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Burst Activation of the Cerebral Cortex by Flash Stimuli during Isoflurane Anesthesia in Rats

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Background: **The degree of suppression of sensory functions during general anesthesia is controversial. Here, the authors investigated whether discrete flash stimuli induced cortical field potential responses at an isoflurane concentration producing burst suppression and compared the spatiotemporal properties and frequency spectra of flash-induced burst responses with those occurring spontaneously.**

Methods: **Rats were equipped with multiple epidural and intracortical electrodes to record cortical field potentials in the right hemisphere at several locations along the anterior–posterior axis. At isoflurane concentrations of 1.1, 1.4, and 1.8%, discrete light flashes were delivered to the left eye while cortical field potentials were continuously recorded.**

Results: **Isoflurane at 1.4–1.8% produced burst suppression. Each flash produced a visual evoked potential in the primary visual cortex followed by secondary bursting activity in more anterior regions. The average latency and duration of these bursts were 220 and 810 ms, respectively. The spontaneous and flash-induced bursts were similar in frequency, duration, and spatial distribution. They had maximum power in the frontal (primary motor) cortex with a dominant frequency of 10 Hz.**

Conclusions: **The results suggest that discrete flash stimuli activate the motor regions of the cerebral cortex during isoflurane anesthesia and that these activations are analogous with those that occur spontaneously during burst suppression. Electrocortical suppression of the cortex during anesthesia does not prevent its response to visual stimuli.**

TO what degree does the brain process sensory information during anesthesia? This is a question of general interest for neuroscience, and it has both theoretical and practical importance for anesthesiologists. Studies in neurophysiology suggest that in the anesthetized, nonresponsive subject, sensory stimuli fail to gain access to the cerebral cortex because of a block or disruption of thalamocortical information transfer.[1–4] It has been recognized, however, that sensory stimuli of various modalities continue to activate the cerebral cortex during surgical levels of anesthesia that arguably produce unconsciousness.[5–11] This raises the question: At what anesthetic depth does the cortex become unresponsive to sensory stimuli?

Various anesthetic agents at clinically relevant concentrations can produce complete or intermittent suppression of electrocortical activity—a state commonly called *burst suppression*.[12–17] Does this depth of anesthesia preclude cortical sensory processing? We noted in previous experiments that in rats anesthetized with isoflurane to burst suppression level, a light flash or hand clap often produced bursts of electrocortical activity. We wondered whether cortical activation by flash in the state of burst suppression was a systematic phenomenon and, if so, what the spatial, temporal, and frequency characteristics of flash-induced cortical bursts were.

Previously, Hartikainen *et al.*[14,16] reported the induction of electrocortical bursts from an isoelectric baseline by somatosensory, auditory, and visual stimuli in patients during isoflurane anesthesia. This has not been systematically examined in rats. Also, the previous studies used flicker stimuli, whereas we saw a burst response to a single flash. Finally, because flash-induced bursts occurred in the background of spontaneously occurring bursts, we sought to determine whether these two types of bursts had anything in common with respect to power, frequency, duration, and spatial distribution properties that have not been examined systematically before. We speculated that a comparison of spontaneous and flash-induced bursts may further our understanding of their generating mechanism and of the pharmacodynamic effects of isoflurane on spontaneous and sensory-evoked cortical activity.

To achieve these goals, we performed multichannel recording of epidural and intracortical field potentials with electrodes arranged along the anterior–posterior axis and applied wavelet power spectral analysis to determine the cortical region with maximum power in isoflurane anesthetized rats.

Materials and Methods

The experimental procedures and protocols used in this investigation were approved by the Institutional Animal Care and Use Committee of the Medical College of Wisconsin, Milwaukee, Wisconsin. All procedures conformed to the Guiding Principles in the Care and Use of Animals of the American Physiologic Society and were in accordance with the *Guide for the Care and Use of Laboratory Animals*, National Academy Press, Washington, D.C., 1996.

Surgical Preparation

In this article, results from 23 adult male Sprague-Dawley rats are reported. The animals were housed on 12-h light–dark cycle at a constant temperature of 23° ±

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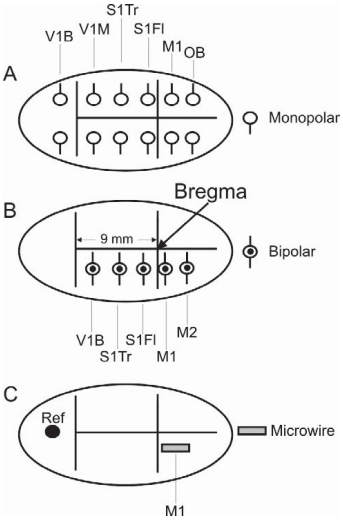

Fig. 1. Approximate positioning of multiple recording electrodes relative to landmarks on the rat skull. (*A*) Monopolar epidural screw electrodes, (*B*) intracortical coaxial bipolar electrodes, (*C*) microwire electrodes. The *rectangle* approximates the area in which 16 microwires are positioned. M1 = primary motor cortex; M2 = secondary motor cortex; OB = olfactory bulb; S1FL = somatosensory cortex, forelimb area; S1Tr = somatosensory cortex, trunk area; V1B = primary visual cortex, binocular region; V1M = primary visual cortex, monocular region.

1°C with free access to food and water for 2 weeks before each experiment. Animals were anesthetized for surgery with isoflurane, tracheotomized, paralyzed with gallamine triethiodide (80 mg intravenous), and artificially ventilated using a rodent ventilator (SAR 830/P; CWE, Ardmore, PA) with the mixture of 30% oxygen in nitrogen plus isoflurane. Inspired and expired isoflurane, oxygen, and carbon dioxide concentrations were monitored using a gas analyzer (POET II; Criticare Systems, Inc., Waukesha, WI). Femoral arterial blood pressure and blood gases were also checked. Rectal temperature was maintained at 37° ± 1°C with a thermostat-controlled water-circulated heating pad.

The head was secured in a stereotaxic frame, and electrodes for recording of field potentials were installed stereotaxically at select positions. All measurements were relative to bregma in the flat skull orientation (bregma and lambda at equal vertical levels). In seven experiments, miniature stainless steel screws were used as epidural electrodes at center coordinates 6.1, 2.9, −0.3, −3.5, −6.8, and −10.0 mm anterior–posterior and 3.5 mm lateral. The screws were placed through burr holes prepared using a dental drill. In the majority of animals, electrodes were placed bilaterally (fig. 1A). According to the stereotaxic atlas of Paxinos and Watson,[18] these coordinates approximately corresponded to the olfactory bulb (OB), primary motor cortex (M1), somatosensory cortex forelimb area (S1FL), somatosensory cortex trunk area (S1Tr), primary visual cortex monocular region (V1M), and primary visual cortex binocular region (V1B), respectively. In nine animals, coaxial, bipolar semimicro electrodes (contact diameter: 0.1 mm, length: 0.25 mm, separation: 0.5 mm; SNEX-100; Rhodes Medical Instruments, Summerland, CA) were used to record field potentials intracortically from the right hemisphere. Five electrodes were arranged along the anterior–posterior axis with an approximate spacing of 2.5 mm. The electrodes were held in a block carrier and inserted at the same time through burr holes with the dura intact at 3.0 mm lateral and −2.3 mm vertical coordinates. The anterior–posterior position of the carrier was varied with the extreme electrode positions ranging from 3.7 to −8.3 mm corresponding to cortical regions from secondary motor cortex to V1B (fig. 1B). In the last seven animals, local field potentials in the frontal cortex of the right hemisphere were recorded with sixteen 50-μm-diameter microwires (Tucker-Davis Technologies, Alachua, FL) (fig. 1C). The wires were placed at coordinates 0–3.5 anterior, 2–3 mm lateral, and 0.5–2.0 mm vertical—a cortical region that corresponds to M1. A stainless steel screw was placed in the occipital bone over the midline and as caudally as possible to serve as an epidural reference electrode.

Our goal in implementing various electrode methodologies was to establish whether the character of field potentials depended on the type of electrode and electrode configuration used. The total number of animals[23] was chosen to ensure that at least seven animals were included in each group, yielding an appropriate sample size for statistical analysis. However, the subsequent inspection of the data revealed no difference in signal characteristics among different techniques. Therefore, data across all groups were pooled for analysis.

Electrophysiologic Recording

Epidural field potentials were recorded as bipolar signals between homotopic electrodes in the two hemispheres or between consecutive anterior–posterior electrodes within the same hemisphere using differential amplifiers built in house. The signals were amplified 10,000 times and analog filtered for 1–100 Hz. Field potentials recorded with bipolar electrodes were amplified and filtered using the same specifications. A notch filter at 60 Hz was used when necessary. Local field potentials picked up by microwires were coupled with a unity gain headstage and amplified with a commercial amplifier (L8; Neuralynx, Inc., Tucson, AZ) with 1–50 Hz pass band. All signals were digitized at a sampling frequency of 500 Hz and recorded using the Windaq Pro data acquisition system (DataQ Instruments, Dacron, OH).

Burst Recording at Rest and with Flash Stimulation

Isoflurane concentration was stabilized at 1.8 ± 0.1%, which was an optimal concentration to obtain 10–20 spontaneous bursts per minute. A 15-min equilibration period was allowed to reach steady state. Sixty to 80

Table 1. Postsurgical Experimental Protocol and Timeline

13 Animals	1. Adjust isoflurane concentration to 1.1%	15-min equilibration
	2. Record spontaneous bursts	2–5 min
	3. Record flash-induced bursts	5–7 min
	4. Adjust isoflurane concentration to 1.4%	15-min equilibration
	5. Record spontaneous bursts	2–5 min
	6. Record flash-induced bursts	5–7 min
	7. Adjust isoflurane concentration to 1.8%	15-min equilibration
	8. Record spontaneous bursts	2–5 min
	9. Record flash-induced bursts	5–7 min
10 Animals	1. Adjust isoflurane concentration to 1.8%	15-min equilibration
	2. Record spontaneous bursts	2–5 min
	3. Record flash-induced bursts	5–7 min

spontaneous bursts were recorded under resting conditions (no flash stimulus given). Recording of a comparable period was then repeated with flash stimulation. Each flash was produced by a blue light emitting diode positioned 10 mm from the left eye. The light emitting diode "on" time was 2 ms at +5 V transistor-transistor-logic pulse. Sixty to 80 flashes were delivered at either equidistant or randomly selected intervals in the range of 5–45 s. We sought to obtain a minimum of 60 bursts to have a sample size suitable for averaging. We found no difference in burst characteristics for different interstimulus intervals. Occasional spontaneous bursts were observed during flash stimulation but, because of their onset variability, were easily eliminated by signal averaging. In 10 of the animals, the concentration-dependent effect of isoflurane on flash-induced bursts was also studied at the levels of 1.1, 1.4, and 1.8% isoflurane with 15-min equilibration times before stimulus presentation. Testing was performed first at the 1.1% level and subsequently at 1.4% and 1.8%. Higher concentrations were not studied because of frequent cardiovascular instability and mortality at greater than 1.8% isoflurane. After the experiment was completed, the animals were killed according to the institutionally approved procedures. A summary of the experimental protocol is presented in table 1. These experiments are independent from our previously published work with isoflurane.[19–21]

Data Analysis and Statistics

Spontaneous and flash-induced bursts were extracted from the record using a simple event detection algorithm based on a threshold/blanking period. An amplitude threshold was set at 65% of the maximum signal amplitude in either trigger or stimulus channel. A local maximum was detected in a 200-ms window after threshold crossing. This local maximum corresponded to the onset of either spontaneous or flash-induced burst. This technique has been used successfully in our previously published work.[19–21]

Time-variant spectral characteristics of the signals were determined using continuous wavelet analysis described by Tallon-Baudry *et al.*[22] To compute the wavelet spectra, the signals were convolved with a series of complex Morlet wavelets with central frequencies ranging from 1 to 100 Hz in increments of 1 Hz. The Morlet wavelet is conceptually simple and has been shown useful for the analysis of sensory evoked potentials.[23] The wavelet amplitudes were normalized to yield their total energy of 1. Temporal duration and spectral bandwidth of each wavelet corresponded to 1 SD of its gaussian envelope in time and frequency domains, respectively, and ranged from 1.1 s and 0.14 Hz at 1 Hz to 22.2 ms and 28.6 Hz at 100 Hz. The wavelet spectra were computed from each burst waveform and then averaged for all bursts of the same experiment and burst type. Peak power frequency was determined as the frequency at which wavelet power was maximal in each experiment and condition. Average burst power as a function of time was calculated by averaging the wavelet spectra across all frequencies. Peak power and time-average burst power were determined from the spectral-averaged power. Burst duration was measured as the period between the two time points where the average wavelet power decreased to 33% of its peak value before and after the peak. Relative peak power was calculated as the peak power normalized to the time-average burst power for a 1-s window. Burst latency relative to flash was calculated as the difference between the time of flash and the time of the first positive going slope of the burst, exceeding a threshold set above the resting baseline. To obtain average poststimulus burst power as a function of time at different isoflurane concentrations, we calculated 2.5–20 Hz band power at 1-s increments, normalized each value to get power ratio as power divided by the average preburst baseline (from the first 200 ms after flash), and then averaged the log of power ratios from different experiments. We used power ratios to reduce the interanimal variation in baseline power and log transform to normalize the statistical distribution of data. The curve was fitted to indicate trend between distance from bregma and relative peak power for both spontaneous and flash-induced bursts using the equation $P = A + \log(B) \cdot B^t$ (Sigma Plot Software; SPSS Inc., Chicago, IL). In this equation, P is the relative peak power; t is time; the constant A had values of 0.568 and 0.474 for spontaneous and flash-induced bursts, respectively; and B was 2.3 for both. The mean values of various calculated parameters were compared between spontaneous and flash-induced bursts as obtained in the same experiment using paired *t* tests. Statistical testing was performed using the software NCSS 2001 (NCSS, Kaysville, UT).

Results

The results obtained with various electrode types and configurations were consistent with each other and therefore will be discussed together. Isoflurane at concentrations between 1.4% and 1.8% produced burst suppression in all animals. These bursts seemed to occur at random intervals. When a flash stimulus was applied, a brief visual evoked potential was seen in V1, followed by a burst of activity in more anterior regions. The latency of flash-induced bursts (burst onset) was between 200 and 260 ms (mean: 220 ± 20 ms). Maximum burst power occurred between 210 and 350 ms (mean: 280 ± 50 ms) after flash.

Figure 2 presents an example of both spontaneous and flash-induced bursts as observed in one experiment. The amplitude and pattern of spontaneous and flash-induced bursts were similar. In addition, both types of burst had the largest amplitude in the frontal cortex.

To quantify these observations in all animals, wideband (1- to 100-Hz) average power and peak power of the bursts were determined. Figure 3 illustrates the relative peak power of spontaneous and flash-induced bursts recorded at different anterior–posterior positions. Clearly, both types of bursts had the highest power in the frontal cortex. Average power, peak power, and duration of spontaneous and flash-induced bursts recorded from the frontal cortex were statistically compared (table 2) and were found to be similar between the two types of bursts.

Because the onset of bursts was variable, an average burst waveform was obtained after temporally aligning the bursts by their onset using threshold crossing detection. An analysis of frontal cortex bursts revealed an early oscillatory component followed by a smaller late component at 200–400 ms (fig. 4A). Pseudocolor plots of burst potentials suggested that the late components were actually larger but were attenuated in the average because of their increased phase dispersion. This was confirmed by wavelet analysis that revealed a robust burst activity extending up to 1 s. The peak power occurred within the first 100 ms, which was then followed by additional "subbursts" of activity (fig. 4B). A short gap between the initial and secondary bursting activities around 150 ms was evident in all experiments. These findings are summarized in individual experimental averages in figure 4C.

From the wavelet transform, we also determined the peak power frequency, *i.e.*, the dominant frequency with maximum power. This frequency varied between 9 and 12 Hz, and its mean value was not different between spontaneous and flash-induced bursts (table 1).

To determine how flash-induced burst properties were influenced by the concentration of isoflurane, we calculated average burst power as a function of poststimulus time (fig. 5). We observed an increase in burst power and duration as the isoflurane concentration was increased. Nevertheless, the qualitative time course of the bursts appeared similar at different isoflurane concentrations.

Discussion

In essence, we found that during cortical burst suppression by isoflurane each light flash elicited a burst of cortical field potentials and that these bursts showed no essential difference in power, frequency, and duration from the bursts occurring spontaneously at the same isoflurane concentration. These findings support the notion of residual responsiveness of the cerebral cortex to visual stimuli during deep general anesthesia normally associated with unconsciousness. They also suggest that the visual evoked response may be mediated by the same neuronal pathway that underlies the spontaneous cortical state fluctuations during burst suppression.

Previously, Hartikainen *et al.*[14,16] found brief bursts of electrocorticographic activation at the onset and offset of 20-Hz trains of light stimuli in patients with isoflurane-suppressed electroencephalogram. Similar results were found in other sensory modalities.[16] Here we showed that a single flash can also elicit similar electrocortical bursts. This is of interest because a single flash has significantly less power than the 20-Hz photic stimulation and has more relevance to physiologic stimuli.

Cortical burst suppression has been viewed as a deep anesthetic state in which the cortex is isolated from thalamic sensory inputs.[24,25] Steriade suggested that anesthetic-induced bursts were generated intrinsically by the cortex because cortical neurons fired in bursts in close temporal relation to the electroencephalography but independent of the firing of thalamic neurons.[17,24] Although anesthetic agents target the thalamus,[1–4] they also suppress cortical neurons directly[7] and may produce burst suppression through cortical glutamatergic synapses.[17]

Although the generation of spontaneous bursts may not require subcortical input, it is difficult to conceive how peripheral sensory stimuli could produce bursts in a disconnected cortex. One could propose that sensory stimulation may transiently open the "thalamic gates" of information flow. Alternatively, flash stimuli may activate the cortex *via* an extrathalamic route.[26] Golanov and Reis[27] suggested that the reticular formation may play a role in the facilitation of both spontaneous bursts and those produced by a stimulation of brainstem nuclei. Orth *et al.*[28] showed that electrical stimulation of the medial reticular formation decreased the periods of isoelectricity between isoflurane-induced bursts. Because the bursts are dominantly frontal and significantly delayed relative to flash, they are likely mediated by polysynaptic pathways. These pathways may be cortico-

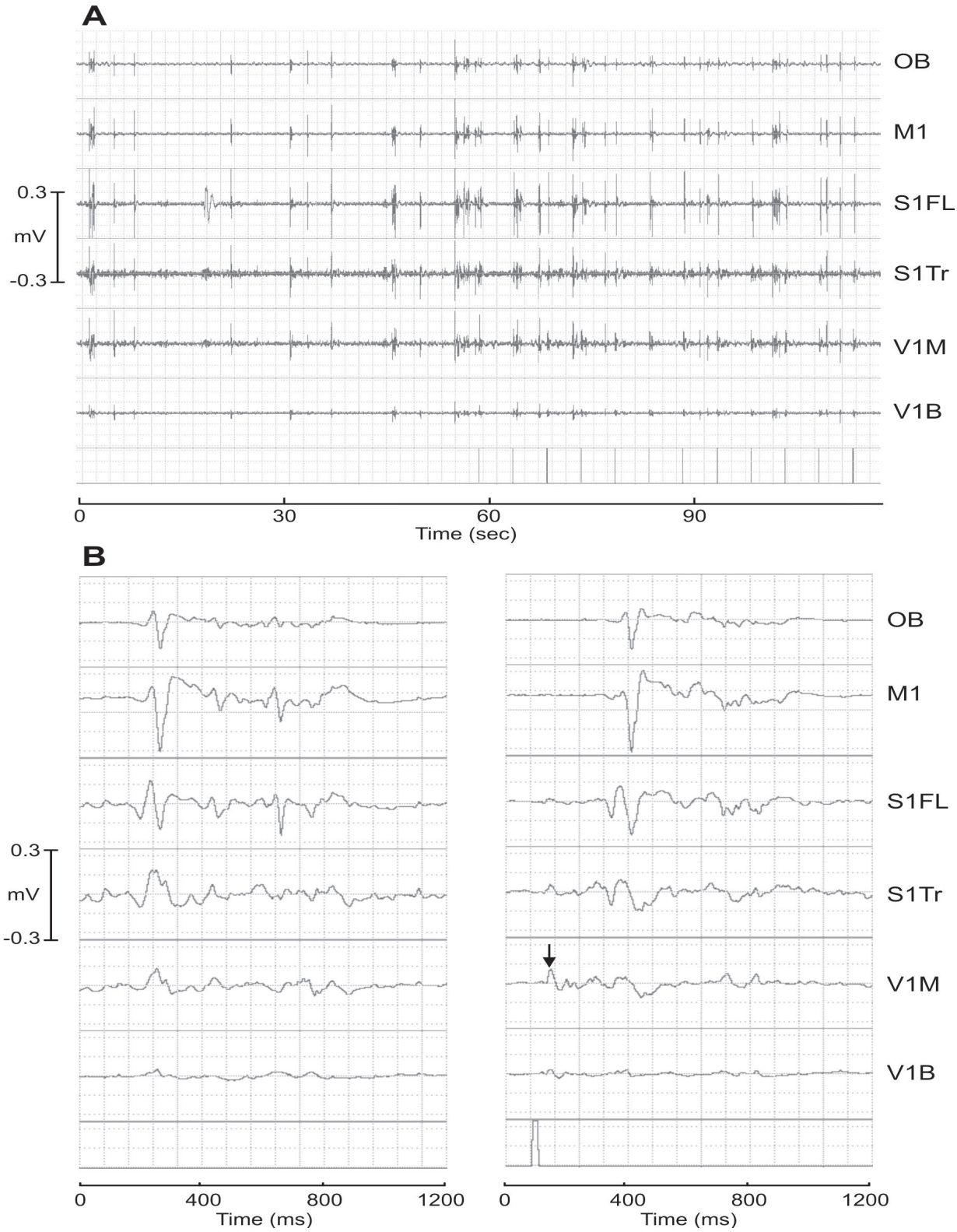

Fig. 2. Original record of spontaneous and flash-induced bursts at 1.8% isoflurane anesthesia in one experiment. (*A*) Spontaneous bursts followed by bursts induced by monocular flash stimulation. In this example, the flashes were presented every 5 s; flash markers are shown in the *lowest trace*. Note that spontaneous bursts can also be seen during flash stimulation. (*B*) Comparison of single spontaneous (*left*) and flash-induced (*right*) bursts on an expanded time scale. Signals were recorded with epidural electrodes at positions that correspond approximately to cortical structures as indicated. M1 = primary motor cortex; OB = olfactory bulb; S1FL = somatosensory cortex, forelimb area; S1Tr = somatosensory cortex, trunk area; V1B = primary visual cortex, binocular region; V1M = primary visual cortex, monocular region. Note the similarity of spontaneous and flash-induced bursts and their maximum amplitude in M1. A visual evoked potential to flash is seen in V1M (marked with *arrow*). This is followed by a burst of larger potentials in more frontal areas with a latency of approximately 300 ms.

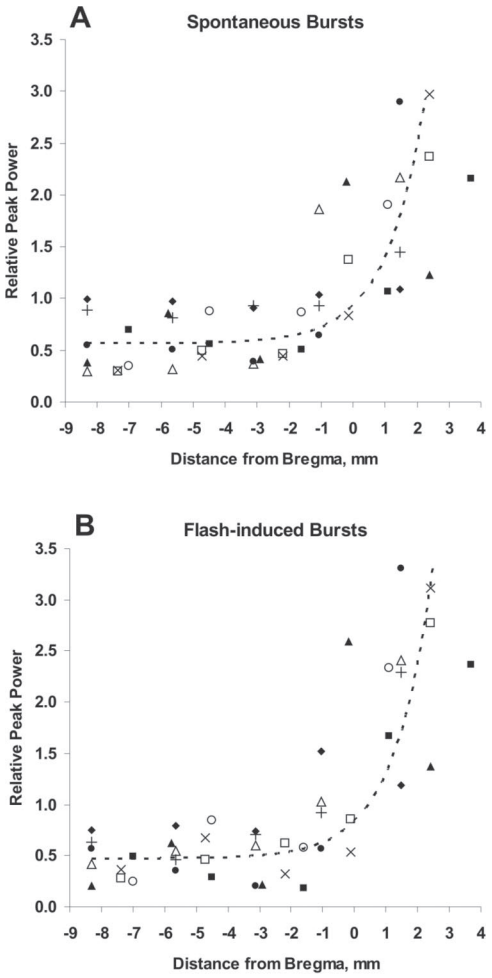

Fig. 3. Distribution of the peak power of spontaneous (*A*) and flash-induced (*B*) bursts along the anterior–posterior axis in nine experiments. Both spontaneous and flash-induced bursts attain maximum power in anterior regions that correspond mainly to primary motor cortex (M1). Relative peak power refers to peak power normalized to average power in the same experiment. Different *symbols* mark data from different experiments. The curve was fitted to indicate trend using the equation $P = A + \log(B) \cdot B^t$, where P is power; t is time; the constant A had values of 0.568 and 0.474 for spontaneous and flash-induced bursts, respectively; and B was 2.3 for both.

cortical, cortico-thalamo-cortical,[29] or extrathalamic,[26] ultimately targeting the sensorimotor cortex.[30] In the rat visual system, several relays including the superior colliculus and the lateral posterior nucleus of thalamus may facilitate nonspecific cortical activation *via* feed-forward projections to the thalamic intralaminar nuclei and feedback projections to the brainstem reticular formation.

Table 2. Comparison of Burst Properties (n = 23)

	Spontaneous Bursts	Flash-induced Bursts	*P* Value
Average power, 10^{-2} mV^2	18.7 ± 7.3	18.2 ± 5.3	NS
Peak power, 10^{-2} mV^2	78 ± 22	87 ± 22	<0.05
Duration, ms	814 ± 159	807 ± 153	NS
Dominant frequency, Hz	10.7 ± 1.7	10.5 ± 1.0	NS

Data are presented as mean ± SD.

n = number of animals; NS = not significant.

In light of their similarity, it would seem plausible that spontaneous and flash-induced bursts are generated by the same or related mechanism. During anesthesia, the cortex undergoes spontaneous state fluctuations as indicated by shifts between high ("up state") and low ("down state") neuronal excitability,[31,32] where the up state is characterized by bursting activity. We surmise that sensory stimuli may increase neuronal excitability and shift the cortex into the up state. Detsch *et al.*[13] showed that the excitability of cortical neurons was higher during isoflurane-induced bursts than during the intervening electrically silent periods. Visual evoked potentials were also augmented during the bursts.[33]

To our best knowledge, the frontal dominance of bursts has not been reported before. The similar topographic distribution of spontaneous and flash-induced bursts suggests that neither burst was specific to visual modality. One could speculate that both types of burst may reflect a component of motor response generation to either endogenous or exogenous stimuli[28] that may represent the default mode of rat's cortical arousal response. Because behavioral responses were blocked by the muscle relaxant as well as by the anesthetic, we had no way to tell whether this was in fact the case. Because far-field potentials could have contributed to the recorded bursts, further studies using multiunit recordings and current source density analysis should be performed to more accurately determine the source of the bursts.

Of further note is the dominant 10-Hz frequency of the bursts that has not been reported before. Rhythms of similar frequency are typically seen over somatomotor cortical regions of the rat during quiet immobility.[26] Motor fields seem to be the primary source of 14-Hz spindle oscillations during propofol-induced burst suppression in humans.[34]

Some investigators concluded that spontaneous and evoked electroencephalographic bursts had different dynamics[35]; however, we had no such indication from our results. The peak power only was slightly smaller in flash-induced *versus* spontaneous bursts, but the dominant frequency and duration were the same. It is possible that because of the random stimulus triggering, some of the flashes were delivered during a relative cortical refractory state, resulting in the occasional attenuation of the flash-induced bursts.

Whether the current results obtained during isoflurane anesthesia can be generalized to other anesthetic agents will have to be examined in the future. Isoflurane was used in this study because it readily suppresses the electroencephalogram at clinically relevant concentrations. In rats, isoflurane produces burst suppression at concentrations of 1.4–1.8%.[12,17,24,36] Although 1.8% isoflurane equates to approximately 1.3 minimum alveolar concentration in the rat and does not always entail

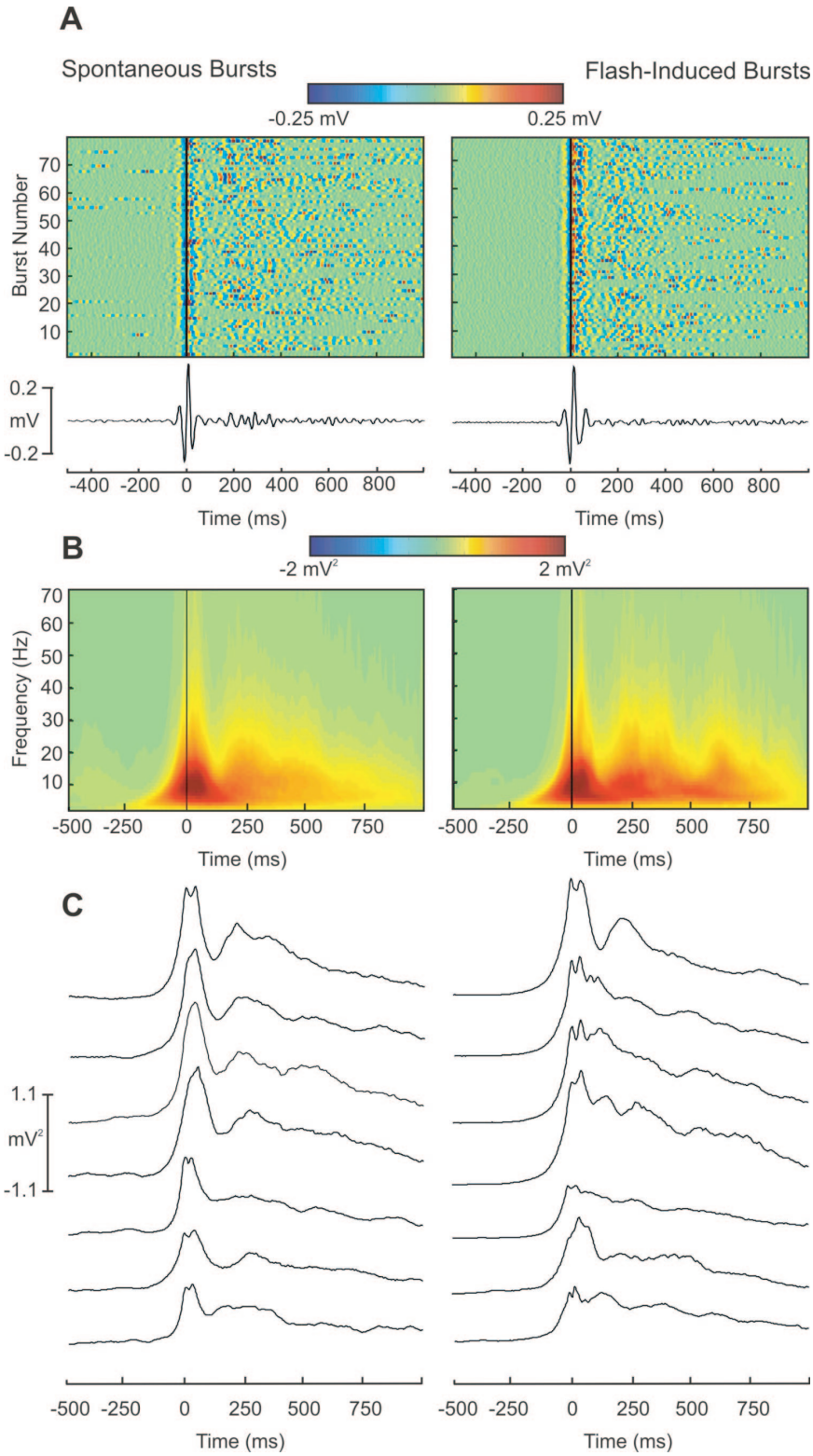

Fig. 4. Comparison of spontaneous and flash-induced bursts in frontal cortex under anesthesia with 1.9% isoflurane. (*A*) Color-coded plot of successive burst potentials from one experiment. Note the similarity of spontaneous (*left*) and flash-induced (*right*) bursts. The average waveforms from 80 burst are shown below each color plot. Average waveforms emphasize the short-latency (< 100 ms) potentials but diminish the long-latency (> 200 ms) components due to their increasing phase dispersion. Time zero is assigned to the initial large positive deflection in the signal. (*B*) Wavelet power spectra of all spontaneous (*left*) and flash-induced (*right*) bursts from the same experiment. Wavelet analysis reveals the long-latency signal power and allows the measurement of burst duration. (*C*) Average wavelet power from each of seven experiments. Spontaneous (*left*) and flash-induced (*right*) power curves from corresponding experiments are plotted in the same order to aid their comparison.

the loss of movement response to noxious stimulation,[36] this anesthetic regimen should be considered "deep" with respect to cortical activity. Spontaneous burst patterns produced by isoflurane, thiopental, etomidate, or propofol in rats were previously compared.[12] Burst power, peak amplitude, and duration were the highest with isoflurane; etomidate and propofol tended to produce shorter, spike-wave patterns. A greater amplitude but shorter duration of bursts was found with isoflurane as compared with propofol in rabbits.[15] These differences should not be considered conclusive because the agents' effects were not compared in a concentration- or

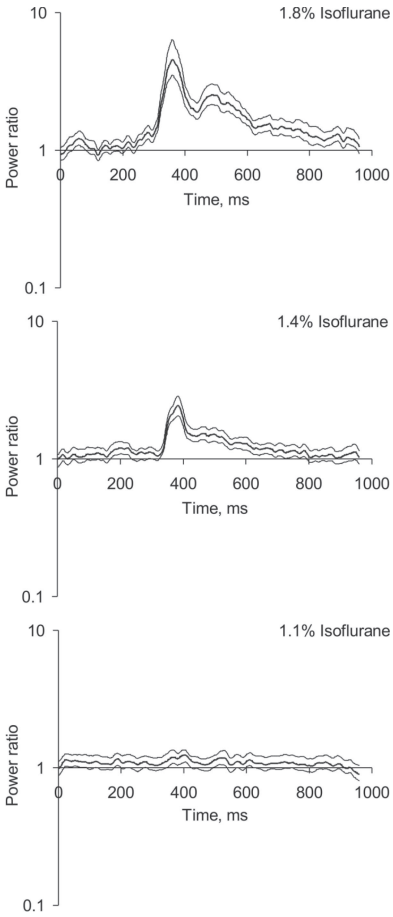

Fig. 5. Comparison of poststimulus power in frontal cortex at three concentrations of isoflurane. Power is calculated for the 2.5- to 20-Hz frequency band and expressed as the ratio of instantaneous power to power at baseline. Baseline is taken from the first 200 ms before burst onset. Flash is administered at time zero. *Heavy line* shows average power from 10 animals; *lighter lines* indicate ±SD.

dose-dependent manner. Also, whether cortical activation could be produced by sensory stimulation was not investigated. We have made preliminary observations with high concentrations of desflurane and propofol that suggest the presence of burst activation by light flashes similar to that found with isoflurane.

Can these results obtained in rats be generalized to human patients? Humans are generally considered more "visual" than rats, which supposedly rely more heavily on audition, olfaction, and vibrissal exploration. Nevertheless, rats show a robust response to flash at all useful anesthetic levels with various agents,[19,37] which makes their visual system a suitable model to study anesthetic effects. In fact, it seems that visual evoked potentials are more resistant to anesthetics in rats than in humans. We speculate that this is due to the multiplicity and complexity of visual processing regions and the associated polysynaptic pathways of humans, which render their visual system more susceptible to anesthetic suppression. On the other hand, it seems that bursting activity is present in response to somatosensory and auditory stimuli in both humans[16] and rats; the latter has been repeatedly observed in our laboratory. These observations suggest that we are studying a general phenomenon with respect to both species and sensory modality.

In this study, we used continuous wavelet transform to compare the spectral and temporal amplitude patterns of spontaneous and flash-induced bursts. This method of analysis was chosen over more traditional techniques, such as short-segment fast Fourier transform, because it offers variable time and frequency resolutions and thus allows a more reliable detection of rapid transient changes in relatively narrow-band signals of short duration, such as bursts. It also offers improved performance over narrow-band filtering because it is designed to minimize side-lobe energy and reduce spectral leakage. The utility of continuous wavelet transform in the analysis of time-variant spectral properties of spontaneous and stimulus-induced brain oscillations has been repeatedly demonstrated.[19,22,38–42] Recently, Zikov *et al.*[43] also showed that wavelet analysis is an attractive alternative to Bispectral Index monitoring of cortical oscillatory activity during anesthesia. Other promising time-frequency methods include Gabor transform,[44] adaptive chirplet transform,[45] and weighted majority with minimum range filtering technique.[46] Whether any of these methods offer significant advantages over continuous wavelet transform remains to be determined.

The current observations bear some relevance to the issue of general anesthetic mechanisms. If flash stimuli are able to activate the cortex during the arguably deep anesthetic state of burst suppression, they should be able to do so at more moderate anesthetic depths as well. Anesthetic unconsciousness may not be due to cortical deafferentation but, as we recently proposed, may arise from an inability of the brain to integrate or perceive, rather than receive, sensory information.[47] One wonders whether the residual cortical activation by sensory stimuli during anesthesia may be limited to a subset of the cortical information processing network, *e.g.*, the motor cortex, but does not really integrate information from higher sensory and critical association regions.

In summary, the current results support the contention that the cerebral cortex preserves a certain degree of sensory responsiveness in electrocortically deep anesthesia and challenges the view of cortical isolation under burst suppression anesthesia. Further research should elucidate whether the spontaneous and flash-induced burst activations may support the thalamocortical transfer of sensory-specific information or reflect nonspecific cortical arousal.

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