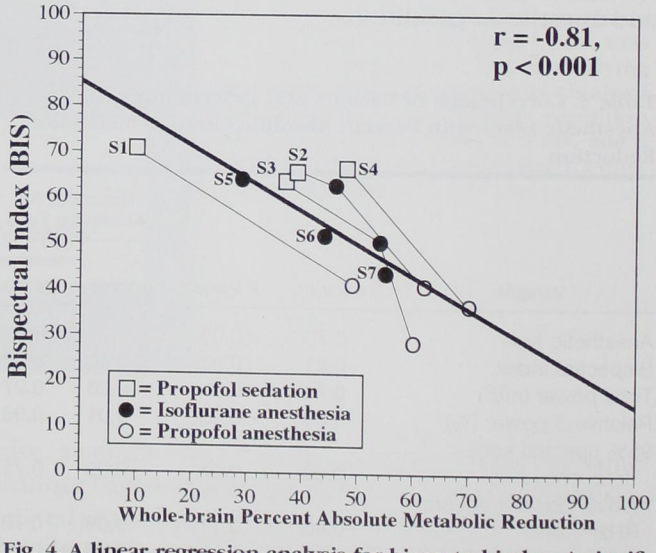

Fig. 4. A linear regression analysis for bispectral index. A significant linear relation is found, such that the decreases in the bispectral index that occur with the different anesthetic levels correlate with the magnitude of the cerebral metabolic reduction caused by the anesthetics. The lines and labels are as shown in figure 2.

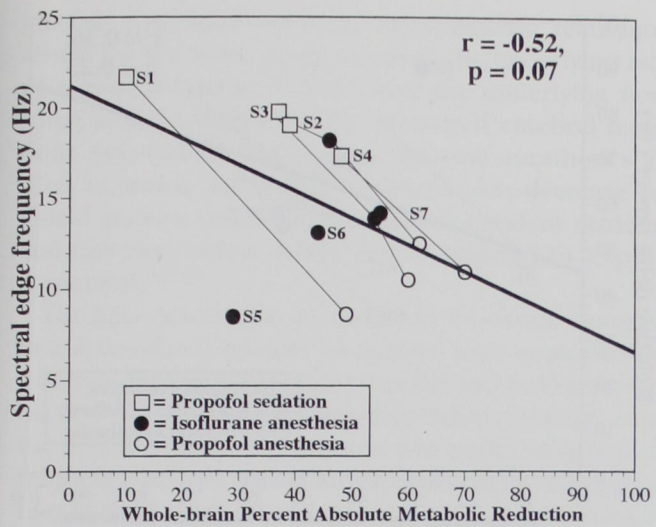

Fig. 5. A linear regression analysis for spectral edge frequency (SEF). The apparent linear relation that occurs between the SEF and the cerebral metabolic reduction evident at the various levels of anesthesia just misses statistical significance. The lines joining each volunteer's data points suggest that increasing levels of anesthesia are, nonetheless, associated with lower SEF values coincident with greater reductions in cerebral metabolism for each volunteer. The lines and labels are as shown in figure 2.

All of the measured variables, except relative α power and relative θ power, showed significant differences across the different anesthetic levels evaluated (table 2). The effect size for propofol sedation was less than that seen for isoflurane anesthesia, which was less than that seen for propofol anesthesia. Most variables decreased in value as cerebral metabolism decreased across the anesthetic conditions. However, relative δ power and total power significantly increased as cerebral metabolism decreased (table 2).

Table 3 shows the correlations that were found between all of the different EEG descriptors evaluated and the PACMR values evident during the various anesthetics administered. The PACMR values correlated significantly with total power (fig. 2), relative β power (fig. 3). and BIS (fig. 4). Although the grouped analyses do not reveal a significant linear correlation between PACMR and the spectral edge (fig. 5) or median power frequencies (fig. 6), a within-volunteer trend occurred for these variables to decrease with greater cerebral metabolic reductions. There was also some within-volunteer tendency for relative θ power (fig. 7) and relative α power (fig. 8) to decrease with increasing cerebral metabolic reductions. Relative δ power, however, tended to increase with greater brain metabolic reductions (fig. 9).

Using nonlinear regression analysis revealed that anesthetic type correlated significantly with cerebral metabolic reduction ($r = 0.70$, $r^2 = 0.49$, $P < 0.05$). In other words, by simply knowing the type of anesthetic used and the targeted clinical endpoint, we can account for approximately 50% of the variance associated with predicting the PACMR. A partial correlation analysis (table 3) revealed that only BIS ($r = -0.40$, $P = 0.08$) and relative α power ($r = 0.37$, $P = 0.10$) approached significance for explaining the residual error in predicting PACMR values after controlling for anesthetic type.

Discussion

It is well established for several different anesthetic agents that progressively higher doses of anesthesia cause progressively greater decreases in brain metabolism.[1,7,23] It is also well established that the EEG changes in predictable ways with increasing doses of various anesthetic agents.[2,6,24] Therefore, the changes that occur in the EEG signal with increasing doses of anesthesia must be accompanied by concurrent changes in brain

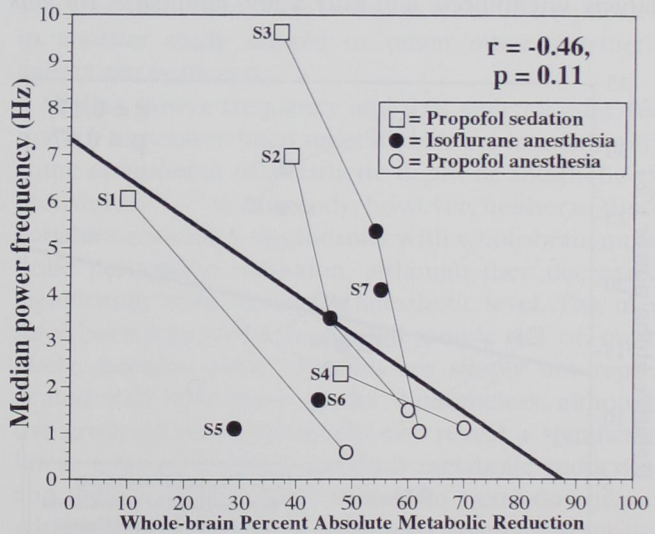

Fig. 6. A linear regression analysis for median power frequency. The apparent linear relation that occurs between the median power frequency and the cerebral metabolic reduction evident at the various levels of anesthesia is not statistically significant. The lines joining each volunteer's data points suggest that increasing levels of anesthesia are, nonetheless, associated with lower median power frequency values coincident with greater reductions in cerebral metabolism for each volunteer. The lines and labels are as shown in figure 2.

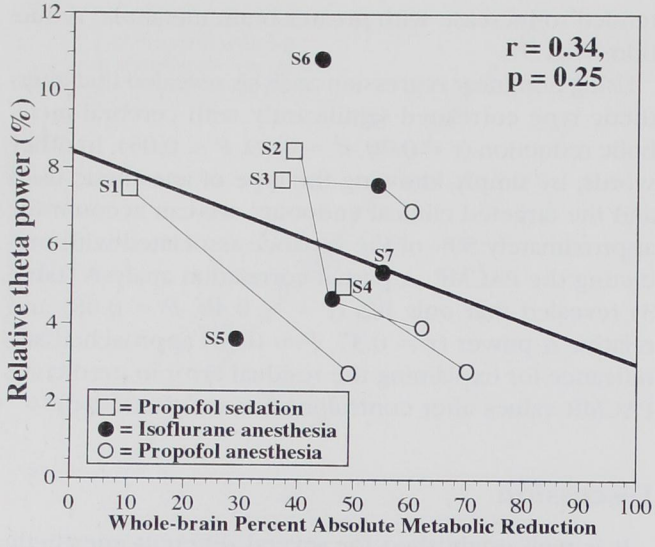

Fig. 7. A linear regression analysis for relative θ power. A significant linear effect is not found. However, the lines joining each volunteer's data points suggest that increasing levels of anesthesia are somewhat associated with lower relative θ power values coincident with greater reductions in cerebral metabolism for each volunteer. The lines and labels are as shown in figure 2.

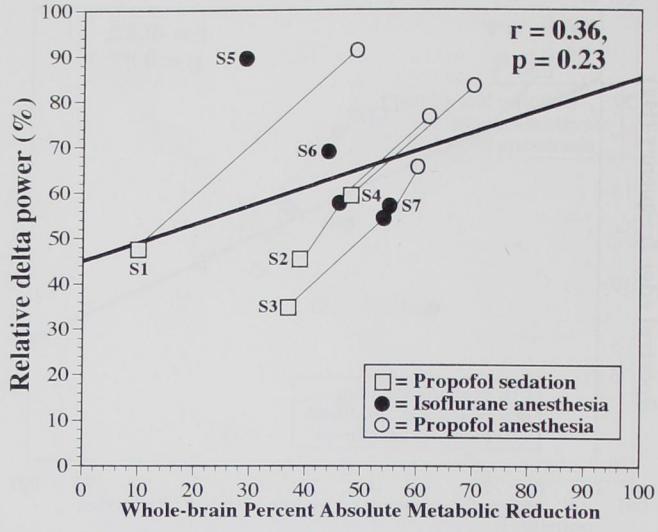

Fig. 9. Linear regression analysis for relative δ power. A significant linear effect is not found. However, the lines joining each volunteer's data points suggest that increasing levels of anesthesia are associated with higher relative δ power values coincident with greater reductions in cerebral metabolism for each volunteer. The lines and labels are as shown in figure 2.

metabolism. Perhaps because the logic of this inference seems obvious, the quantifiable nature of the relation between cerebral metabolism and the EEG has been left largely unexplored, and only a few landmarks for this relation have been determined (*e.g.*, a cerebral metabolic reduction of approximately 50% equates with EEG burst suppression). The current results extend our knowledge about this relation and show that for a clinically relevant dosage range of propofol and isoflurane anesthesia several processed EEG descriptors correlate approximately in a linear manner with the magnitude of the cerebral metabolic reduction caused by anesthesia. In other words, the magnitude of the anesthetic-induced changes in the EEG evident during sedation and light anesthesia closely paralleled the magnitude of the reduction in global cerebral metabolism caused by the anesthesia.

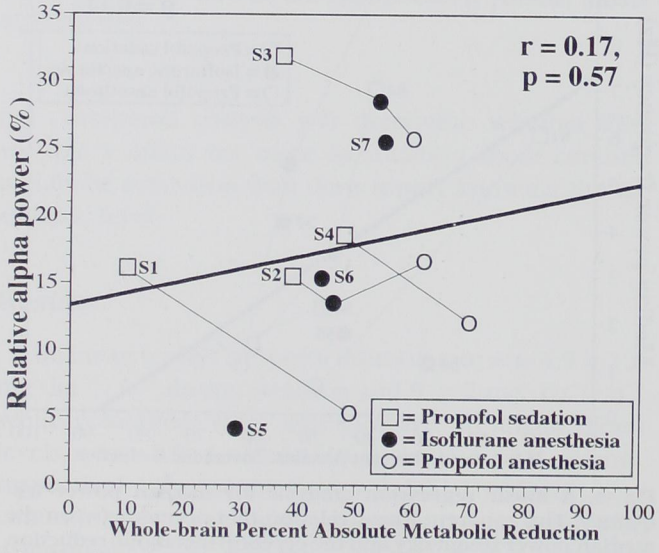

Fig. 8. A linear regression analysis for relative α power. A significant linear effect is not found. However, the lines joining each volunteer's data points suggest that increasing levels of anesthesia are somewhat associated with lower relative α power values coincident with greater reductions in cerebral metabolism for each volunteer. The lines and labels are as shown in figure 2.

The common physiologic ground for a "linear" relation between EEG changes and cerebral metabolic rate during anesthesia is probably the total number of neurons firing, or the rate at which large groups of neurons fire. The relation between neuronal firing and EEG activity has been investigated directly in several different paradigms, and the general tendency is for lower firing rates to equate with a lower-frequency EEG pattern.[25,26] Because anesthetics tend to produce lower-frequency EEG patterns, it seems reasonable to expect that anesthetics should also be associated with decreased rates of neuronal firing. In fact, electrophysiologic studies support this expectation.[27-29] The rate of cerebral metabolic activity determined by measurement of regional

glucose utilization with the deoxyglucose technique also is known to be proportional to the underlying rate of neuronal activity.[30] The lower the underlying neuronal activity, the lower the measured cerebral metabolic rate will be. Thus, again, because anesthetics inhibit neuronal activity, they should also decrease regional glucose utilization in a dose-dependent manner, and this expectation is also well supported by experimentation.[9,31,32]

The EEG descriptors measured in this study changed in a dose-related manner consistent with expectations from the literature for both propofol and isoflurane (table 2).[13,15,33] The higher-frequency activity evident over the frontal lobe during sedation was replaced by lower-frequency activity during unresponsiveness. Generalization of these findings to other anesthetics, and even to a broader dosage range of these same anesthetic agents is, however, unwarranted. Different anesthetics affect the EEG signal differently and show different dose–response characteristics. Nonetheless, because the common basis for both the anesthetic-induced EEG changes and the cerebral metabolic changes evident during anesthesia is likely to be the underlying rate of neuronal activity, we can justly speculate that some relation between these EEG descriptors and cerebral metabolic rate would still be found with other anesthetic agents and doses.

The reduction in cerebral metabolism caused by the anesthetics used appeared to be linear. Therefore, the dependent variable, PACMR, seems to be modeled well by a linear model. However, the data available for analysis in this retrospective study are limited in number and range of metabolic reduction values, with most of the data points found in a narrow range of metabolic reduction values between 40% and 60%. Given these limitations, the possibility that a nonlinear relation exists between anesthetic level and PACMR in humans cannot be ruled out. Some animal data suggest that a nonlinear relation should exist between anesthetic dose and cerebral metabolic reduction.[7] Nonetheless, nothing within these data suggest that linear modeling of PACMR is wrong *per se*.

The EEG is a complex signal that changes in complex ways that are not necessarily linear with increasing anesthetic doses. The fact that the BIS had the highest simple correlation value for any of the EEG descriptors is probably a result of the extensive "linearizing" inherent in the BIS algorithm. In other words, the BIS was constructed to perform in a linear manner with increasing anesthetic dose, therefore, the finding that it correlates highly with another variable that also happens to change in approximately a linear manner with increasing anesthetic dose (*i.e.*, the PACMR) should not be seen as surprising, but rather as simply more evidence that something inherent in the EEG signal may be useful for estimating the magnitude of the cerebral metabolic reduction evident during anesthesia.

Because the BIS was linearized to a scale that ranges from 0 to 100, an interesting relation is noted between the mean PACMR values and the mean BIS values. The mean percentage of whole-brain metabolic reduction that occurred during the sedate condition on propofol was 34 ± 16% or, alternatively, a value at which 66% of baseline metabolism remained. This corresponded to a mean BIS, at that time, of 66 ± 3. The mean whole-brain metabolic reduction seen during isoflurane anesthesia was 46% (or 54% of baseline metabolism remaining), with a corresponding mean BIS of 54 ± 9. The amount of metabolic reduction seen during propofol anesthesia was 60% (or 40% of baseline metabolism remaining) with a corresponding BIS of 37 ± 6. In this grouped analysis, it appears that the BIS values approximate the value of cerebral metabolism remaining during anesthesia. No doubt this is a coincidence of the BIS linearizing process and these particular types and doses of anesthesia studied. It remains to be determined whether this coincidental relation would be replicated in another study sample or when other anesthetic agents are evaluated.

Median power frequency and 95% spectral edge frequency have often been suggested for use in monitoring some component of anesthetic depth or anesthetic effectiveness.[11–14] In this study, however, neither of these variables correlated significantly with whole-brain metabolic percentage reduction, although they decreased significantly with increasing anesthetic level. This may have been a result of the limited sample size or, more likely, because these variables are simply not represented well by a linear model. Nonetheless, although the grouped data analysis did not reveal a significant linear relation between cerebral metabolic reduction and these variables, both seemed to trend downward with increasing doses of anesthesia, as physiologically expected, for each person. This can be seen when each volunteer's data points are connected (figs. 5 and 6, respectively).

In addition, during sedation and anesthesia, total power significantly increased as the percentage change in baseline whole-brain metabolism also increased (tables 2 and 3). Relative β power also significantly de-

creased as the percentage change in baseline whole-brain metabolism increased (tables 2 and 3). Both findings are again consistent with the expected physiology of the EEG during increasing doses of anesthesia.[13]

The partial correlation analysis revealed that BIS was the most effective for explaining residual variance in PACMR prediction after controlling for anesthetic type. This partial correlation with BIS was not significant ($r = -0.40$, $P = 0.08$), although this may have been related to the limited sample size used. Nonetheless, the partial correlation analysis suggests that more information about PACMR can be obtained from using BIS values than from simply knowing the anesthetic type and dose. However, relative α power ($r = 0.37$, $P = 0.10$) had nearly the same amount of residual explanatory power as the BIS. This suggests that if a model for PACMR prediction were to be developed, relative α power might be as important a component of such a model as the BIS. Another way to interpret the meaning of the partial correlation results is to suggest that if one sedated everyone to the same anesthetic level, there would be some tendency for the person in the group with the highest BIS value, or the highest relative α power, to have the higher cerebral metabolic rate.

If a much larger sample size were available for study, a multiple linear regression analysis might be able to select those EEG descriptors that best predict PACMR changes. The question then becomes: Is PACMR the ideal physiologic variable that should be modeled? In other words, if the BIS, for example, were to be "tuned" to better predict PACMR, would it then be a better measure of hypnosis? These questions await further experimentation but offer the interesting hypothesis that perhaps the physiologic variable of interest for understanding anesthetic depth related to hypnosis is the magnitude of the cerebral metabolic reduction caused by an anesthetic agent.

A standard crossover paradigm for determining anesthetic concentration at loss of consciousness was not used because of the time constraints imposed by the necessary use of a short-lived radioisotope. Because crossover design was not used, the volunteers were slightly more anesthetized during the measurement of cerebral metabolism than when they first lost consciousness. Blood samples for propofol confirm, as previously reported,[9] that volunteers were more anesthetized during metabolism assessment than when they first lost consciousness. Nonetheless, this slight overshoot in clinical depth is not an important issue for the current analyses because the EEG values obtained at the time of the cerebral metabolism measurements, when steady-state conditions were approximated, were the ones used in the current correlational analyses and not the EEG values that occurred coincident with the precise moment that consciousness was lost.

In conclusion, these data show that in a clinically relevant dosage range of propofol and isoflurane anesthesia, several processed EEG descriptors correlate approximately in a linear manner with the magnitude of the cerebral metabolic reduction caused by anesthesia. This suggests that a fundamental physiologic link exists between the EEG and cerebral metabolism during anesthesia that may prove to be mathematically quantifiable.

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