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Isoflurane disrupts anterio-posterior phase synchronization of flash-induced field potentials in the rat

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Abstract

Consciousness presumes a set of integrated functions such as sensory processing, attention, and interpretation, and may depend upon both local and long-range phase synchronization of neuronal activity in cerebral cortex. Here we investigated whether volatile anesthetic isoflurane at concentrations that produce loss of consciousness (LOC) disrupts long-range anterio-posterior and local anterior synchronization of neuronal activity in the rat. In six rats, deep electrodes were chronically implanted in the primary visual cortex (V1) and in two areas of the motor cortex (M1 and M2) for recording of intracortical event-related potentials (ERP). Thirty discrete flashes were presented at random interstimulus intervals of 15–45 s, and ERPs were recorded at stepwise increasing isoflurane concentrations of 0–1.1%. Neuronal synchronization was estimated using wavelet coherence computed from the ERP data band-pass filtered at 5–50 Hz. We found that (1) in the waking state, long-range anterio-posterior coherence in 5–25 Hz and 25–50 Hz frequency bands was significantly higher than local anterior coherence; (2) anterio-posterior coherence in both 5–25 Hz and 26–50 Hz bands was significantly reduced by isoflurane in a concentration-dependent manner; (3) local anterior coherence was not affected by isoflurane at any of the concentrations studied. These findings suggest that a disruption of long-range anterio-posterior rather than local anterior synchronization of neuronal activity precedes the anesthetic-induced loss of consciousness.

Keywords: Synchronization; Consciousness; Anesthesia; Event-related potential; EEG; Gamma

Identification of neuronal targets and mechanisms of hypnotic action of general anesthetics has been a major challenge to anesthesia research. While significant advances have been made in understanding of the anesthetic pharmacology and anesthetic-receptor interaction, a mechanistic model of anesthetic ablation of consciousness has not emerged. Our limited understanding of what phenomenal consciousness is, how it may arise from neurophysiologic events, and how to objectively assess its presence or absence, has hampered the elucidation of the mechanisms of anesthetic-induced unconsciousness.

Neurophysiologic evidence suggests that consciousness is an emergent phenomenon of complex functional interactions of various systems of the brain, including primary sensory and association cortical areas that form neuronal networks mediating selective attention [19,27] and working memory [24]. Long-range cortico-cortical phase synchronization of neuronal activity has been hypothesized as a potential mechanism of the integration or "binding" of sensory information necessary for the emergence of conscious sensory awareness and its respective behavioral manifestations [4,6,8,25]. A support for this hypothesis comes from various studies in humans and animals that have shown that synchronization of EEG, local field potentials, and unit activity among distributed cortical regions, especially between anterior and posterior cortices [24,29], mediates perception [6,22], attention [2,32], and memory [33].

It has been proposed that a potential mechanism of anesthetic-induced unconsciousness is the disruption of synchronization of neuronal activity among anterior and posterior cortical regions [15]. A support for this hypothesis comes from a study by John et al. [16], who showed in a large patient population that resting anterio-occipital EEG coherence was significantly decreased after the loss of consciousness (LOC) achieved with general anesthetics. Since the experimental protocol in this study did not involve an incremental increase in the anesthetic concentration, this study could not easily isolate the anesthetic-induced changes in neuronal synchronization precisely at the point of

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LOC. Furthermore, the effect of anesthetics on cortical coherence of local field potentials with sensory stimulation in humans or animals has not been systematically investigated. Recording of local field potentials would offer an advantage over scalp EEG recording because it allows for better spatial localization of electrophysiologic activity.

In this study, we examined the concentration-dependent effect of the volatile anesthetic isoflurane on long-range anterio-posterior flash-induced phase synchronization of local field potentials in the rat. For comparison, we also examined the local synchronization in the rat's anterior cortex. We applied wavelet coherence analysis to assess changes in neuronal synchronization as a function of time and frequency. Coherence is a linear measure of constancy of phase relationship between two signals, and thus, can be used to assess phase synchronization of neuronal activity. As we were interested in the neural correlate of anesthetic-induced LOC, we examined cortical coherence in the waking state and at sedative-hypnotic concentrations of isoflurane.

The experimental procedures and protocols were reviewed and approved by the Institutional Animal Care and Use Committee (Medical College of Wisconsin, Milwaukee, WI). All procedures conformed to the *Guiding Principles in the Care and Use of Animals* (American Physiological Society, Bethesda, MD) and were in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Academy Press, Washington, D.C., 1996). Every effort was made to minimize the number of animals used and their possible discomfort.

In six adult male Sptrague-Dawley rats, an array of 16 polyimide-insulated tungsten microwire electrodes (Tucker-Davis Technologies, Alachua, FL) and one coaxial stainless steel semi-micro electrode (Rhodes Medical Instruments, Inc., Woodland Hills, CA) were stereotaxically implanted for recording of intracortical field potentials. Using implantation methods previously described [10,12], the electrode array was positioned in the motor cortex (1.5–1.7 mm lateral, 2–2.2 mm vertical at 0–15° angle) spanning primary motor (M1) and secondary motor (M2) cortices. The coaxial electrode was implanted in the primary visual cortex (V1) (7 mm posterior, 2–3 mm lateral, 2–2.2 mm vertical). The electrode array terminated in a miniture connector (Omneticks Connector Corporation, Minneapolis, MN) compatible with a 16-channel head stage (Neuralynx, Model HS16, Tucson, AZ). The coaxial semi-micro electrode was connected through implanted gold pins, and signals were led to the amplifier through shielded cables. The coaxial electrodes were used in our previous studies [10–13], and proved effective in recording robust event-related potentials (ERP). We chose to use the microwire electrode array in the anterior cortical regions, M1 and M2, to examine local neuronal synchronization with multichannel recordings. The active electrode tips for visual and motor cortices were at the same vertical depth. A stainless steel machine screw in the opposite hemisphere from the array was used as an epidural reference electrode. Following the implantation, the animals were kept in the reversed dark/light cycle room for 7–10 days.

On the day of the experiment, the rat was placed in a cylindrical plastic restrainer inside a plexiglass anesthesia box under 1.5% isoflurane anesthesia, allowing limited movement of its head and limbs. The animal was breathing spontaneously, and its body temperature was controlled at 37 °C. Once all connections were in place, the anesthetic was turned off, and 1 h of equilibration period was allowed for the animal to regain consciousness and to accommodate to its physical environment.

Following 1 h of equilibration, ERPs elicited by binocular flash stimulation were recorded. Thirty discrete flashes were presented at interstimulus intervals varying randomly from 15 to 45 s. The flash stimulation was achieved with a stroboscopic light source (EG & G Electro-Optics, Salem, MA) housed in a sound-proof box. Subsequently, isoflurane concentration was raised from 0 to 1.1% in increments of 0.1–0.2%, and was allowed to reach steady state for 20 min at each anesthetic level. The anesthetic concentration was monitored using a gas analyzer (POET II, Criticare Systems, Inc., Waukesha, WI). ERPs were recorded at each increased concentration.

The signals from all 17 electrodes were amplified simultaneously at a gain of 10,000, analog bandpass-filtered at 1–100 Hz, and digitally sampled at 500 Hz (WINDAQ Data Acquisition Software, DATAQ Instruments, Akron, OH).

The qualitative assessment of the microwire recordings from the anterior cortex revealed that all recordings contained well-identifiable ERPs that were similar among all 16 channels. For that reason, two representative recordings obtained from the two most spatially separated electrodes (anterior and posterior ends of the array corresponding to M1 and M2) were selected for coherence analysis.

Single-trial 1-s-long ERPs were extracted from V1, M1, and M2 field-potential records. To remove the low-frequency afterdischarge component of the ERP characteristic of the rat's flash-induced response, the single-trial ERPs were band-pass filtered to 5–50 Hz using a bi-directional Butterworth digital filter ($N = 2$). The flash-induced afterdischarge activity likely does not play a role in the mechanism of anesthetic-induced LOC, as its suppression has been previously demonstrated at very low anesthetic concentrations with preserved consciousness [1].

The synchronization of neuronal activity between M1 and V1, M2 and V1, and within the motor cortex (between M1 and M2), was assessed using wavelet coherence. Wavelet coherence allows an estimation of coherence as a function of time and frequency, and has an advantage over FFT-based methods, as it offers sufficient balance between temporal and spectral resolutions for a subset of short-time, relatively narrow-band, and fast-changing signals, such as ERP [23]. The mathematical equation describing wavelet coherence $\tilde{\Gamma}^2_{xy}(s, \Delta n)$ between two signals $x(n)$ and $y(n)$ for given frequency scale and translation factors, s and Δn, is shown below.

$$\tilde{\Gamma}^2_{xy}(s, \Delta n) = \frac{\left|\tilde{S}^{W}_{xy}(s, \Delta n)\right|^2}{\tilde{S}^{W}_{xx}(s, \Delta n)\tilde{S}^{W}_{yy}(s, \Delta n)} \quad (1)$$

In Eq. (1), $\tilde{S}^{W}_{xx}(s, \Delta n)$, $\tilde{S}^{W}_{yy}(s, \Delta n)$, and $\tilde{S}^{W}_{xy}(s, \Delta n)$ are the auto- and cross-wavelet spectra of $x(n)$ and $y(n)$. Wavelet coherence was computed from single-trial ERPs using Morlet's

wavelets with central frequency of 5–50 Hz in increments of 1 Hz [30], and then averaged across multiple trials.

As an estimate of band coherence at intermediate (5–25 Hz) and high (26–50 Hz) frequencies, the coherence data from each animal were averaged within two spectral windows of 5–25 Hz and 25–50 Hz. Subsequently, to examine changes in the flash-induced coherence with respect to prestimulus coherence, a band coherence ratio (BCR) was computed by dividing each poststimulus value by the temporal mean of prestimulus band coherence of the last 200 ms before flash. Finally, the peak BCR was found in the 0–200 ms period after stimulus, since the strongest coherence was localized to that time interval in all experiments.

To test for a significant effect of anesthetic concentration on BCR, a Repeated Measures ANOVA with planned comparisons was carried out with the peak BCR as a response variable, the anesthetic concentration as a fixed factor, and the rat as a subject variable. To test for a significant difference in long-range and local peak BCR estimates, a paired *t*-test was performed. In all tests, $p \leq 0.05$ was accepted for statistical significance.

Fig. 1 shows an example from one experiment of the average ERP from V1 and M1 in the waking state and at various isoflurane concentrations. In V1, isoflurane augmented the amplitude of the early (0–100 ms) ERP component and, in this example, also suppressed the amplitude of the late (200–300 ms) component already at 0.5%. In M1, isoflurane reduced the amplitude of the entire ERP in a concentration-dependent manner. In all other frontal locations, the effect of isoflurane on the ERP was similar to that in M1.

The effects of isoflurane on M1-V1 and M2-V1 coherence were similar in all experiments. For that reason, the corresponding BCR and peak BCR data were pooled and averaged across all experiments. These averages will be referred to as M1/M2-V1 BCR and M1/M2-V1 peak BCR to represent long-range anterio-posterior coherence. Fig. 2 shows group-average effects

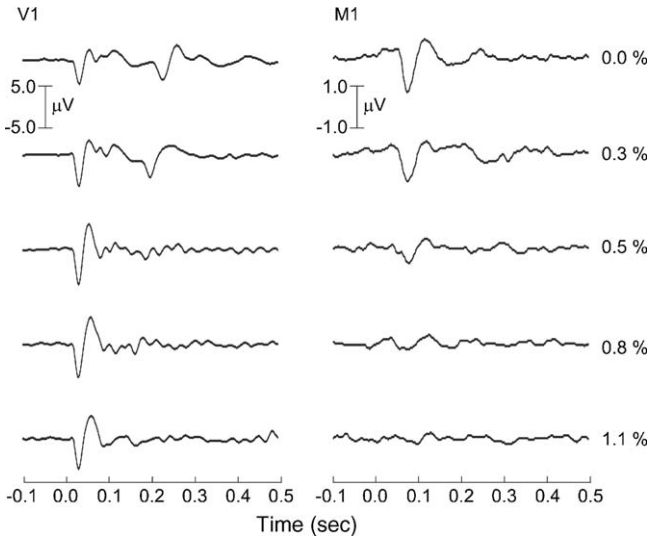

Fig. 1. Event-related potentials in primary visual (V1) and primary motor (M1) cortices in the waking state and at increased isoflurane concentrations from the same animal. Each trace shows 100 ms of prestimulus and 500 ms of poststimulus activity averaged across 30 trials. In V1, the anesthetic agent augmented the amplitude of the early (0–100 ms) ERP component and, in this example, also suppressed the amplitude of the late (200–300 ms) component already at 0.5%. In M1, isoflurane reduced the amplitude of the entire ERP in a concentration-dependent manner. All consecutive analyses were performed on the single-trial ERP data.

of isoflurane on M1–M2 and M1/M2-V1 BCR in intermediate (5–25 Hz) and high (26–50 Hz) frequency bands. Note that the standard error associated with BCR was due to animal-to-animal variability in both the time of occurrence and amplitude of the BCR peak. An insert in each of the four panels of Fig. 2 shows the standard errors associated with the time of occurrence of the BCR peak. The standard errors associated with the peak BCR amplitude are included in Fig. 3. Fig. 2 shows that

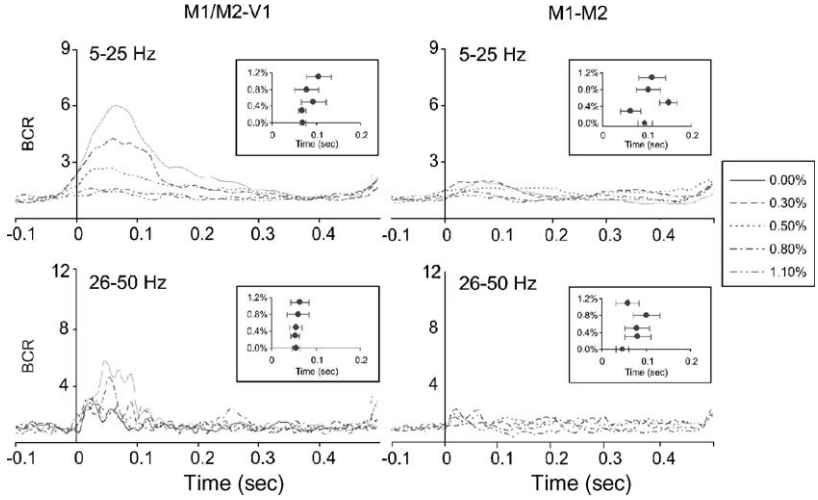

Fig. 2. Concentration-dependent effect of isoflurane on band coherence ratio (BCR) between primary visual and motor cortices (M1/M2-V1), and within motor cortex (M1–M2) in intermediate (5–25 Hz) and high (26–50 Hz) frequency bands. The standard error associated with BCR was due to animal-to-animal variability in both the time of occurrence and amplitude of the BCR peak. An insert in each of the four panels shows the standard errors associated with the time of occurrence of the BCR peak as a function of isoflurane concentration. Isoflurane had no effect on M1–M2 BCR either in the intermediate or in the high frequency band. However, isoflurane produced a concentration-dependent reduction in M1/M2-V1 BCR in both bands. Note that in the waking state and at sedative concentrations (0.3–0.5%) M1/M2-V1 BCR was localized to the 0–200 ms time interval and was considerably higher than M1–M2 BCR in both frequency bands.

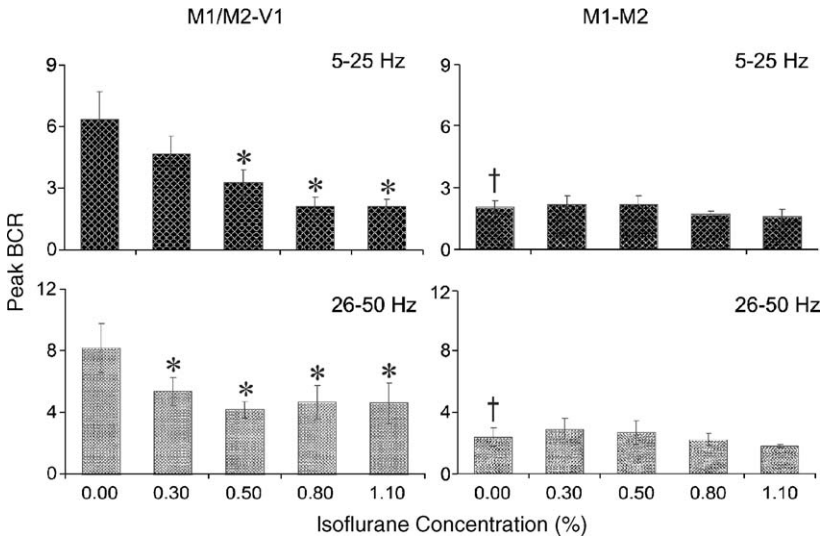

Fig. 3. Concentration-dependent effect of isoflurane on peak band coherence ratio (peak BCR) between primary visual and motor cortices (M1/M2-V1), and within motor cortex (M1–M2) in intermediate (5–25 Hz) and high (26–50 Hz) frequency bands. The peak BCR represents the maximum band coherence ratio between 0 and 200 ms after flash. Bars represent averages from all animals, and the corresponding standard error bars represent indices of variability in the peak BCR amplitude. Significant differences from waking control and between waking controls are indicated by * and †, respectively at ($p \leq 0.05$) level. Isoflurane had no effect on M1–M2 peak BCR either in the intermediate or in the high frequency band. However, isoflurane significantly reduced M1/M2-V1 peak BCR in both bands in a concentration-dependent manner. Note also that in the waking state, M1/M2-V1 peak BCR was significantly higher than M1–M2 peak BCR in both bands.

isoflurane had no effect on M1–M2 BCR either in the intermediate or in the high frequency band. However, isoflurane produced a concentration-dependent reduction in M1/M2-V1 BCR in both bands. Note that in the waking state and at sedative concentrations (0.3–0.5%) M1/M2-V1 BCR was localized to the 0–200 ms time interval and was considerably higher than M1–M2 BCR in both frequency bands.

Fig. 3 shows group-average effects of isoflurane on M1/M2-V1 and M1–M2 peak BCR in intermediate and high frequency bands. Consistent with Fig. 2, isoflurane had no effect on M1–M2 peak BCR either in the intermediate or in the high frequency band, whereas it produced a concentration-dependent reduction in M1/M2-V1 peak BCR in both bands. Note also that in the waking state, M1/M2-V1 peak BCR was significantly higher than M1–M2 peak BCR in both bands. Specifically, the M1/M2-V1 peak BCR was 3.8 and 3.2 times greater than M1–M2 peak BCR in intermediate and high frequency bands, respectively. Some difference in the concentration dependence of BCR (Fig. 2) and peak BCR (Fig. 3) is explained by the fact that the precise temporal location of the peak BCR between 0 and 200 ms varied from animal to animal.

In summary, we found that long-range anterio-posterior coherence in both, intermediate (5–25 Hz) and high (26–50 Hz) frequency bands was significantly stronger than local anterior coherence in the waking state. The volatile anesthetic isoflurane significantly reduced anterio-posterior coherence in a concentration-dependent manner, but had no effect on local anterior coherence.

The role of long-range cortical interactions in consciousness has been suggested by a number of studies in humans and animals [21,26,31]. Recently, it has been proposed that visual consciousness itself may depend upon a sparse network of neurons involved in recurrent interactions between anterior and posterior cortical regions [5,18]. Our goal was to find the neural correlate of anesthetic-induced unconsciousness presumably as an abrupt change in neural activity pattern. Instead of an abrupt change in neuronal synchronization, isoflurane produced a gradual, concentration-dependent reduction in long-range anterio-posterior coherence that spread over a concentration range spanning from wakefulness to LOC. This graded suppression of coherence is consistent with the known effect of general anesthetics on various indices of EEG and evoked potential activity that are routinely used for anesthetic depth monitoring to assess the loss and return of consciousness [7,14,20,28,34]. Thus, from our current findings one cannot ascertain if a critical value of coherence would predict LOC. Future studies on coherence among cortical and subcortical regions previously implicated in conscious perception may help in determining the neural correlate of LOC.

Also of interest is our finding that long-range coherence greatly exceeded local coherence in the waking and sedated states. Furthermore, local coherence was unaffected by isoflurane at any of the concentrations studied. Taken together, these findings suggest that local interactions do not play a significant role in the mechanism of anesthetic-induced LOC.

The anesthetic-induced suppression of anterio-posterior coherence has been previously found by John et al. [16] in all EEG-relevant frequency bands. John et al. [16] also showed that, in contrast to coherence in lower frequency bands, coherence in gamma (20–60 Hz) band only was restored to the pre-LOC levels upon return of consciousness. Due to a much longer washout time required for emergence from than for induction of anesthesia, our current study did not include an emergence protocol, and thus could not ascertain if anterio-posterior cortical interactions

at any frequency are restored upon return of consciousness in the rat. The study of long-range coherence during emergence as well as induction of anesthesia would help establish whether the anterio-posterior coherence is causal rather than correlative, and thus represents another potential extension of this project.

The results of this work could be compared to our previously published study [11] that used transfer entropy as an alternative measure of multiregional functional interactions. While the goal of both studies was to assess anesthetic-induced changes in cortico-cortical functional interactions, two distinct methodologies, transfer entropy and wavelet coherence, allowed us to evaluate different aspects of these interactions. Namely, transfer entropy is a probabilistic measure of directional information transfer between two regions that is based on the ability to improve the prediction of one signal from itself given the knowledge of another signal, but this method provides no information about temporal phase relation between two signals. Conversely, wavelet coherence is a measure of constancy of phase relationship between two signals over time, but it does not provide any directional information. The fact that both methods showed similar results provides support for the contention that the mechanism of anesthetic action on the CNS may involve concentration-dependent suppression of recurrent, phase-synchronous cortico-cortical functional interactions.

How anesthetic agents may suppress long-range synchronization of neuronal activity is unclear. Volatile anesthetics including isoflurane are known to potentiate neurotransmission at $GABA_A$ receptors involved in maintaining local synchrony within a monosynaptic neuronal network [3,9]. However, this mechanism may not apply to long-range cortical interactions, as the latter may largely depend on polysynaptic circuits. Long-range pathways may be more susceptible to anesthetic suppression because multiple potential sites are available for anesthetic action, and the superposition of anesthetic effects at these sites may occur. The results of neuronal network modeling also suggest that the anesthetic-induced suppression of a single unit along a long-range polysynaptic pathway may lead to a conduction failure of the entire pathway [17], which is consistent with our result. Another interesting potential mechanism underlying the anesthetic-induced suppression of long-range cortical interactions may be a disturbance of the coincidence detection between sensory-specific and nonspecific inputs to cortical pyramidal cells [15].

In conclusion, our findings suggest that isoflurane at increasing concentrations that lead to LOC preferentially impairs anterio-posterior rather than local anterior cortical phase synchronization of local field potentials, consistent with the proposed role of anterio-posterior interactions in conscious perception [4].

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