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Differential Dynamic of Action on Cortical and Subcortical Structures of Anesthetic Agents during Induction of Anesthesia

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Background: **Dynamic action of anesthetic agents was compared at cortical and subcortical levels during induction of anesthesia. Unconsciousness involved the cortical brain but suppression of movement in response to noxious stimuli was mediated through subcortical structures.**

Methods: **Twenty-five patients with Parkinson disease, previously implanted with a deep-brain stimulation electrode, were enrolled during the implantation of the definitive pulse generator. During induction of anesthesia with propofol (n = 13) or sevoflurane (n = 12) alone, cortical (EEG) and subcortical (ESCoG) electrogenesis were obtained, respectively, from a frontal montage (F3–C3) and through the deep-brain electrode (p0–p3). In EEG and ESCoG spectral analysis, spectral edge (90%) frequency, median power frequency, and nonlinear analysis dimensional activation calculations were determined.**

Results: **Sevoflurane and propofol decreased EEG and ESCoG activity in a dose-related fashion. EEG values decreased dramatically at loss of consciousness, whereas there was little change in ESCoG values. Quantitative parameters derived from EEG but not from ESCoG were able to predict consciousness *versus* unconsciousness. Conversely, quantitative parameters derived from ESCoG but not from EEG were able to predict movement in response to laryngoscopy.**

Conclusion: **These data suggest that in humans, unconsciousness mainly involves the cortical brain, but that suppression of movement in response to noxious stimuli is mediated through the effect of anesthetic agents on subcortical structures.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

This article is accompanied by an Editorial View. Please see: Schneider G, Kochs EF: The search for structures and mechanisms controlling anesthesia-induced unconsciousness. ANESTHESIOLOGY 2007; 107:195–8.

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RECENT progresses in brain imaging have shown that the effects of anesthetics are specific rather than global on the brain.[1] In particular, subcortical brain structures such as the thalamus seemed to be specifically involved during general anesthesia.[2,3] By analogy with the physiology of sleep, the neuronal networks involving the thalamus and the cerebral cortex (thalamocortical–corticothalamic loops) has been hypothesized to play a major role in determining unconsciousness during general anesthesia.[4,5] However, functional neuroimaging has a poor temporal resolution and needs sequential acquisitions with stable anesthetic depth, making it difficult to explore the dynamic nature of anesthesia.[6]

Another important goal during anesthesia is the ability to predict responses to pain. Unfortunately, methods based on the electroencephalogram, such as spectral edge (90%) frequency (SEF_{90}), median power frequency (MPF),[7–9] or, more recently, the Bispectral Index,[10,11] have failed to predict movement during surgery. Whether this is due to improper electroencephalographic processing or to other methodologic issues related to pain processing remains debated. One advantage of electrophysiologic methods is an excellent temporal resolution, within milliseconds. But this methodology is usually limited to the exploration of the superficial cortical layers in humans. The implantation of deep-brain electrodes for Parkinson disease surgery allows an access to subcortical structures. This model offers a unique opportunity to record the dynamic electrophysiologic changes at cortical (EEG) and subcortical (ESCoG) levels during induction of anesthesia.

We hypothesized that the cortex and subcortical structures have different sensitivities to anesthetics with a corticosubcortical dissociation at loss of consciousness (LOC) during induction of anesthesia. The aim of this study was first to study, during induction of anesthesia with propofol or sevoflurane, the sensitivities of the cortex and subcortical structures, with a high-temporal-resolution method. Second, we aimed to compare the respective efficacy of EEG and ESCoG quantitative parameters (linear: SEF_{90} and MPF; nonlinear: dimensional

activation) for predicting LOC and movement in response to laryngoscopy as a standard noxious stimulus.

Materials and Methods

Patients

After we obtained Ethics Committee approval (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale, Marseille, France) and written informed consent, we studied 25 consecutive patients with advanced Parkinson disease undergoing functional stereotactic surgery, aged 45–72 yr, with American Society of Anesthesiologists physical status of II or III. Exclusion criteria included propofol allergy, regular use of sedative–hypnotics, seizure disorders, and anticipated difficult intubation.

Implantation Procedure of the Subcortical Electrodes

Patients with Parkinson disease included in this study previously underwent successful implantation with an electrode in the subthalamic nucleus. The criteria for implantation were patients with Parkinson disease (according to the United Kingdom Parkinson's Disease Society Brain Bank[12]) with a good response to levodopa (improvement of at least 50% on the motor portion of the Unified Parkinson's Disease Rating Scale between the "off-drug" and "on-drug" conditions) and without cognitive dysfunction or severe psychiatric disorders. The surgical procedure for implantation of electrodes in the subthalamic nucleus was based on preoperative stereotactic magnetic resonance imaging, and intraoperative microrecording.[13,14] The electrodes used (model 3387; Medtronic, Inc., Minneapolis, MN) were quadripolar, thus permitting stimulation to be applied at four individual contacts numbered 0, 1, 2, and 3 from the tip of the electrode (fig. 1). For 5–7 days after this procedure, the wires from each of the four contacts were led out through the scalp and could be connected to external amplifiers. During this period, the pulse generator was fine-tuned to choose the optimal contact through which the stimulation alleviated symptoms of Parkinson without inducing permanent side effects and the optimal electrical parameters (frequency, pulse width, and voltage). Our study was performed during the implantation in the subclavicular area of the definitive pulse generator during general anesthesia.

Study Design

The evaluation was conducted as a nonrandomized prospective, open-label study. No oral intake was allowed 8 h before the operation, and no premedication except dopatherapy was given. After arrival in the operating room, an intravenous catheter was inserted into a forearm vein, and patients were monitored with standard anesthetic monitoring (Eagle 4000; GE Marquette, Buc, France). We measured heart rate, oxygen saturation, and noninvasive mean arterial blood pressure at 1-min intervals. The concentrations of end-tidal carbon dioxide, oxygen, and end-tidal sevoflurane were measured continuously using an infrared spectrophotometric analyzer of an anesthesia workstation (Julian®; Dräger, Antony, France). Cortical and subcortical electroencephalograms were recorded for 5 min before induction to obtain an awake baseline. Patients in the supine position were asked to relax and to keep their eyes closed during the recording period to minimize muscle artifact (see acquisition procedure below).

After 3 min of preoxygenation, the patients received either propofol (n = 13) or sevoflurane (n = 12) alone. Propofol was infused for induction *via* target-controlled infusion with a Diprifusor device (Fresenius Vial SA, Grenoble, France) using the pharmacokinetic parameters published by Marsh *et al.*[15] Induction of anesthesia

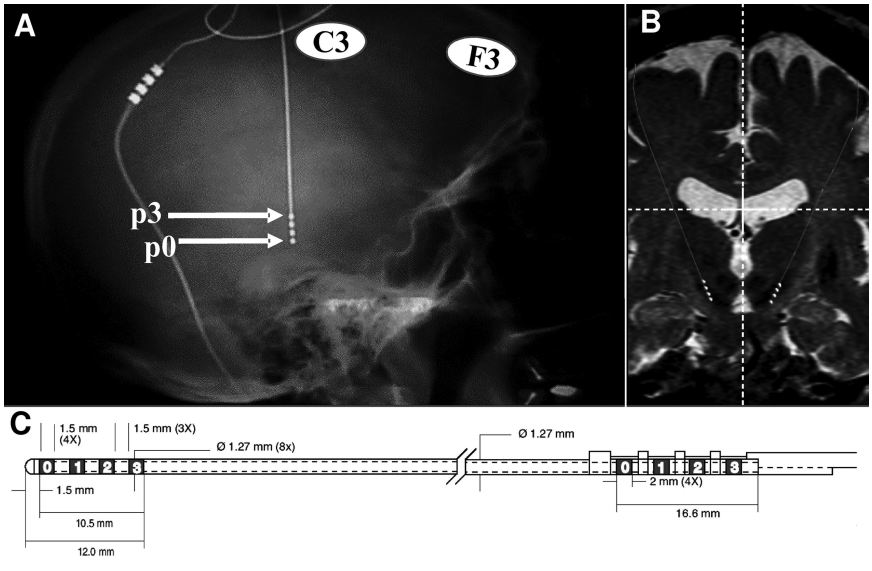

Fig. 1. Postoperative lateral skull radiograph (*A*) and magnetic resonance image (*B*) obtained after implantation of the quadripolar electrodes into subthalamic nuclei. Schematic drawing (*C*) of the Medtronic model 3387 electrode.

was started with a target plasma propofol concentration of 6 μg/ml. Sevoflurane was administered for induction *via* a facemask. Anesthesia was induced with 2% sevoflurane in 100% O_2 (Dräger vaporizer; Antony, France), using an open circuit with a fresh gas flow of 9 l/min.

Loss of consciousness was assessed every 20 s during induction by loss of response to loud voice command (open your eyes) with light tapping on the shoulder. End-tidal sevoflurane or target plasma propofol concentration was increased every 3 min by, respectively, an additional 2% to a maximum of 8% or 2 μg/ml to a maximum of 10 μg/ml. In case of inadequate spontaneous ventilation (oxygen saturation < 92% or signs of upper airway obstruction), a free airway was reinstituted by inserting an oropharyngeal airway, and if necessary, ventilation was manually assisted by facemask to maintain end-tidal carbon dioxide between 35 and 40 mmHg. Laryngoscopy was performed when the depth of anesthesia was adequate as judged by clinical signs. The anesthesiologists were blinded to the EEG and ESCoG values obtained during the administration of anesthesia. As soon as the trachea was intubated, mechanical ventilation was adjusted to maintain normocapnia (35–40 mmHg end-tidal carbon dioxide), anesthetic concentration was reduced to obtain 2% end-tidal sevoflurane or a target plasma propofol concentration of 6 μg/ml, and this concentration was maintained for 5 min. Hemodynamic data, EEG, and ESCoG were recorded continuously from the beginning of induction until 5 min after tracheal intubation.

All data were analyzed at baseline before anesthesia (T_0), immediately after LOC (T_1), before laryngoscopy (T_2), after tracheal intubation (T_3), and 5 min after tracheal intubation, without nociceptive stimulations, when anesthetic concentration was equal to 1.0 minimum alveolar concentration (MAC) or 1.0 EC_{50} (T_4). Movers were defined as patients who showed any visible spontaneous muscle movements, such as withdrawal or flexor movement of the arms and legs, frowning of the forehead muscles, or coughing, during laryngoscopy and within 1 min of tracheal intubation.[10] Nitrous oxide, opioids, and muscle relaxants were not used during the entire study period. Surgery started after completion of the study.

Cortical and Subcortical Electrogenesis Acquisition and Analysis

Electrogenesis was continuously recorded from the cortical (EEG) and subcortical (ESCoG) level. EEG was acquired, after skin preparation, using silver–silver chloride electrodes (Aquabond; Newlifetech, Midlothian, VA), with a bipolar longitudinal frontal montage, ipsilateral to the subcortical electrode (F3–C3 or F4–C4: international 10-20 system). Electrode impedance was kept below 2,000 Ω. ESCoG was acquired through the deep-brain electrode (fig. 1), using a bipolar montage, between poles p0 and p3 (impedance < 1,500 Ω; distance p0–p3 = 10.5 mm). The ground electrode for EEG and ESCoG was placed at the midforehead (Fz). Raw signals from the EEG and ESCoG were amplified and filtered analogically (low-pass filter [−6 dB at 450 Hz; Teledyne Electronic, Los Angeles, CA]; high-pass filter [−6 dB at 0.5 Hz; Teledyne Electronic]; notch filter [50 Hz]), digitized at 128 Hz (A/D converter; Teledyne Electronic), with 12-bit resolution, and stored on a computer hard disk. Bandpass digital filters were set at 0.5–30 Hz, and amplifier sensitivity was 200 μV. The EEG and ESCoG were displayed continuously to enable removal of artifacts and noted periods of burst suppression. Power spectral analysis and nonlinear analysis were performed on-line with Synapsys® software (version 1.3; Synapsys, Marseille, France). All EEGs and ESCoGs were reviewed by a clinical neurophysiologist familiar with anesthesia EEG (M.F.R.) to assess whether seizure-like activity was present.

Linear Analysis: Power Spectral Analysis by Fast Fourier Transform

Spectral analysis of EEG and ESCoG signals was performed using fast Fourier transformation on 4-s epochs. The following parameters were calculated: total spectral power, defined as the area under the curve of the spectrum (μV^2); SEF_{90}, defined as the frequency below which 90% of the electroencephalographic power is located; and MPF, defined as the frequency below which 50% of the electroencephalographic power is located. Spectral bands of 0.5–3 Hz (δ), 3.25–8 Hz (θ), 8.25–13 Hz (α), and 13.25–30 Hz (β) were analyzed, and the power of the spectral bands was calculated and expressed as a percentage of total spectral power. The values for each of the derived parameters were determined by averaging the data from five consecutive epochs (5×4 s = 20 s). When the value for an individual epoch was more than two deviations from the mean, it was omitted and replaced by an additional epoch. Any periods of burst suppression in the EEG and ESCoG were noted and also excluded.

Nonlinear Analysis: Dimensional Activation

The pattern of ESCoG power spectrum changes during anesthesia is unknown in humans. To compare EEG and ESCoG time series, another method of analyzing brain electrophysiology based on deterministic chaos theory, independent of fast Fourier transformation,[16] was used. Nonlinear analysis of EEG and ESCoG signals was performed using the dimensional activation (Da) derived from the correlation dimension D_2, which can be estimated by the Grassberger and Procaccia algorithm[17] (appendix). The measure of dimensionality denotes the minimum number of essential variables needed to model the dynamics of a general dynamical system. Schematically, Da estimated the complexity of EEG and ESCoG

signals: The more alert the patient is, the more complex the EEG is, and the higher the Da is; the deeper the sleep or anesthetic state is, the simpler the EEG is, and the lower the Da is. Da values for EEG and ESCoG varied between 12 (awake) and 2 (deep anesthesia).

Statistical Analysis

Data are expressed as mean (SD) unless otherwise indicated. Time to achieve clinical endpoints, heart rate, and mean arterial blood pressure were compared between propofol and sevoflurane, using an unpaired *t* test. Comparison of EEG and ESCoG data at the different time points was performed with one-way analysis of variance followed by *post hoc* Tukey test for multiple comparisons. Statistical analysis was performed with SigmaStat 2.03 and SigmaPlot 8.0 software (SSPS Inc., San Rafael, CA). A value of $P < 0.05$ was considered statistically significant.

The ability of derived EEG and ESCoG parameters (Da, SEF_{90}, and MPF) to predict consciousness *versus* unconsciousness and movers *versus* nonmovers was measured with prediction probability (*P*k) as described by Smith *et al.*[18] A *P*k value of 1 means that the values of the predicting variables always correctly predicts the variable to be predicted. A *P*k value of 0.5 means that the prediction is no better than chance alone. A paired-data jackknife analysis[18] was used to determine whether the *P*k value for one indicator differed from that of another indicator. *P*k values were calculated with an Excel macro (PKMACRO) provided by Smith *et al.*[18]

The area under the receiver operating characteristic (ROC) curve for discrete index threshold values was used to summarize the accuracy of Da EEG and ESCoG to predict unconsciousness and movement during laryngoscopy. The ROC curve for each index plots sensitivity (fraction of unresponsive patients who are correctly predicted to be unresponsive) against 1 − specificity (fraction of responsive patients correctly identified) reflects the discriminating power of the index. The area under the ROC curve was calculated with SE and 95% confidence interval by maximum-likelihood estimation as described by Metz *et al.*[19]

Results

The trial was completed without complication in any patient and no adverse effects after anesthesia. Patients anesthetized with propofol or sevoflurane did not differ in their demographic variables (table 1). No difference was seen in hemodynamic baseline values between the anesthetics (table 2). During the remainder of the procedure, sevoflurane produced similar changes in heart rate and mean arterial blood pressure values when compared with propofol. Time to LOC after induction was significantly shorter with propofol than with sevoflurane (138 ± 18 *vs.* 270 ± 78 s; $P < 0.05$), but there was no significant difference in intubation times (11.0 ± 4.4 *vs.* 12.8 ± 3.7 min).

Table 1. Demographics Data

	Propofol	Sevoflurane
n	13	12
Sex, F/M	2/11	2/10
Age, yr	58 (7)	62 (8)
Weight, kg	68 (13)	74 (10)
Height, cm	171 (8)	174 (6)
ASA, II/III	11/2	10/2
UPDRS motor score drug "off"	43 (14)	46 (13)

Values are presented as mean (SD).

ASA = American Society of Anesthesiologists (physical status); UPDRS = Unified Parkinson's Disease Rating Scale.

EEG and ESCoG Analysis

A total of 281 min of artifact-free EEG and ESCoG (4,215 four-second epochs; 9% of the total epochs were rejected) from 25 patients were recorded and analyzed. Cortical awake raw data from one patient under propofol and two patients under sevoflurane anesthesia were excluded from analysis owing to the presence of numerous artifacts related to rest tremor (4 Hz). No seizure-like activity at cortical or subcortical levels was recorded in any patient during induction of anesthesia. Figure 2 shows typical changes in EEG and ESCoG electrogenesis waveform data during induction of anesthesia. Awake values of SEF_{90}, MPF, and Da were comparable at baseline at the cortical and subcortical levels and between propofol and sevoflurane (fig. 3). With both anesthetics, induction of anesthesia was associated with EEG and ESCoG slowing. Quantitative parameters (SEF_{90}, MPF, and Da) decreased with increasing propofol or sevoflurane concentration at cortical and subcortical levels. This decrease occurred at a later time point at the subcortical than at the cortical level. Additional information regarding this is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org (Web fig. 1).

Compared with the awake state, EEG parameters (SEF_{90}, MPF, and Da) decreased significantly at T_1, T_2, T_3, and T_4 at the cortical level and only at T_2, T_3, and T_4 at the subcortical level. LOC was associated, at the cortical level, with a dramatic increase in δ activity and decrease in β activity (fig. 4). At the subcortical level, this increase in δ and decrease in β activity appeared later and more gradually. The relative power of δ waves was significantly higher for EEG than ESCoG with both propofol and sevoflurane from T_1 to T_2. Moreover, compared with the awake state, δ activity increased significantly at T_1 at the cortical level and only at T_3 at the subcortical level. In propofol-treated patients, spindle wave oscillations were observed in eight patients on the ESCoG (fig. 5). No spindle waves were observed with sevoflurane.

EEG Da values were significantly lower in unconscious

Table 2. Concentrations, Time, and Hemodynamic Data at the Five Clinical Endpoints

	T_0		T_1		T_2		T_3		T_4	
	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane
Concentration, μg/ml/ETsevo %	—	—	1.4 ± 0.3	2.2 ± 0.6	5.0 ± 1.7	4.1 ± 0.9	6.9 ± 2.2	4.7 ± 0.7	6.6 ± 2.2	2.1 ± 0.5
Time, min	—	—	2.3 ± 0.3	4.5 ± 1.3*	7.2 ± 3.1	9.0 ± 1.5	11.0 ± 4.4	12.8 ± 3.7	16.0 ± 4.4	17.1 ± 4.9
HR, beats/min	76 ± 20	80 ± 1.3	73 ± 16	81 ± 10	76 ± 20	80 ± 16	86 ± 13	66 ± 13	66 ± 13	71 ± 15
MAP, mmHg	105 ± 15	103 ± 13	94 ± 15	90 ± 8	80 ± 13	101 ± 18	113 ± 19	69 ± 14	69 ± 14	76 ± 9

Values are presented as mean ± SD.

* $P < 0.05$ *vs.* propofol.

ETsevo = end-tidal sevoflurane; HR = heart rate; MAP = mean arterial blood pressure; T_0 = before anesthesia; T_1 = immediately after loss of consciousness; T_2 = immediately before laryngoscopy; T_3 = immediately after tracheal intubation; T_4 = 5 min after tracheal intubation.

than in conscious patients (9.6 ± 1.2 *vs.* 6.1 ± 0.7; $P < 0.05$; fig. 6). ESCoG Da values were significantly lower in nonmovers than in movers (7.7 ± 1.1 *vs.* 5.4 ± 0.9; $P < 0.05$). No statistical difference was noted between conscious and unconscious patients at the subcortical level (ESCoG) and between movers and nonmovers at the cortical level (EEG). Similar results were obtained with SEF_{90} and MPF (data not shown).

The ability of EEG and ESCoG SEF_{90}, MPF, and Da to predict consciousness *versus* unconsciousness and movement in response to laryngoscopy, used calculation of the *P*k values (table 3) and construction of ROC curves (fig. 7) pooling data of propofol and sevoflurane patients. *P*k values for consciousness *versus* unconsciousness were significantly greater for all EEG parameters than for ESCoG ones. The performance of ESCoG parameters to predict movers *versus* nonmovers was statistically significantly better than EEG parameters. For predicting unconsciousness, the area under the ROC curve for Da EEG was 0.969 (SE, 0.031; 95% confidence interval, 0.846–0.995) and for Da ESCoG was 0.607 (SE, 0.093; 95% confidence interval, 0.433–0.763). For predicting movement at laryngoscopy, the area under the ROC curve for Da EEG was 0.627 (SE, 0.074; 95% confidence interval, 0.488–0.751) and for Da ESCoG was 0.947 (SE, 0.030; 95% confidence interval, 0.853–0.988).

Discussion

The first result from our study is that the effect of both propofol and sevoflurane appeared at a later time in the subcortex compared with the cortex. At LOC, profound and dramatic EEG slowing occurs at the cortical level when only few changes are seen at the subcortical level. *P*k values and ROC curves showed that the prediction of consciousness *versus* unconsciousness was significantly better for EEG than for ESCoG variables. These results were consistent among several EEG-derived measures: SEF_{90}, MPF, and Da.

It is important to understand what was recorded through the subcortical electrode for the interpretation of our results. Although the target of the implantation was the subthalamic nucleus and not the thalamus, a series of reasons support the hypothesis that the electrical activity recorded between contacts p0 and p3 from the deep-brain electrode was essentially thalamic. The overall length of the electrode between contacts p0 and p3 was 7.5 mm. Therefore, the regional electrical activity recorded was more likely to be produced by the thalamus than by the subthalamic nucleus, which is a small structure (less than 3 mm at its maximal height). When the distal pole is in the subthalamic nucleus, the most proximal plot of the electrode is located in the

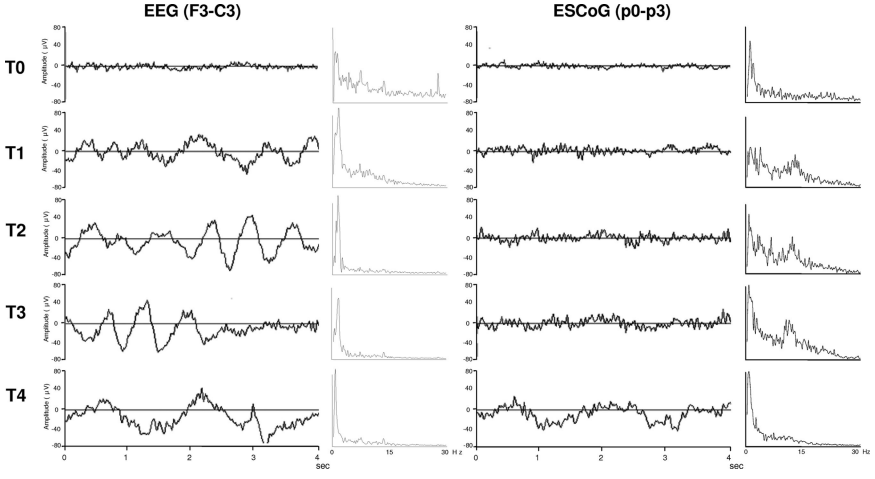

Fig. 2. Representative cortical (EEG) and subcortical (ESCoG) electrogenesis waveform data with the corresponding power spectra. The power spectrum was calculated by averaging the data from five consecutive epochs (5 × 4 s = 20 s) of EEG and ESCoG signals (although only one epoch [4 s] is shown for clarity). Tracings recorded during induction of anesthesia from a single subject (No. 5) anesthetized with propofol. Before anesthesia (T_0), immediately after loss of consciousness (T_1), before laryngoscopy (T_2), after tracheal intubation (T_3), and 5 min after tracheal intubation (T_4). Cortical δ waves appeared suddenly with loss of consciousness (T_1). Subcortical δ waves appeared later than cortical ones. High δ waves were acquired on EEG and ESCoG only after intubation (T_4).

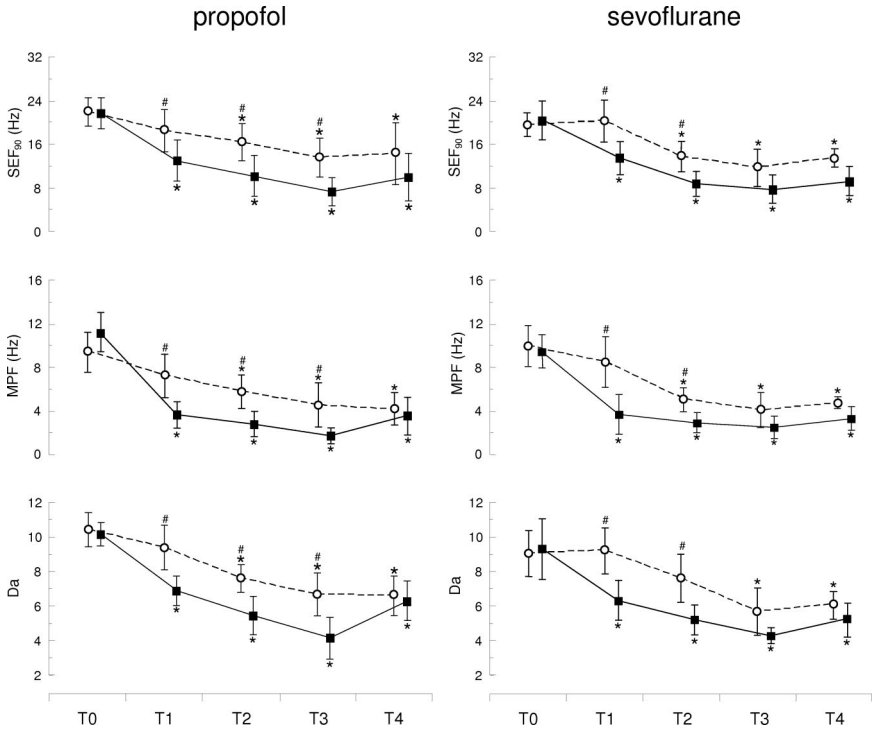

Fig. 3. Variation of spectral edge frequency 90 (SEF_{90}), median power frequency (MPF), and dimensional activation (Da), during induction of anesthesia at five times, in propofol and sevoflurane groups at cortical (EEG; —) and subcortical (ESCoG; ----) levels. T_0 = before anesthesia; T_1 = immediately after loss of consciousness; T_2 = immediately before laryngoscopy; T_3 = immediately after tracheal intubation; T_4 = 5 min after tracheal intubation. * $P < 0.05$ *versus* T_0. # $P < 0.05$, ESCoG *versus* EEG.

external nuclei of the thalamus. This has been demonstrated by perioperative microelectrode recording in our patients. Several other electrophysiologic arguments suggest that the subcortical recordings were mainly thalamic activity. First, the thalamus is the largest nucleus near the electrode, and the most powerful synaptic activity in this region clearly originates from the thalamus. Second, we observed spindles with propofol. Spindle activity is a specific thalamic electrophysiologic pattern[20] and has never been recorded in the subthalamic nucleus. Finally, Priori *et al.*[21] recorded specifically the activity of the subthalamic nucleus. They did not find any difference in subthalamic nucleus activity at different vigilance levels (sleep, awake, eyes closed, and eyes

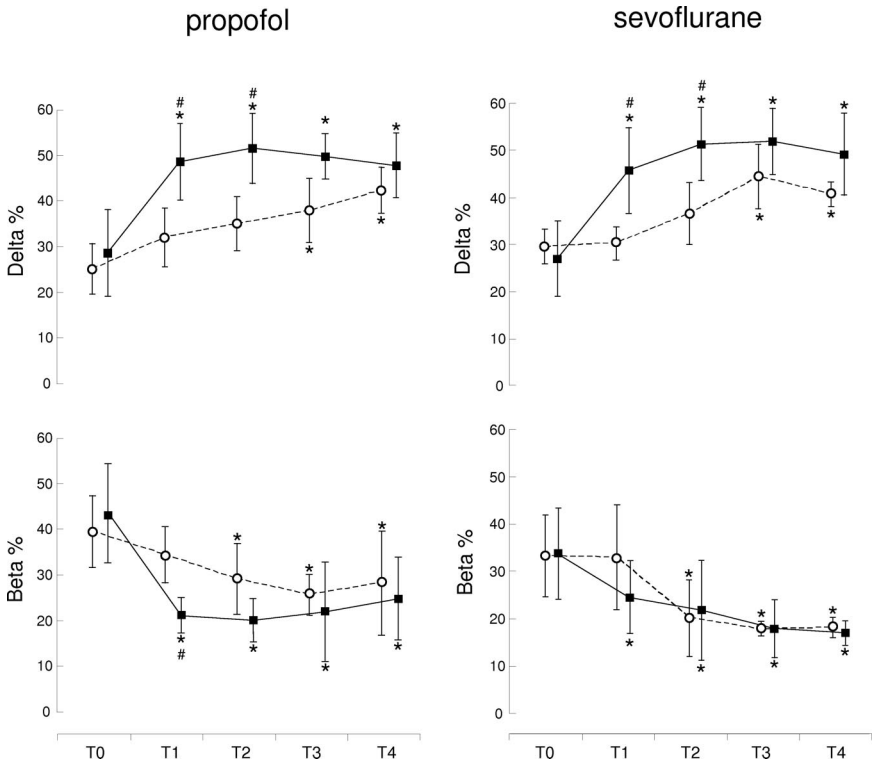

Fig. 4. Variation of relative power in frequency bands, δ (0.5–3 Hz) and β (13.25–30 Hz), during induction of anesthesia at five times, in propofol and sevoflurane groups at cortical (EEG; —) and subcortical (ESCoG; ----) levels. T_0 = before anesthesia; T_1 = loss of consciousness; T_2 = immediately before laryngoscopy; T_3 = tracheal intubation; T_4 = 5 min after tracheal intubation. Relative power of the spectral bands was calculated and expressed as a percentage of total spectral power. * $P < 0.05$ *versus* T_0. # $P < 0.05$, ESCoG *versus* EEG.

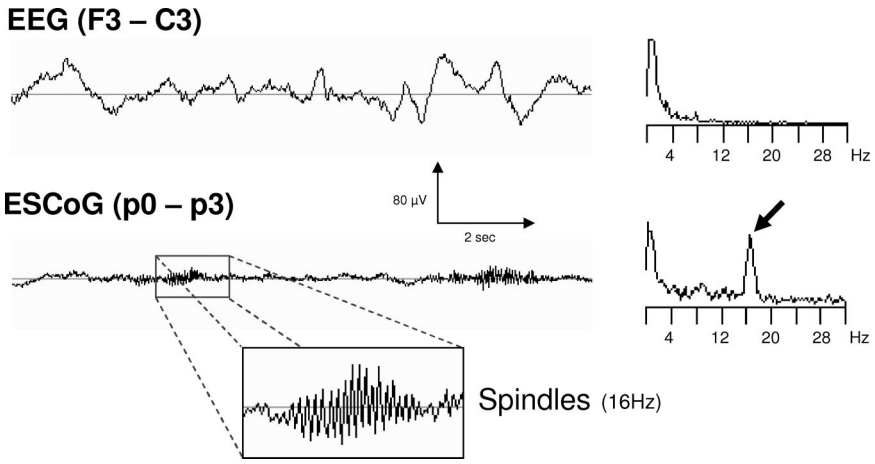

Fig. 5. Representative cortical (EEG; F3–C3) and subcortical (ESCoG; p0–p3) electrogenesis waveform data with the corresponding power spectra. Typical aspect of spindle activity (16 Hz) in ESCoG recording in one patient (No. 12) anesthetized with propofol.

opened), in agreement with the involvement of this nucleus in motor control and not in sleep. Because we used a bipolar recording, we recorded synaptic activity in the vicinity of the electrode and not far field potentials. Therefore, the subcortical activity we measured was probably mainly thalamic. Finally, one problematic issue in combined EEG and ESCoG recording is that of volume conduction to subcortical regions of cortically generated electrical potentials or the opposite. Wennberg *et al.*[22,23] have emphasized that scalp potential recordings in the subthalamic nucleus with monopolar montage totally disappear with a bipolar montage.

Our results are in agreement with the literature showing that anesthetics exert their action by affecting specific structures of the brain.[3,24] This may explain why different components of unconsciousness, such as amnesia and sedation, are affected differently by anesthetic agents. Two main brain structures affected by hypnotic agents are the cortex and the thalamus. A correlation between a subject's level of consciousness and the amount of thalamic activity has been demonstrated both with propofol[3] and with inhaled agents.[4] This has led to the hypothesis that unconsciousness was produced by suppressing activity in thalamocortical circuits.[4,6] There is little doubt that suppression of subcortical activity, mainly in the thalamus, is an important effect of anesthetics, because the thalamus is a major relay of sensory and reticular pathways.[25–27] However, in the studies using positron emission tomography, there was also an overall decrease of absolute cerebral blood flow in the gray matter.[3] Unfortunately, positron emission tomography techniques have poor temporal resolution. Therefore, it is difficult to assess from these studies the dynamic action of anesthetics on different brain regions during changes in anesthetic concentration, *i.e.*, to determine which brain structure is affected first. The neurophysiology technique has an excellent temporal resolution and offers a unique opportunity to study the dynamic action of hypnotics on cortical and subcortical brain structures in humans. Our study shows that cortical EEG slowing appears before electrophysiologic subcortical effects. This finding is in agreement with human studies using functional magnetic resonance imaging[28] and experimental neurophysiologic data in rats.[27,29,30]

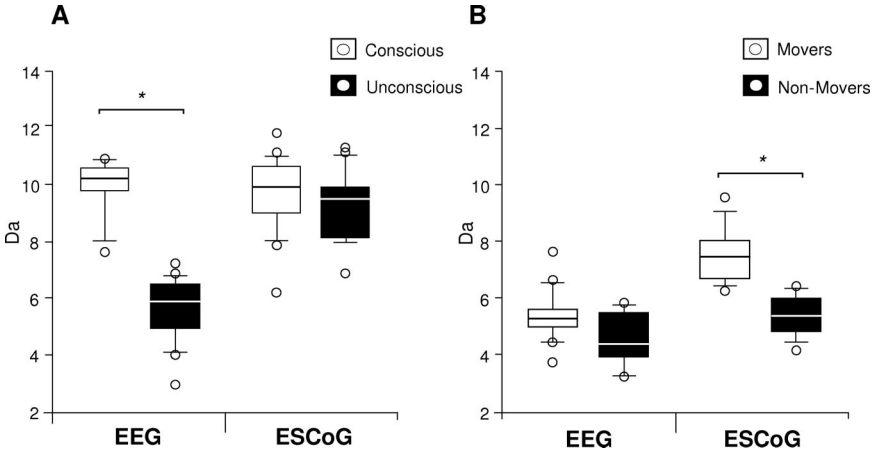

Fig. 6. Variability and discrimination of cortical (EEG) and subcortical (ESCoG) dimensional activation (Da) values split by the actual response. Da mean values for EEG and ESCoG (n = 25) during consciousness and unconsciousness (*A*) and between movers and nonmovers (*B*). Conscious Da values were defined as those recorded within 30 s before induction of anesthesia. Unconscious Da values were defined as those recorded within 30 s after loss of consciousness. EEG and ESCoG Da values between movers and nonmovers were recorded within 1 min before laryngoscopy. Movers were defined as patients who showed any visible spontaneous muscle movements, such as withdrawal or flexor movement of the arms and legs, frowning of the forehead muscles, or coughing, during laryngoscopy and within 1 min of tracheal intubation. Box plots indicate medians (*horizontal line in the box*), 25th and 75th percentiles (*lower and upper box margins*), 10th and 90th percentiles (*lower and upper error bars*), and individual patients in the lower 10th percentiles (*open circles*) for each group separately. * Statistically significant comparison between conscious *versus* unconscious and mover *versus* nonmover, two-tailed Student t test, $P < 0.05$.

Table 3. Prediction Probability Scores (n = 25)

	Pk for (Un) consciousness	*Pk* for Response to Noxious Stimuli
Dimension of activation		
EEG	0.96 (0.03)*	0.62 (0.07)
ESCoG	0.61 (0.09)	0.91 (0.04)*
Median power frequency		
EEG	0.93 (0.04)*	0.48 (0.08)
ESCoG	0.68 (0.08)	0.88 (0.05)*
Spectral edge frequency 90		
EEG	0.82 (0.07)*	0.54 (0.08)
ESCoG	0.60 (0.09)	0.83 (0.06)*

Values are presented as mean ± SE.

* $P < 0.05$, electroencephalogram (EEG) *vs.* electrosubcorticogram (ESCoG).

Pk = prediction probability.

The first *in vitro* evidence that anesthetics slow cortical oscillatory activity independent of subcortical structure was provided by Lukatch *et al.*[30] using brain slices. Hentschke *et al.*[29] showed *in vivo* that inhaled agents in rats, at concentrations inducing hypnosis, decreased discharge rates of cortical neurons by 50% independently of subcortical structures. Antognini *et al.*[28] showed in humans that light anesthesia (0.7% isoflurane) suppressed the somatosensory cortical but not the thalamic response to painful stimulation. Therefore, experimental data suggest a predominant effect of anesthetics on the cortex at low concentrations, which is consistent with our observations at the early stage of anesthetic induction.

This anesthetic effect is in contrast with the neurophysiology of natural sleep, suggesting that the mechanisms leading to LOC during anesthesia may not be inferred from those of sleep. Other evidence that the mechanism leading to LOC is not comparable to sleep comes from the observation of EEG and ESCoG patterns. During sleep, spindles occur at the beginning of sleep (stage 2), and then δ waves appear at the cortical level with the deepening of sleep (stages 3 and 4). In this study, δ waves appeared first at the cortical level with LOC, and then spindles appeared at the thalamic level. The role of the thalamus in spindle generation has been largely demonstrated in sleep[20] as well as in the anesthetic state.[27] Destexhe[27] demonstrated that the cortex can drive the activity of the thalamus *via* massive corticothalamic projection, suggesting that cortical slow waves can induce spindles at the thalamic level.

The suppression of motor responses to painful stimuli is an important component of anesthesia. In this study, the scalp EEG recording before laryngoscopy could not differentiate movers from nonmovers. This is not surprising, because several studies have shown that EEG-derived parameters could not predict movement with ac-

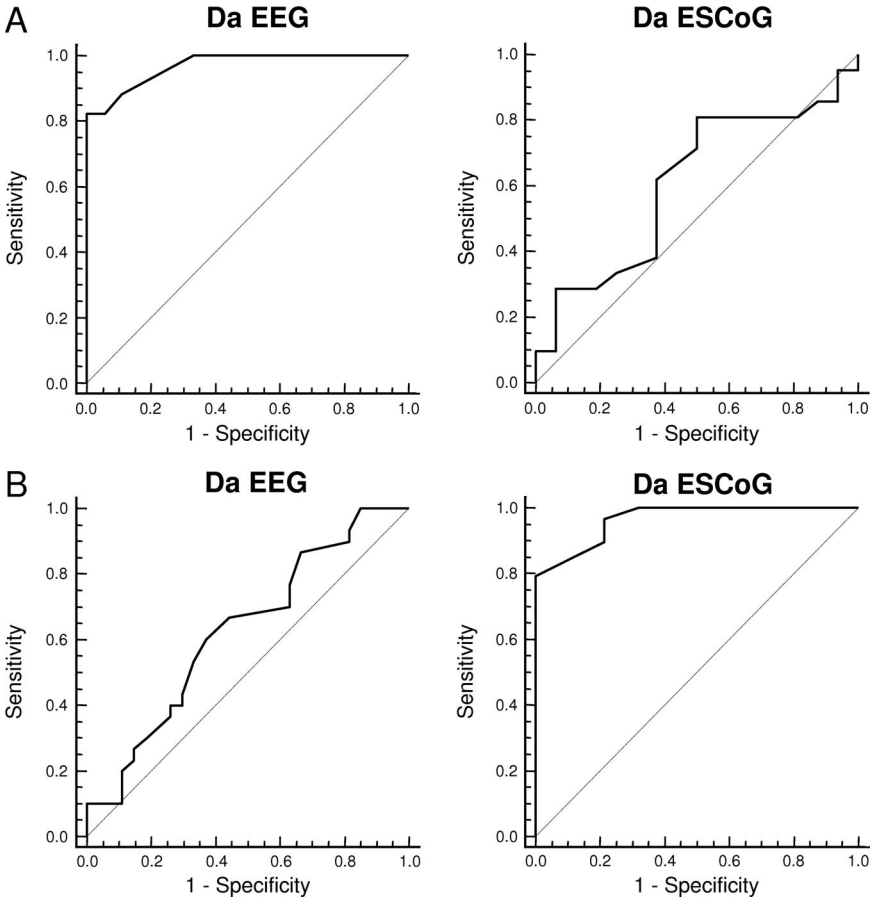

Fig. 7. Receiver operating characteristics curves for discrete threshold values of cortical (EEG) and subcortical (ESCoG) dimensional activation (Da) values to predict unconsciousness (*A*) and movement during laryngoscopy (*B*). The receiver operating characteristic curve for each index plots sensitivity (fraction of unresponsive patients who are correctly predicted to be unresponsive) against 1 − specificity (fraction of responsive patients correctly identified) and reflects the discriminating power of the index.

curacy.[31,10] Moreover, several studies using the Bispectral Index monitor have shown that analgesics, such as nitrous oxide[32] or remifentanil,[33] significantly decreased the number of movers after laryngoscopy without affecting the Bispectral Index. This is in agreement with experimental data showing that cortical depression *per se* does not contribute substantially to movement suppression.[34] In animals, anesthetic agents prevent movement in response to noxious stimulation mainly *via* an action in the spinal cord[35] and thalamus.[36,37] Our results also show a clear difference in ESCoG activity between movers and nonmovers before laryngoscopy. Which subcortical structures were involved in the suppression of movement was unclear. Antognini *et al.*[38] demonstrated in goats that isoflurane depressed medial thalamic responses to noxious stimulations *via* an indirect spinal action. In this model, cranial bypass permitted differential anesthetic delivery to the cranial and spinal cord circulations. When the spinal cord isoflurane concentration was low, pain evoked an arousal reaction by activation of the thalamus and then the cerebral cortex. But increasing the cranial isoflurane concentration blunted the thalamic response to the noxious stimulus. Detsch *et al.*[37] showed that isoflurane directly interacts with the thalamic inhibitory mechanisms, leading to a blockade of sensory information transfer to the cerebral cortex. Therefore, it is likely that anesthetics suppress movement by an action on several subcortical structures. Another important question is to understand how anesthetics affect motor patterns. Do they gradually decrease motor activity and movement in response to stimulation, or is it an all-or-none phenomenon? At sub-MAC concentrations, Antognini *et al.*[39] demonstrated in rats that isoflurane decreased the number of movements but not the force of the movement. Above 1.1 MAC, there was a steep decrease in the number and the force of movements. The authors hypothesized different effects on motor pathways at different concentrations. Detsch *et al.*,[36] by using 0.2% stepwise increases in isoflurane concentration in rats, showed a dose-dependant reduction in response activity of the thalamus. In our study, we observed a slow decrease in subcortical activity. It is possible that anesthetics induce a dose-dependant decrease in the activity of some subcortical regions (*e.g.*, the thalamus) which act as a filter for the transmission of peripheral stimulation. The level of activity of these filters might allow the transmission of specific inputs from the periphery. Whether there is a direct effect of anesthetics on subcortical brain structures such as the thalamus,[36,37,40] an indirect effect due to an action on the spinal cord[38] or the cortex,[27] or both remains to be determined.

The dissociation between cortical and subcortical effects of hypnotics in this study may have important consequences for monitoring depth of anesthesia. Because EEG monitors cannot assess subcortical activity, prediction of movement based on the EEG would seem a difficult goal to achieve. These data are also in agreement with common clinical practice requiring an increase in the doses of hypnotics after LOC to suppress responses to noxious stimulations even if the patient is apparently in a deep anesthetic state before pain stimulation.[41] Thus, we speculate that the effect of anesthetics on subcortical structures (including the spinal cord) is important during noxious stimulation to avoid arousal reactions or movement but does not play a major role in the absence of stimulation. Therefore, as suggested in a recent study, the level of hypnosis during surgery or the electroencephalographic status would be determined by the interaction of the hypnotic effect, the effectiveness of analgesia, and the intensity of surgical stimuli.[42]

The dissociation between the cortical and subcortical effects of propofol and sevoflurane can be explained by several mechanisms. A pharmacokinetic effect cannot be excluded. However, the concentration of the anesthetics was increased slowly, giving enough time for equilibration in the central nervous system. We performed a retrospective comparison of β-activity onset in the two brain structures that did not reveal any difference, making this hypothesis unlikely. Another mechanism would be a different sensitivity of the cortex and the subcortex to hypnotics. This hypothesis is consistent with the results from the study of Veselis *et al.*[43] using evoked potentials showing that sedation and amnesia are separate phenomena. Moreover, subcortical evoked response amplitudes are known to be relatively resistant to the effects of anesthetics.[44] Alkire *et al.* showed that the metabolic reduction caused by propofol was not uniform throughout the brain.[45] It was more pronounced in the cortex than the subcortex. This could be explained by the disparity of γ-aminobutyric acid type A ($GABA_A$) receptor distribution in the central nervous system.[46] $GABA_A$ receptors are considered as the major molecular target of general anesthetics because they are constituents of the most important inhibitory neurotransmitter system in the central nervous system.[47,48] There is increasing evidence from recent experimental studies that the actions of anesthetics on the neocotex[29] and the thalamus[36,37] are mediated mainly by an enhancement of $GABA_A$ receptor–mediated synaptic inhibition. Historical *ex vivo*[49,50] and positron emission tomography studies[51] showed that $GABA_A$ receptor density is higher in neocortex than in subcortical structures. A clear correlation between the metabolic reduction caused by propofol, using positron emission tomography, and the *ex vivo* density of $GABA_A$ receptors has been demonstrated in humans.[52] This lower density of $GABA_A$ receptors in subcortical structures (as the thalamus) than in the cortex could explain a difference in sensitivity between cortex and subcortex to anesthetics.

A few limitations of our study must be addressed. First,

as in any clinical study, the human model used may have influenced the results. Parkinson disease results from functional alteration of several subcortical structures. We used two anesthetics with different mechanisms of action, not to compare the effect of these two agents, but to avoid a drug-induced bias due to an unexpected specificity of Parkinson disease. Another limitation of the model is that we did not study the whole brain but only two brain structures. Therefore, it is difficult from this study to make hypothesis about the mechanism of anesthesia, which probably involves complex interactions between several brain regions. It is also important to keep in mind that electrophysiologic derivatives, as any imaging technique, do not have any direct physiologic meaning. Corticosubcortical interactions are certainly complex during anesthesia. We cannot conclude from our data that the thalamus does not play any role in inducing unconsciousness but rather that the main site of action of anesthetics at LOC is the cortex. The bandwidth in our study was limited to 30 Hz to decrease the electromyographic contamination of the scalp EEG signal. To keep the comparability of EEG and ESCoG signals, the same bandwidth was used for both. Raw EEG and ESCoG data analysis did not reveal any evidence of electromyographic activity. However, because the patients were not paralyzed, it was still possible that some data were contaminated by electromyographic activity, which exceptionally occurs below 30 Hz. Finally, from a statistical point of view, the *P*k value or the area under the ROC curve for EEG Da are probably overrated because we compared time-related data (before and after unconsciousness) rather than comparing two conditions at a given time point. However, the aim of this study was not assess the threshold value of any EEG parameter to predict unconsciousness, but to compare cortical and subcortical electrophysiologic changes. At LOC, the differences between EEG- and ESCoG-derived values were clear-cut.

In conclusion, our study shows that anesthetics at low concentrations induce LOC by acting on cortical targets. But movement in response to noxious stimulation depends mainly on subcortical activity. This has important implications for predicting movements with EEG-derived parameters. It is likely that refinements in algorithms for analyzing the EEG will improve our ability to detect consciousness or unconsciousness. But the risk of movement in response to noxious stimulation will probably be much more difficult to assess because it is under the control of brain structures not monitored by the EEG. This supports Kissin's view that "the search for a reliable index of anesthetic depth should be transformed into a search for separate indices of different components of anesthesia."[53]

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Appendix

Dimensional activation (Da) is based on the correlation dimension (D_2), which can be estimated by using the Grassberger and Procaccia algorithm.[17] Briefly, EEG or ESCoG scalar time series are embedded in a high-dimensional-space R^d, according to the time delay method, where d is the dimension of the embedding space and τ is the time delay. Then, the correlation integral $C_n(r)$ is calculated:

$$C_n(r) = \frac{2}{n(n-1)} \sum_{i<j}^{n} \Theta(r - \|X_i - X_j\|),$$

$i \neq j$,

where $C_n(r)$ corresponds to the empirical probability that a randomly chosen pair (X_i, X_j) of points will be separated by a distance smaller than r, where Θ is the heavy-side step function (*i.e.*, $\Theta = 1$ if its argument is nonnegative and 0 otherwise), and where X_i and X_j are vectors defined by

$$X_i = [u_i, u_{i+t}, u_{i+2t}, \ldots, u_{i+(d-1)t}]$$

$$X_j = [u_j, u_{j+t}, u_{j+2t}, \ldots, u_{j+(d-1)t}],$$

from a time series (*e.g.*, a segment of one channel EEG or ESCoG data) of n coordinates $\{u_1, \ldots, u_i, \ldots, u_N\}$ corresponding to the N potential values of the electroencephalogram separated with a constant time delay τ.

The correlation dimension D_2 is defined as

$$D_2 = \lim_{r \to 0} \frac{\log [C(r)]}{\log(r)}.$$

However, for EEG or ESCoG signals, the $C_n(r)$ variation is generally not a linear function such as expected for homogeneous attractors, so the D_2 calculation is not relevant. This is why Da is based on the calculation of $C_n(r)$ upon a local gliding window and used a weighted coefficients method as described by Guillemant *et al.*[54] to extract pertinent parameter from the $C_n(r)$ function.

The dimensional activation Da is defined as

$$D_a = \frac{\sum_{i<j} W_{i,j} P_{i,j}}{\sum_{i<j} W_{i,j}},$$

where

$$P_{i,j} = (C_n(r_i) - C_n(r_j))/(i - j)$$

$$W_{i,j} = F_{ij} \cdot G_i,\ F_{ij} = C_n(r_j) - C_n(r_i), \text{ and } G_i = C_n(r_i)^2.$$

We used the parameter set n = 1,000, t = 1/64 (15,625 ms), d = 20, which was found to exert the best performance for electroencephalographic Da in a preliminary study.

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