The sensory thalamus and cerebral motor cortex are affected concurrently during induction of anesthesia with propofol: a case series with intracranial electroencephalogram recordings

Le thalamus sensoriel et le cortex moteur cérébral sont simultanément affectés pendant l'induction de l'anesthésie au propofol: une série de cas fondée sur des enregistrements d'électroencéphalogrammes intracrâniens

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Abstract

Purpose *Brain imaging studies suggest that loss of consciousness induced by general anesthetics is associated with impairment of thalamic function. There is, however, limited information on the time course of these changes. We recently obtained intracranial electroencephalogram (EEG) recordings from the ventroposterolateral (VPL) nucleus of the thalamus and from the motor cortex during induction of anesthesia in three patients to study the time course of the alterations of cortical and thalamic function.*

Clinical features *The patients were American Society of Anesthesiologists physical status I-II males aged 33-57 yr with intractable central pain caused by brachial plexus injury (patient 1 and 2) or insular infarct (patient 3). Anesthesia was induced with propofol (2.5-3.1 mg·kg^{-1} over 30-45 sec) followed, after loss of consciousness, by rocuronium for tracheal intubation. The data retained for analysis are from one minute before the start of propofol to 110 sec later during ventilation of the patients' lungs before tracheal intubation. Spectral analysis was used to measure absolute EEG power. Propofol caused significant increases of cortical and thalamic power in the delta to beta frequency bands (1-30 Hz). These increases of cortical and thalamic power occurred either concomitantly or within seconds of each other. Propofol also caused a decrease in cortical and thalamic high-gamma (62-200 Hz) power that also followed a similar time course.*

Conclusion *We conclude that induction of anesthesia with propofol in these patients was associated with concurrent alterations of cortical and sensory thalamic activity.*

Résumé

Objectif *Selon les études d'imagerie cérébrale, la perte de conscience induite par les anesthésiques généraux serait*

Author contributions *Olivier Verdonck* performed data analysis and wrote the first draft of the manuscript. *Sean J. Reed* contributed to data analysis. *Jeffery Hall* was the attending neurosurgeon and performed the implantation of the electrodes. *Jean Gotman* designed the plan for electroencephalogram analysis. *Gilles Plourde* oversaw the project, planned the acquisition of clinical and electroencephalogram data, contributed to data analysis, and revised the manuscript in final form. All authors reviewed and contributed to the final version of the manuscript.

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associée à une détérioration de la fonction du thalamus. Toutefois, nous ne disposons que d'informations limitées quant au profil temporel de ces modifications. Nous avons récemment obtenu les enregistrements d'électroencéphalogrammes (EEG) intracrâniens du noyau ventro-postéro-latéral (VPL) du thalamus et du cortex moteur pendant l'induction de l'anesthésie chez trois patients afin d'étudier le profil temporel des modifications des fonctions corticale et thalamique.

Éléments cliniques *Les patients étaient des hommes de statut physique I-II selon l'American Society of Anesthesiologists âgés de 33 à 57 ans et souffrant de douleur centrale réfractaire causée par une lésion du plexus brachial (patients 1 et 2) ou d'un infarctus insulaire (patient 3). L'anesthésie a été induite avec du propofol (2,5-3,1 mg·kg^{-1} sur 30-45 sec), lequel fut suivi, après la perte de conscience, par du rocuronium pour l'intubation trachéale. Les données retenues pour analyse couvrent la période allant d'une minute avant l'administration du propofol à 110 sec plus tard, pendant la ventilation des poumons des patients avant l'intubation trachéale. Nous avons utilisé une analyse spectrale pour mesurer la puissance absolue de l'EEG. Le propofol a provoqué des augmentations considérables de la puissance corticale et thalamique dans les bandes de fréquence delta à bêta (1-30 Hz). Ces augmentations de puissance corticale et thalamique sont survenues soit simultanément, soit à quelques secondes d'intervalle. Le propofol a également provoqué une réduction de la puissance corticale et thalamique gamma élevée (62-200 Hz), laquelle a également suivi un profil temporel semblable.*

Conclusion *Nous concluons que l'induction de l'anesthésie au propofol chez ces patients a été associée à des modifications simultanées de l'activité corticale et thalamique sensorielle.*

There is compelling evidence that unconsciousness induced by most general anesthetics is associated with impairment of thalamic function in both animals[1,2] and humans.[3-6] The evidence in humans is based mainly on functional imaging studies which have revealed that the thalamus is a brain region where metabolism or blood flow is most consistently reduced during anesthetic-induced unconsciousness. There is, however, only indirect and limited electrophysiological evidence in humans indicating that the general anesthesia is associated with impaired thalamic function. The evidence is based on general anesthetics of sensory evoked potential peaks that possibly originate from the thalamus (such as the N18 peak of the median nerve sensory evoked potential).[7,8]

We obtained intracranial electroencephalogram (EEG) recordings from the sensory thalamus (ventroposterolateral [VPL] nucleus) and from the dura overlying the ipsilateral motor cortex during standard induction of general anesthesia in three patients. A few days before, the three patients had undergone implantation of an intracranial electrode in the VPL nucleus for intractable central pain. The epidural electrode overlying the motor cortex had been implanted years earlier during a previous attempt to treat their pain. The patients required general anesthesia for internalization of the leads and connection to the pulse generator in the subclavicular area. These recordings offered an opportunity to assess thalamic function during loss of consciousness induced by general anesthetics. Prior reports of *in situ* thalamic recordings during induction of general anesthesia in humans are lacking. Rather than refer to "intracerebral EEG" throughout the paper, we simply use "EEG" since our paper does not include the use of scalp EEG.

Description of patients

The patients were three American Society of Anesthesiologists physical status I-II males aged 33-57 yr with chronic severe intractable central pain caused by brachial plexus injury (patient 1 and 2) or by an insular infarct (patient 3). See Table 1 for detailed information. The patients gave written consent for publication of this report.

Stereotaxic placement of the epidural electrode (Medtronic Model 3587A) (Medtronic of Canada Ltd., Brampton, Ontario) overlying the hand and face region of the motor cortex had been performed 2-5 yr before. This is a flat electrode with four circular contacts (platinum/iridium, 12 mm^2 placed one cm apart and designated 0 (most distal), 1, 2, and 3 (most proximal). Stereotaxic placement of the thalamic (VPL nucleus) electrode (Medtronic Model 3387) had been performed under general anesthesia 3-5 days earlier. This is a cylindrical electrode with four ring-shaped contacts (platinum/iridium: 1.5 mm wide, 1.27 mm in diameter, 1.5 mm apart, designated as above). The coordinates for the VPL nucleus were 12 mm lateral and 7 mm posterior to the mid-commissural point at the depth of the anterior-posterior commissure plane.[9] Figure 1 shows an example of the anatomical images used for stereotaxic guidance of electrode insertion. The electrode connectors were left externalized for adjustment of stimulation parameters and for obtaining continuous 24-hr EEG recordings to ensure that no anomaly (i.e., epileptiform activity) was present. The patients agreed to keep the portable EEG recordings system during induction of anesthesia for the second stage of the implantation procedure (internalization of the leads

Table 1 Clinical summary

|	Patient 1	Patient 2	Patient 3
Age	33	35	57
Sex	M	M	M
History	Right brachial plexus injury 10 yr before (motor vehicle accident)	Left brachial plexus injury 6 yr before (motor vehicle accident)	Right insular stroke 4 yr before
			Right carotid endarterectomy 4 yr before
	Repair of brachial plexus 7 yr before	Repair of brachial plexus 5 yr before	Trial of motor cortex stimulation 2 yr before
	Trial of spinal cord stimulation 5 yr before	Trial of spinal cord stimulation 5 yr before	Pulse generator subsequently turned off
	Trial of motor cortex stimulation 2 yr before	Trial of motor cortex stimulation 5 yr before	
	Pulse generator subsequently turned off	Pulse generator subsequently turned off	
Implantation side	Left	Right	Right
Comorbidity	None	None	Arterial hypertension
			Smoker
Medication	None at time of surgery despite multiple trials	Baclofen 10 mg *tid*	Ramipril 5 mg *qd*
		Gabapentin 1,800 mg AM and noon	Rosuvastatin 10 mg *qd*
		Gabapentin 1,200 mg *qhs*	Acetylsalicylic acid 80 mg *qd* (off for 10 days)
		Methotrimeprazine 50 mg *qhs*	Mirtazapine 30 mg *qd*
			Transdermal fentanyl ($50 \ \mu g \cdot hr^{-1}$)
			Clonazepam 2 mg *qhs prn*
Weight	69 kg	79 kg	56 kg
Resting BP	120/82	109/69	115/75
Resting HR	62 beats·min^{-1}	68 beats·min^{-1}	62 beats·min^{-1}
ASA	I	II	II
Lab	CBC, INR, and PTT normal	CBC, INR, and PTT normal	CBC, INR, and PTT normal
			Routine biochemistry normal
			EKG normal
Sufentanil	None	None	0.09 μg·kg^{-1} 92 sec before propofol
Propofol	2.9 mg·kg^{-1} in 34 sec	2.5 mg·kg^{-1} in 38 sec	3.1 mg·kg^{-1} in 42 sec
Rocuronium	0.7 mg·kg^{-1} at 73 sec (0 is start for propofol)	0.6 mg·kg^{-1} at 65 sec	0.7 mg·kg^{-1} at 61 sec
Propofol - 2nd dose	0.7 mg·kg^{-1} at 122 sec	0.6 mg·kg^{-1} at 121 sec	None

CBC = complete blood count; EKG = electrocardiogram; INR = international normalized ratio; PTT = partial thromboplastin time; ASA = American Society of Anesthesiologist physical status; BP = blood pressure; HR = heart rate

after connection to the pulse generator in the subclavicular area). The anesthetic technique was left to the discretion of the attending anesthesiologist. A trained observer wrote down the timing of events.

After placement of standard monitors (EKG, noninvasive blood pressure, pulse oximeter), an 18G cannula was inserted in a forearm vein. Patient 3 received sufentanil (0.09 μg·kg^{-1}) 92 sec before propofol. The other patients received no medication before propofol. After preoxygenation for 60-90 sec, propofol (2.5-3.1 mg·kg^{-1}) was given over 30-45 sec. After loss of consciousness and loss of eyelid response, rocuronium (range 0.6-0.7 mg·kg^{-1}) was given and the patients' lungs were ventilated for about one minute. A second dose of propofol (0.6-0.7 mg·kg^{-1}) was given to patients 1 and 2 before tracheal intubation. The trachea was easily intubated with direct laryngoscopy. The EEG data retained for analysis are from one minute before the start of the first injection of propofol to 110 sec

Fig. 1 Magnetic resonance imaging from patient 1 used for stereotaxic guidance for electrode insertion in the left ventroposterolateral nucleus. Distance between tick marks on the crosshair is one cm
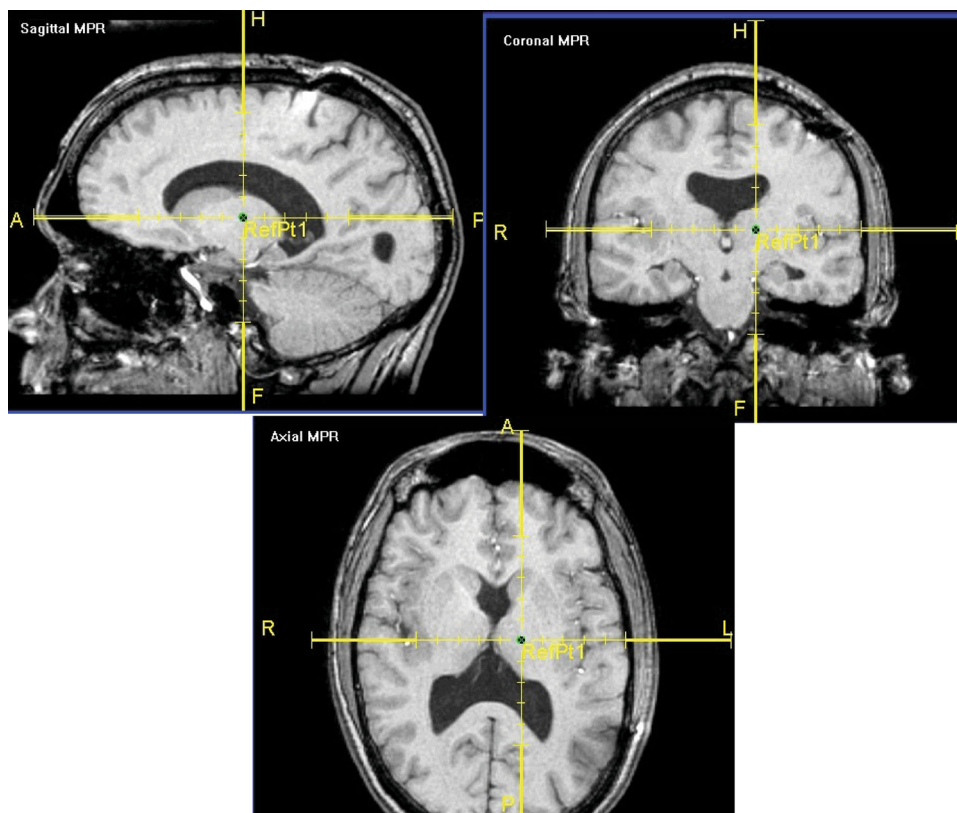
afterwards during ventilation of the lungs by facemask and before the second injection of propofol and tracheal intubation. All analyses are referenced to the start of the propofol injection, set at time 0.

The EEG was recorded from the eight contacts with reference to a scalp electrode at Pz with Lamont amplifiers (Stellate, Montreal, QC, Canada). Electrode impedances (30 Hz) were < 2 kOhm. For the first patient, the analog bandpass was 0.3-70 Hz, and the signal was digitized at 200 Hz. For the other patients, the analog bandpass was 0.3-500 Hz, and the signal was digitized at 2000 Hz. This wider bandpass was selected to examine the effects of propofol on spectral power in the high-gamma frequency range ($\sim$62-200 Hz).[10,11] The data were reformatted offline to a bipolar montage between adjacent contacts (C0-C1, C1-C2, and C2-C3) to obtain three channels for each electrode.

The raw EEG traces were reviewed for identification of artefacts. For patient 1, cortical channels one and three contained too many artefacts and were excluded from analysis. For the other data of patient 1 and the data of patients 2 and 3, EEG segments contaminated by artefacts based on visual inspection were excluded from analysis. Spectral power was computed by Fast Fourier Transform on non-overlapping EEG epochs of 2.56 sec (512 data points) for patient 1 and EEG epochs of 2.048 sec (4,096 data points) for the other patients.

We relied on absolute spectral power in the frequency bands up to 30 Hz (delta 1.0-4.0 Hz, theta 4.5-8.0 Hz, alpha 8.5-13.0 Hz, and beta 13-30 Hz) for comparing the time course between the thalamus and cortex because the effects of propofol in these frequency ranges are well characterized.[12] Due to the recent interest in the gamma (30-58 Hz) and high-gamma (62-200 Hz) ranges,[11] we also examined the effects of propofol on these bands. Power in the high-gamma range (62-200 Hz) was measured after excluding power at 118-122 Hz and 178-182 Hz to avoid contamination from power-line harmonics of 60 Hz noise. It was not possible to assess high-gamma power in the first patient because the EEG was recorded with a low-pass filter of 70 Hz. Recording of the EEG was performed with Harmonie Software (version 7.0, Stellate, Montreal, QC, Canada). Analysis was performed with MATLAB (MathWorks Inc. Sherborn, MA, USA).

A loose wire in the electrode connector box caused intermittent loss of the signal from the most distal contact (C0) of the thalamic electrode in all patients. Consequently, we have recordings for contacts C1, C2, and C3, allowing for two bipolar channels between adjacent contacts (C1-C2, C2-C3) for the thalamus.

For the cortex and thalamus, the power values were normalized for each channel separately such that the

Fig. 2 Electroencephalogram tracings. The top row shows the entire period for the five channels. The start of the propofol injection is denoted by the arrow. The injection of rocuronium is denoted by the triangle. The small square dots labelled A to I indicate two second segments shown in the other rows. The order of the channels is the same as for the upper row. Notice that the cortex and thalamus have different amplitude scale bars. Cx = cortex; Th = thalamus. The digits refer to the electrode contacts used
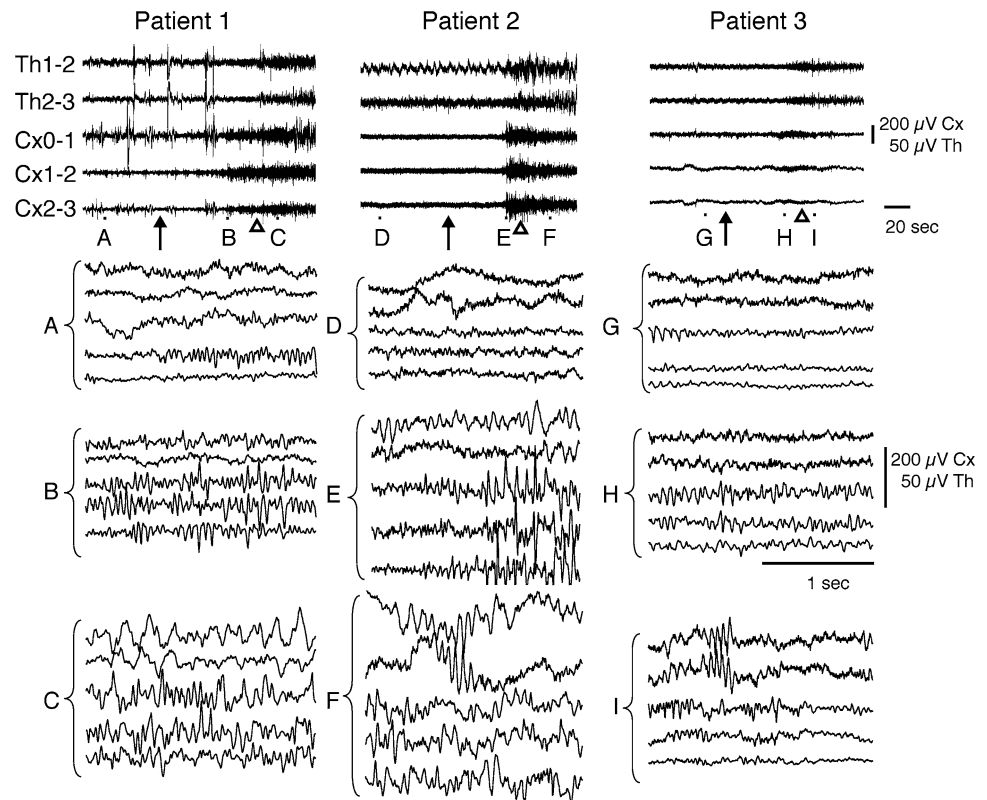
minimum value was 0 and the maximum value was 1 using:

$$N_i = (P_i - P_{min})/(P_{max} - P_{min})$$

where P_i is the ith power value (P_1, P_2, P_3…. P_{last}); N_i is the normalized value of P_i, and P_{max} and P_{min} are the maximum and minimum, respectively, of all values of P_i for the whole duration of the recording. Normalization was done to avoid undue influence of channels with higher mean power and to facilitate comparisons of time course between cortex and thalamus. For patient 1, there was only one cortical channel retained for analysis. In the other patients, the three cortical channels revealed similar changes, and the values for the three channels were averaged to obtain a single measure of cortical spectral power. For all patients, the two thalamic channels also revealed similar changes and were averaged.

We compared the mean of serial measures of normalized spectral power obtained during baseline (time −60 to 0 sec, with 0 corresponding to the start of propofol injection) with that of serial measures obtained during induction of anesthesia (50-110 sec after the start of the propofol injection). This was done for each recording site (cortex and thalamus) and frequency band (delta, theta…) separately. The use of serial measures makes it possible to use statistical tests despite the small number of patients.

We used a mixed model analysis[A] in order to take into account the possible correlation of the repeated observations within each subject. This approach includes a fixed effect (baseline vs induction) and a random effect (patients). We assumed that the correlation structure for within-subject observations was in a spatial power law form, which assumes that observations closer together are more correlated than observations further apart and does not require repeated observations to be equally spaced in time[A] — the observations were not equally spaced because EEG segments contaminated by artefacts were excluded from analysis. The usual assumptions for linear modelling (randomness, normality, homoscedasticity of errors) and the presence of outliers were checked via analysis of residuals. Inspection of the residuals following a preliminary analysis with untransformed data led us to use a natural logarithm transformation to stabilize the variance and to bring the distribution of errors closer to a normal distribution. Final results were then back transformed and reported as geometric means and their respective ratios (instead of as arithmetic means and their respective differences).[13] The *P* values were adjusted for

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[A] *Littell RC, Milliken GA, Stroup WW, Wolfinger RD, Shabenberger O*. SAS System for Mixed Models. Cary, NC, USA: SAS Institute, Inc; 2006.

Table 2 Spectral power during baseline and induction

Band	Base	Induction	Ratio	CI_low	CI_high	P	Corrected P
Cortex							
Delta	0.02	0.14	0.16	0.04	0.59	0.011	0.023
Theta	0.06	0.26	0.22	0.10	0.48	0.001	0.005
Alpha	0.02	0.25	0.07	0.02	0.19	0.002	0.008
Beta	0.04	0.27	0.15	0.03	0.78	0.030	0.030
Gamma	0.05	0.22	0.21	0.08	0.60	0.007	0.017
High-Gamma	0.42	0.19	2.28	1.41	3.69	0.002	0.008
Thalamus							
Delta	0.06	0.18	0.34	0.15	0.77	0.014	0.027
Theta	0.01	0.21	0.07	0.03	0.14	<0.0001	<0.0004
Alpha	0.01	0.27	0.04	0.02	0.09	<0.0001	<0.0004
Beta	0.02	0.33	0.07	0.04	0.10	<0.0001	<0.0004
Gamma	0.18	0.23	0.76	0.25	2.25	0.581	0.581
High-Gamma	0.71	0.17	4.23	1.94	9.24	0.002	0.005

Because the data were log transformed for analysis, the results are reported as geometric means and their respective ratios (instead of as arithmetic means and their respective differences). The Base and Induction columns are the geometric means for the normalized power during Baseline and Induction. Base is from −60 sec to time 0 (start of propofol). Induction is from 50 to 110 sec after the start of propofol injection. The Ratio column is the ratio of Base/Induction, and the CI_low and CI_high columns define the 95% confidence interval for this ratio. The null value (indicating no difference) for the ratio is 1

$P = P$ value for the fixed effect (baseline *vs* induction); corrected $P = P$ value after correction for multiple comparisons (6 per recording site)

multiple comparisons (six bands for each recording site) using Hommel's procedure.[14] All tests of hypothesis were two sided and performed at the 0.05 level of significance. Statistical tests were computed with SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA).

Observations

The EEG traces are shown in Fig. 2. Electroencephalogram power increased in the thalamus and cortex 30-45 sec after the start of the injection of propofol, as revealed in the upper part of the figure by widening of the time-compressed traces. The lower part of the figure shows short EEG segments with the usual time scale at three time points. They clearly illustrate the energy increase in broadband activity after propofol injection. Gamma activity is of very low amplitude and difficult to appreciate visually.

In the analysis for patient 1, 15 observations were retained for baseline and 23 for induction. For patient 2, there were 27 and 22 observations, respectively, and for patient 3, there were 25 and 21 observations, respectively. Inspection of the residuals showed no substantial departures from the assumptions for a mixed model analysis; however, it identified a few possible outliers or influential observations. We conducted a second analysis after exclusion of these observations, and results were the same in the sense that ratios and confidence intervals were of similar magnitudes and no new significant difference appeared despite the increase in significance levels (i.e., smaller *P* values). For the sake of simplicity, we report only the results of the first analysis, which included all available observations.

Table 2 shows that both cortical and thalamic power in the delta to beta ranges increased significantly. There was also a significant increase in cortical, but not thalamic, gamma power. Both cortical and thalamic high-gamma power decreased significantly.

Inspection of Fig. 3 reveals that, in most instances, the increase in cortical and thalamic power in the delta to beta bands followed a very similar time course. The only clear exceptions are for alpha and beta power in patient 3 where the increase in cortical power preceded the increase in thalamic power by more than ten seconds. It is important to emphasize that there is at least one frequency band for each patient where the increase in cortical and thalamic power occurred at the same time. The increases in cortical and thalamic power occurred shortly before the injection of rocuronium or very soon afterwards in the case of Patient 1 (delta, theta, and alpha bands). Figure 3 also shows that the decrease in cortical and thalamic high-gamma power followed a similar time course.

Discussion

We draw two conclusions from the present observations. First, the initial changes in cortical and thalamic power for
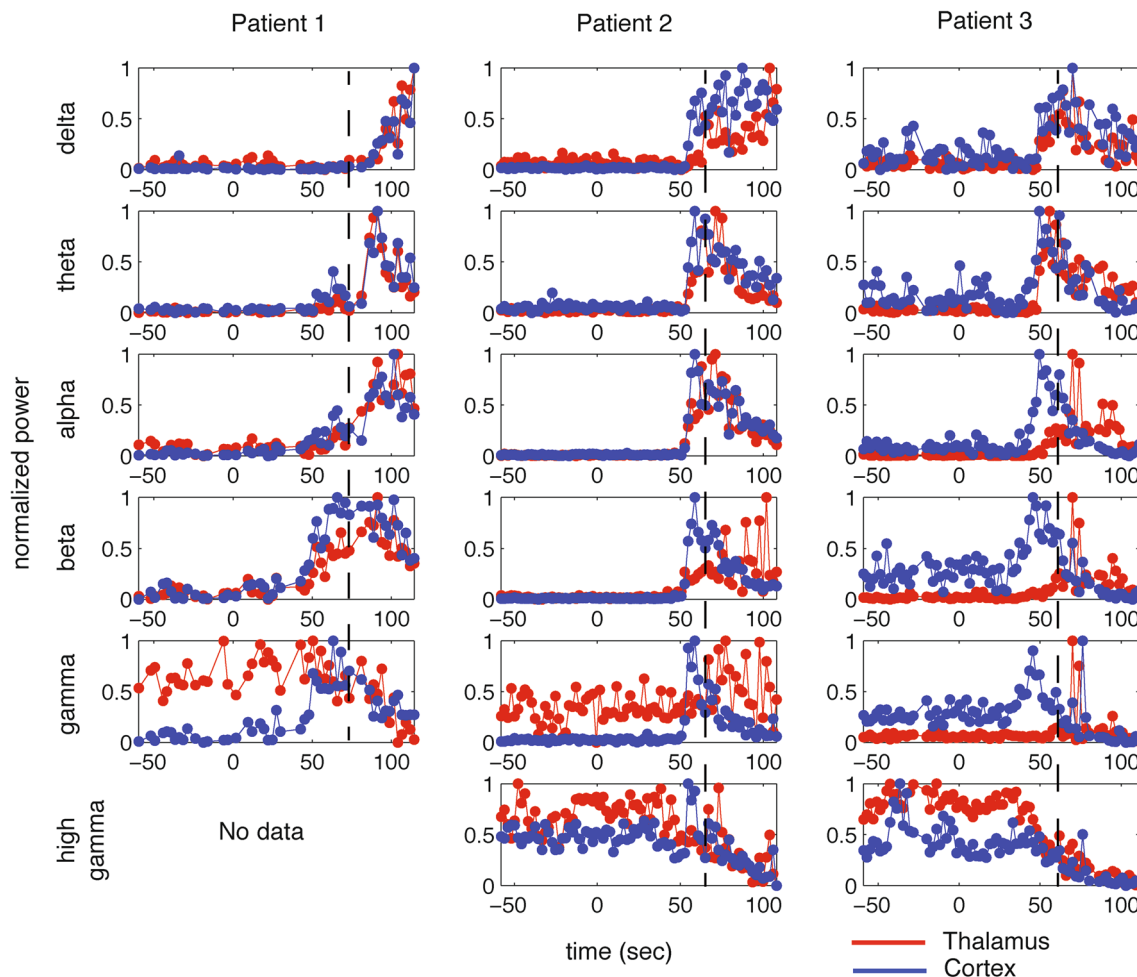
Fig. 3 Time course of spectral power for the cortex and thalamus. Normalized magnitude. Time 0 is the start of the injection of propofol. The black dash line shows the time when rocuronium was given (a few seconds after confirmation of loss of consciousness)

the delta to beta bands followed a similar time course, occurring either at the same time or within ten seconds of each other in all instances except two. Second, there are alterations of sensory thalamic activity that are present within seconds of loss of consciousness with propofol. The precise timing of these alterations in relation to loss of consciousness has not been assessed, but it is clear that a change of thalamic activity, as revealed by an increase in power in at least one frequency band, could be documented in all patients when we had confirmation that consciousness had been lost (i.e., when rocuronium was given).

The present findings are in sharp contrast to those of Velly *et al.*[15] who reported that change of subcortical (presumably mainly thalamic) activity occurs only minutes after loss of consciousness during induction of anesthesia with propofol. We have no definite explanations for this discrepancy, but two factors may be relevant. First, the recording contacts in the present study were located in the VPL nucleus, and we used a bipolar montage between adjacent contacts to capture local activity. In Velly's paper,

the electrode was aimed at the subthalamic nucleus, and they used a bipolar montage between the most distant contacts in an attempt to record thalamic activity. Second, Velly *et al.* studied patients with advanced Parkinson's disease, which exerts widespread effects on cerebral function.[16]

An objection might be made that the strength and importance of the present observations are limited because of the small number of subjects. While we agree that a study based on a large number of patients would provide the best evidence, we also point out that robust evidence can be obtained from studies with only two subjects if multiple repeated measures are available. For example, the standard approach in monkey electrophysiological work is to use only two animals (see for example reference).[17] The main limitation of the present report is that we cannot rule out the possibility that central pain may have influenced the response of the thalamus to propofol.

Our observations do not imply that unconsciousness results uniquely from a direct effect of propofol on the

thalamus, or the cerebral cortex, or both. Propofol, like other general anesthetics, acts on multiple cortical and subcortical structures involving multiple neuronal cell types and molecular targets.[18] Thus, the changes of cortical and thalamic function observed during propofol anesthesia may result from direct or indirect effects. Our observations show, however, that unconsciousness induced by propofol is associated with nearly simultaneous alterations of both cortical and thalamic function on a time scale in the order of one second. The effects of propofol on auditory evoked potentials in humans are consistent with an involvement of both cortical and subcortical (brainstem) structures,[19] and so, it would be surprising if the thalamus was spared.

The present report also has relevance with regard to the effects of propofol on gamma and high-gamma power. There was a significant increase in cortical but not thalamic gamma power. Increases in gamma power with propofol have been observed in human subjects using electrodes in the medial temporal lobe (32-48 Hz)[20] or EEG recordings from the scalp (25-40 Hz).[21] Other studies, also in human subjects, have reported decreases of gamma power with propofol with recordings from the scalp (30-50 Hz)[4,20] or from the surface of the cortex (37-45 Hz).[22] It thus appears that the change of spontaneous gamma power induced by propofol varies across studies and recording sites. This is in contrast to the gamma frequency components of auditory evoked potentials (middle latency auditory evoked response and 40 Hz auditory steady-state response) that are consistently attenuated by propofol (and most other general anesthetics) in a concentration-dependent manner.[23] It is thus important to distinguish between gamma rhythms that occur spontaneously and those that are evoked by sensory stimulation.

How can the inconsistent effects of propofol and other general anesthetics on spontaneous gamma power be explained? We do not have a definite explanation, but we propose that this inconsistency occurs because the gamma range occupies the intermediate transition zone between the low frequency range (below 30 Hz), where general anesthetics increase power, and the high frequency range (80-200 Hz and above), where general anesthetics decrease power, as discussed next.

Both cortical and thalamic high-gamma (62-200 Hz) power decreased significantly and followed a similar time course. We recently reported that propofol reduces power in the 80-200 Hz range in the ventroposteromedial (VPM) nucleus of rats (the equivalent of the VPL nucleus for the trigeminal system),[24] and Breshears et al.[22] reported that propofol decreases high-gamma power (75-165 Hz) in the EEG recorded from the surface of the cortex in patients. Hudetz et al.[11] reported that isoflurane produces concentration-dependent attenuation of high-gamma power (70-140 Hz) in neocortical and hippocampal

recordings in rats. Consequently, there is converging evidence that high-gamma power is reduced during anesthesia. Studying the effects of general anesthetics on high-gamma power may also help explain the effects of propofol and other general anesthetics on blood oxygenation level-dependent (BOLD) signals revealed by functional magnetic resonance imaging (fMRI),[25] since numerous studies have shown that high-gamma power and BOLD fMRI show congruent changes during sensory stimulation or cognitive tasks.[26]

Our report carries some limitations. It is based on a small number of patients. These patients were suffering from intractable central pain that may have altered their response to propofol. The recordings were obtained in the context of routine clinical care without any alteration to the normal practice. There was restricted time for baseline recording and the induction period was brief. The time scale of the measures is in the order of two seconds and does not permit the identification of sequential processes in the millisecond range. The dose and rate of administration of propofol were not standardized. The exact time when consciousness was lost is not known. Patient 3 received a small amount of opioid before induction.

On the basis of EEG recordings obtained with intracranial electrodes sited in the sensory thalamus, we conclude that, in these patients, loss of consciousness during induction of anesthesia with propofol was associated with concurrent alterations of cortical and sensory thalamic activity.

Conflicts of interest None declared.

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