Evoked response potential markers for anesthetic and behavioral states

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Rojas, Manuel J., Jinna A. Navas, and David M. Rector. Evoked response potential markers for anesthetic and behavioral states. Am J Physiol Regul Integr Comp Physiol 291: R189–R196, 2006. First published February 2, 2006; doi:10.1152/ajpregu.00409.2005.—The rodent whisker sensory system is a commonly used model of cortical processing; however, anesthetics cause profound differences in the shape and timing of evoked responses. Evoked response studies, especially those that use spatial mapping techniques, such as fMRI or optical imaging, will thus show significantly different results depending on the anesthesia used. To describe the effect of behavioral states and commonly used anesthetics, we characterized the early surface-evoked response potentials (ERPs) components (first ERP peak: gamma band 25–45 Hz; fast oscillation: 200–400 Hz; and very fast oscillation: 400–600 Hz) using a 25-channel electrode array on the somatosensory cortex during whisker stimulation. We found significant differences in the ERP shape when ketamine/xylazine, pentobarbital sodium, isoflurane, and propofol were administered and during sleep and wake states. The highest ERP amplitudes were observed under propofol anesthesia and during quiet sleep. Under isoflurane, the ERP was nearly absent, except for a very late component, which was concomitant with burst synchronization. The slowest responses were seen under urethane and propofol anesthesia. Spatial mapping experiments that use electrical, NMR, or optical techniques must consider the anesthetic dependency of these signals, especially when stimulation protocols or electrical and metabolic responses are compared.

whisker; barrels; rat

FOR BOTH BASIC RESEARCH AND clinical practice, different anesthetics are used, but how they affect nociceptive and normal sensory processing is still under investigation (22, 23, 33). Anesthetics may have profound influences on systems responsible for arousal and conscious states (22), and the design of many studies may be affected by the profound metabolic and electrical effects of using different anesthetics. Additionally, it is critical to understand and compare electrophysiological and optical imaging results between investigators who use different anesthetics (e.g., Refs. 4, 7, 25, 29, 32, 39). Thus there is a dire need to systematically study the effects of different anesthetics on optical and electrical recordings (41). Only a few studies have attempted to compare among anesthetics and behavioral conditions (sleep/awake) (2, 17, 20, 23, 27), but a more comprehensive survey has not been performed.

Neurosurgeons often use the evoked response potential (ERP) as a physiological marker to diagnose nerve disorders, locate the site of nerve damage, and evaluate the patient’s condition after treatment or during surgery. The waveform pattern may reveal certain problems and show where damage is located along the nerve pathways being tested (21, 40). The surface-evoked response is also an electrophysiological model widely used in brain mapping studies. Because the processing of sensory information in the cerebral cortex has been described as a hierarchical process, the temporal shape of the evoked response contains signatures of these processes. For example, the earliest ERP components represent input to layer IV, and later components have been implicated in higher processing (19). Several investigators have observed a fast oscillation burst (FO; 200–400 Hz) and a very fast oscillation burst (VFO; 400–600 Hz), which are a series of small-amplitude deflections superimposed on the ERP and generated by population action potentials (15, 18). The sequence of events produced by different levels of neuronal integration through the whole sensory process involve many possibilities to block, disrupt, or change the final cortical evoked response.

To assess the effects that particular agents will have on the evoked response, it is important to consider agent-specific mechanisms that drive general anesthesia (1, 10, 11, 17, 27). Several investigators have found evoked potential differences in latency and amplitude under various anesthetic conditions with the use of in vivo and in vitro approaches on different physiological systems (e.g., Refs. 2, 11, 26), but a systematic comparison across many different types of anesthetics and behavioral conditions has not been performed with consistent methodologies.

On a molecular level, many mechanisms and biochemical pathways are affected by anesthetics. For instance, the release of some central neurotransmitters, such as glutamate, GABA, and norepinephrine, is modulated by different anesthetics in unique ways (26, 27). Indeed, anesthetics affect many biochemical and physiological mechanisms, have different and unknown mechanisms of action, and might not always be affecting the same neuronal groups, resulting in profound differences in the evoked response components. In this scenario, we would expect the amplitude and temporal components of the ERP to be dependent on the type of anesthetic used. Additionally, we would expect profound differences in the metabolic response to stimulation under different types of anesthetics. Thus imaging experiments that rely on coupling between neural activation and metabolic events could be confounded by the type of anesthesia used or by the behavioral state of the animal. At least two studies have shown significant differences when metabolic responses were mapped between waking and anesthetized states (3, 6).

To test the effect of the most commonly used anesthetics, we investigated ketamine/xylazine, pentobarbital sodium, isoflurane, urethane, and propofol on the early components of the ERP recorded from the somatosensory cortex after whisker stimulation. We were especially interested in how different anesthetic agents affect the time course of neural activation and
how these time course differences may affect neural imaging results. Preliminary experiments from our laboratory and others suggest that there are profound differences between ketamine and xylazine injected in separate muscles (intramuscularly), compared with combined intraperitoneal administration. Separate intramuscular injections may also produce a more stable preparation. We included both routes of administration for ketamine and xylazine in this study. We also characterized the early ERP components under awake and sleep conditions.

MATERIALS AND METHODS

Stimulations from 9 adult male and 15 female Sprague-Dawley rats were recorded by a 25-channel electrode array placed on the surface of the somatosensory cortex. Surgical procedures were carried out in accordance with the “Guide for the Care and Use of Laboratory Animals” and was approved by the Washington State University Animal Care and Use Committee. A 5 × 5-mm area of bone was removed over the somatosensory cortex (bregma −1 mm to −6 mm and 5 mm from midline), and the 25-channel electrode array was placed tangentially over the intact dura mater (Fig. 1). The 25-channel electrode array was made from Delrin (Dupont Chemical) in our laboratory by use of a computer-controlled mill and a 80-wire drill. The electrode array was important to unambiguously map and identify the whisker barrel being stimulated for each recording. Without this procedure, variation in the ERP shape and amplitude could result from differences in electrode position relative to the activated column. All electrophysiological signals were wideband filtered by two pole butterworth analog filters between 0.1 Hz for DC rejection and 3 kHz for anti-aliasing of the digitizer. Subsequent filtering was performed for data analysis using infinite impulse response digital filters. All of the signals were sampled at 20 kHz by a custom data system (30), and packets of ~200 ERP averages were recorded.

ECG and respiration rates were monitored along with the EEG to assist in determining anesthesia depth (Fig. 2). We began each experiment with the recommended doses, as per the American Veterinary Medical Association (AVMA) guidelines (5, 28). However, individual animals responded differently to these doses, depending on gender, age, body fat, etc. For each anesthetic condition, the minimum dose was used to maintain surgical levels described below. The traces in Fig. 2 represent a typical period during a surgical steady state that we used for recording. Cortical EEG contains unique patterns for each anesthetic and is not comparable between anesthetics as an indication of depth of anesthesia. Surgical anesthetic levels require the presence of characteristic cortical EEG (depending on type of anesthesia) and stable heart and respiration rates. Stable cardiorespiratory parameters show that painful stimuli do not induce autonomic responses; the absence of a toe pinch motor response also confirms stable surgical anesthesia. The absolute parameters, such as heart rate, cannot be compared between anesthetics, because of different mechanisms of action for anesthetics. The fact that the animal is stable during the recording shows that the animal is in a well-defined state for each test. For example, under ketamine/xylazine anesthesia, the dissociative effects of ketamine and the sedative effects of xylazine have a unique effect on heart rate. Xylazine induces bradycardia and is expected to cause a lower heart rate than the other anesthetics used in these experiments. Thus the specific pharmacology of each anesthetic exerts effects on peripheral systems, such as heart rate and respiration, as well as central neural pathways. Surgical procedures were performed under the same anesthetic conditions used during the experimental recordings. To perform intravenous perfusion of propofol, the femoral vein was cannulated under brief isoflurane anesthesia.

Six chronically implanted rats were trained so that they could be recorded for 2-h sessions under movement-restrained conditions in a head-restraining apparatus (model 1430; Kopf) while whisker-twitching stimuli were given. Sleep/wake states were assessed by the frequency spectrum in the EEG and EMG signals (31). High-frequency, low-amplitude EEG and high-amplitude EMG defined the waking state, and high-amplitude delta frequencies (0.1–3 Hz) with low-amplitude EMG represented the quiet sleep state. Rapid eye movement sleep was not observed in our restrained animals. To avoid adaptation and synchronization, random stimulation was given in 1- to 2-s intervals while EEG and local field potentials were continuously recorded. Single-click stimuli (0.2-ms pulse width) were given by placing a selected whisker into a laboratory-made solenoid deflector (79.4 ± 0.9 μm deflection) and driving the solenoid with a pulse generator.

The use of a 25-channel electrode array allowed us to enhance the spatial resolution of the recordings (750 μm), making it possible to identify the cortical column corresponding to the whisker being twitched. To identify whisker barrels, the recorded ERP signal for each of the 25 electrodes was plotted in two dimensions on a topographical map of the surface (Fig. 3). Whisker B1 was twitched during all of the recordings because the corresponding barrel was consistently located under the electrode array area. The electrode from the array, which was located over the barrel of whisker B1, was used for subsequent analysis.

Three animals were recorded with each of six anesthetics and injection routes as follows: ketamine (100 mg/kg im)-xylazine (10 mg/kg im), ketamine (100 mg/kg ip)-xylazine (10 mg/kg ip), urethane (1.5 to 2 g/kg ip), propofol (500 μg·kg⁻¹·min⁻¹ iv), isoflurane (1.5–3.0%), and pentobarbital sodium (50–70 mg/kg ip). Depth of anesthesia was continuously monitored by toe pinch reflex test and by heart beat frequency, respiration, and EEG (Fig. 2). Supplemental doses of anesthetic were administrated as needed to maintain a stable anesthetic state. However, we were sometimes able to reduce the anesthesia level after the surgery and during the recordings. For isoflurane, we usually began the experiment at a high level (2.5–3.0%) for induction and then reduced this level to 2.0% or 1.5% depending on how the animal was responding. The AVMA-recommended dose of 1.5 g/kg urethane was usually not sufficient to attain surgical anesthesia levels. Although we began the experiments with this dose, we usually gave supplements with a final dose of 2.0 g/kg. Similarly, for pentobarbital sodium anesthesia, our initial dose was 50 mg/kg,

![Fig. 1. The 25-channel electrode array. The 3 × 3-mm 25-channel electrode array (E) was placed on the somatosensory cortex. Each 250-μm stainless steel electrode in the array was separated by 750 μm. M, middle line; B, bregma; L, lambda; T, temporal ridge. Screw electrode positions for recording frontal and parietal EEG. A reference screw was placed over the occipital lobe.](Image)
slightly lower than the recommended dosage because the safe dosage window for this anesthetic is narrow. With pentobarbital sodium supplements, the final dose was between 50 and 70 mg/kg. Animals were usually stable under 100 mg/kg ketamine and 10 mg/kg xylazine, with supplements of 10 mg/kg ketamine and 1 mg/kg xylazine given every 2 h. We used the AVMA-recommended 10 mg/kg as the initial dose of propofol, with a maintenance dose of 500 μg·kg⁻¹·min⁻¹, which attained good surgical anesthesia.

Because only one of our chronically implanted animals was instrumented with a 25-channel electrode array, the values reported here were obtained from three separate sessions with this animal. Results from all of the chronic animals were comparable, with similar temporal patterns but with differences in absolute amplitude because the electrode array allowed precise localization of the whisker barrel being stimulated. To test the effect of anesthesia dose on the evoked response, we used one of our chronic animals and induced anesthesia with 3.0% isoflurane and then recorded evoked responses continuously as we reduced the isoflurane concentration until the animal recovered from anesthesia.

The gamma, FO, and VFO signals were obtained by digitally filtering the EEG between 25 and 35 Hz (gamma), 200 and 400 Hz (FO), and 400 and 600 Hz (VFO). The signals appeared as a burst of wavelets occurring after the stimulus, typically at least three times larger than the baseline amplitudes for each frequency range. The signal amplitude for each frequency was measured by recording the peak-to-peak value of the largest cycle after the stimulus. The latency was measured as the time between the stimulus and the largest peak in the burst. The latency and amplitude values were based on averages obtained from three animals (~200 trials of each condition for each animal) per anesthetic type, and we reported the SEs across animals. ANOVA tests were used to compare group averages, and t-tests were used to compare parameters between anesthetics. We present means ± SE for ERP amplitude (μV) and peak latency (ms) measurements.

**RESULTS**

We found significant differences in the shape of the evoked responses from rats under anesthetized conditions and sleep and wake states, with variations in amplitude and latency for the first ERP peak, gamma, FO, and VFO bursts. Figure 4 illustrates a typical response under the various conditions. The second peak seen in many of the evoked responses may represent activation of secondary pathways within the cortical

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**Fig. 2.** EEG and ECG under anesthetized, wake, and sleep conditions. For each condition, we show the occurrence of stimuli (Stim) as short tick marks above the middle traces, which corresponds to the parietal EEG. Bottom traces: ECG. Anesthesia depth was monitored by EEG, ECG, respiration, and toe pinch reflex test. Each anesthetic induced a unique EEG pattern. Both urethane and isoflurane produce characteristic burst-suppression patterns. Spindles were present under ketamine and quiet sleep conditions. Comparable levels of surgical steady state were maintained for all the anesthetics used in this study.

**Fig. 3.** The evoked response potential (ERP) two-dimensional (2D) mesh. A 2D display of mean ERP across the 25-channel array during whisker B1 twitching shows good localization of the corresponding whisker barrel. This image was collected with 200 averages during the rising phase of the first ERP peak under ketamine-xylazine anesthesia.

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**Fig. 4.** ERP waveforms under anesthetized, wake, and sleep conditions. The top traces represent the evoked response potential (ERP) waveforms for wake (WAKE), quiet sleep (QUIET SLEEP), ketamine (KETAMINE), pentobarbital (PENTOBARBITAL), and propofol (PROPOFOL) conditions. The middle traces show the occurrence of stimuli (Stim) as short tick marks above the EEG trace, which corresponds to the parietal EEG. The bottom traces represent the electrocardiogram (ECG). Anesthesia depth was monitored by EEG, ECG, respiration, and toe pinch reflex test. Each anesthetic induced a unique ERP pattern. Both urethane and isoflurane produce characteristic burst-suppression patterns. Spindles were present under ketamine and quiet sleep conditions. Comparable levels of surgical steady state were maintained for all the anesthetics used in this study.
column and is absent when secondary processing of the stimulus is inhibited by some anesthetics. Because we were interested in the earliest components of the evoked response and because many of our signals only showed one peak, we focused our measurements on the first component of the evoked response. Also in Fig. 4, a clear dose-dependent effect can be seen because one of our chronic animals woke up from isoflurane anesthesia. As the animal recovered, the evoked responses appeared to transition from low amplitudes during the anesthetic state, with a similar temporal profile through sleep, and then to wakelike characteristics. The anesthesiadependent temporal response patterns were similar across all animals tested; data from all animals are summarized in Fig. 5.

**ERP latency analysis.** We found a close correspondence in latency for the first ERP peak under ketamine/xylazine and pentobarbital sodium conditions (14.05 ± 1.30 and 17.13 ± 1.54 ms, respectively), and the earliest peaks occurred later than under awake and sleep states. The ERP under ketamine/xylazine showed a similar shape to that observed during awake and sleep states. The first peak of the ERP under pentobarbital sodium, isoflurane, and urethane occurred later than under awake and sleep states. **Bottom left:** plot of responses observed under progressively lower isoflurane levels as the animal recovered from anesthesia, showing a dose response to the anesthetic dose. When the EEG exhibited bursts with long silent periods under isoflurane anesthesia, the bursts synchronized to the stimuli. The resulting signals look like an evoked response, as shown in **bottom middle trace**, with a very long latency. However, this trace was not an evoked response generated by synaptic events; rather, it originated from the temporal smoothing of the synchronized bursts. The mean frequency is displayed on the bottom of each example (~200 trials per animal, 3 animals per condition).

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Fig. 4. ERP, gamma, fast oscillation (FO), and very fast oscillation (VFO) shape. Representative traces of the evoked response from each condition are plotted across time and also filtered for 3 frequency ranges. We observed the same temporal pattern for each anesthetic condition tested in the other animals, with differences only in amplitude across animals (see Fig. 5). Profound differences in the shape of the evoked responses (gamma, FO, and VFO bursts) appear under ketamine/xylazine, pentobarbital sodium, isoflurane, urethane, propofol, awake, and sleep conditions. The ERP under ketamine/xylazine showed a similar shape to that observed during awake and sleep states. The first peak of the ERP under pentobarbital sodium, isoflurane, and urethane occurred later than under awake and sleep states. **Bottom left:** plot of responses observed under progressively lower isoflurane levels as the animal recovered from anesthesia, showing a dose response to the anesthetic dose. When the EEG exhibited bursts with long silent periods under isoflurane anesthesia, the bursts synchronized to the stimuli. The resulting signals look like an evoked response, as shown in **bottom middle trace**, with a very long latency. However, this trace was not an evoked response generated by synaptic events; rather, it originated from the temporal smoothing of the synchronized bursts. The mean frequency is displayed on the bottom of each example (~200 trials per animal, 3 animals per condition).
between the first ERP peak (wake and sleep) and the first ERP peak (urethane and propofol) (Fig. 5A). No significant difference occurred in the ERP peak latency when ketamine and xylazine was injected intramuscularly separately into different legs and when ketamine and xylazine was mixed and injected intraperitoneally (Fig. 5A).

**ERP amplitude analysis.** The first ERP peak amplitudes were highly dependent on anesthesia and behavioral state, with the highest amplitude recorded under sleep, and propofol (428.13 ± 134.65 and 263.17 ± 98.16 μV, respectively) and the lowest amplitude corresponding to the evoked response under isoflurane (3.48 ± 2.56 μV) (Fig. 5B). Although the isoflurane ERP early peak was nearly absent, we observed a very late response, >250 ms, that corresponded to burst synchronization under this state (Fig. 5; see also Ref. 13).

Fig. 5. ERP, gamma, FO, and VFO latency and amplitude under anesthetized, wake, and sleep conditions. Summary values from all animals under all conditions are graphed with their SEs. Values were obtained from the average response across animals, with each animal’s average calculated from ~200 trials. The electrodes used for each result were selected for each individual animal by locating the electrode in the center of the activated whisker barrel within each mapping of the animal’s somatosensory cortex (e.g., see Fig. 3). This usually corresponded to the electrode with the largest and earliest response. The earliest ERP responses occurred during the wake and quiet sleep states (A), and the latest ERP responses occurred under urethane and propofol. The highest ERP amplitudes are observed under sleep and propofol and nearly absent under isoflurane (B). The latency of the gamma burst was significantly longer under intraperitoneal ketamine and propofol than other conditions (C), whereas its amplitude followed the same pattern as the first ERP peak amplitude changes for all conditions (D and B). The earliest FO and VFO bursts were seen under pentobarbital sodium anesthesia (E and G), and the largest FO and VFO responses were obtained under wake and quiet sleep states but were severely limited by all anesthetics (F and H).
**Gamma (25–45 Hz) differences.** The gamma burst showed a significantly longer latency under ketamine-xylazine intraperitoneally and propofol than other conditions (Fig. 5C). The gamma burst amplitude followed the same pattern as the first ERP peak amplitude changes for all conditions (Fig. 5, B and D).

**FO (200–400 Hz) differences.** The FO showed significant differences in latency across conditions \( P < 0.05 \). The FO occurred earlier than the first ERP peak during pentobarbital sodium, urethane, and propofol, but with similar latency as the first ERP peak during wake, sleep, and ketamine/xylazine conditions (Fig. 5E). The FO also showed significant differences in amplitude across conditions \( P < 0.05 \). The FO followed the first ERP peak amplitude changes only under wake, sleep, and ketamine conditions but were much lower under propofol, urethane, and pentobarbital sodium (Fig. 5F).

**VFO (400–600 Hz) differences.** The VFO latency was shorter for pentobarbital sodium, urethane, and propofol than the first ERP peak latencies (Fig. 5G). The VFO burst did not show significant differences between sleep and wake, as seen for the first ERP peak amplitude (Fig. 5, H and B).

**DISCUSSION**

Our findings show significant differences in the early components of sensory-evoked response under different anesthetics. We found a similar ERP shape under ketamine/xylazine and unanesthetized (awake/sleep) conditions, with the first ERP peak occurring earliest during awake conditions. Additionally, the FO and VFO bursts occurred relatively close to the first ERP peak during ketamine, awake, and sleep conditions. This suggests that at least part of the neuronal circuits processing the somatosensory stimuli during wakefulness remain intact or are hyperexcited under ketamine/xylazine anesthesia. A reduction in inhibitory influences, an increase in activation, or decreased random events might make the ERP appear larger over background noise. Under quiet sleep and deep anesthetic states, cortical cells may initially be in hyperpolarized state (down), and stimulation may drive the membrane potential by a greater amount compared with their normal depolarized (up) state (35).

The VFO burst (400–600 Hz) showed no significant differences in latency among the different conditions. However, the VFO occurred earlier than the first ERP peak under pentobarbital sodium, urethane, and propofol conditions and close to the first ERP peak during ketamine, awake, and sleep conditions. Because the amplitude and latency values for VFO, FO, and the first ERP peak are not proportionally similar, these results suggest that the FO, VFO, and ERP are generated by different neuronal groups and affected differently by condition. In fact, the VFO may arise from thalamic input, whereas the FO may be derived from intercortical circuits, and cortical structures may evoke FO without depending on thalamic inputs (9, 16, 34). Additionally, the FO and VFO amplitudes under all anesthetized conditions are lower than during sleep and awake conditions, indicating that neuronal groups generating high-frequency oscillations during behavioral states (sleep/wake) are profoundly affected by the anesthetics used in this study.

The ERP amplitude changes were similar to the gamma burst (25–45 Hz) for all the conditions of this study; however, the gamma burst reached the highest amplitude much later than the first ERP peak, suggesting that the gamma burst might be generated by the same neuronal groups as the ERP, although delayed differently by the thalamocortical network (36).

In addition to pharmacologically induced alterations of cortical state, cortical stimulus processing has also been shown to alter the ERP shape, thus imparting state-dependent signatures. For example, results from this study and others show significantly higher ERP values recorded from animals and humans in the quiet sleep state (31, 38). Investigators have also shown attention-related ERP changes (14).

The amplitude of the ERP to whisker stimulation is close to zero under isoflurane because of a predominance of silent EEG, followed by bursts of cortical activity (Fig. 2). Experiments performed in this laboratory and others (13) have shown that, during deep isoflurane anesthesia, bursts can occur in response to the stimuli, and averaging the trials across time makes the synchronized bursts begin to look like a late evoked response. This indicates that isoflurane can suppress the sensory signal at earlier stages but generate a large volley of activity much later in time, which is less specific to the stimulated pathway.

Because the ERP is virtually absent under isoflurane conditions, this anesthetic state is clearly unlike sleep, and the results of this study reinforce the notion that we cannot consider anesthesia a sleeplike state. Although there are clear physiological differences between sleep and anesthesia, some investigators have proposed that similar brain regions may be responsible for sleep and anesthesia states (12, 37).

Under many experimental conditions, the animal must be under deep anesthesia during the surgery to alleviate painful stimuli; however, when the surgery has been completed and data collection begins, a protocol may allow for a reduction in the anesthesia depth because some of the painful stimuli may no longer be present. Because anesthetics are commonly reduced after the surgery, this might reduce the striking differences between anesthetics. In fact, some types of meaningful sensory responses are often obtained despite the absence of a typical ERP at surgical levels. However, the results of this study should caution interpretation of results that are based solely on correlates of the ERP (such as metabolic or optical responses), without also recording the actual electrical response.

A clear dose-dependent effect can be seen as the animal woke up from an anesthesia such as isoflurane (Fig. 4). As the animal recovered, the evoked responses appeared to transition from the anesthetic state through sleep and then to wakelike characteristics. However, if anesthetic levels are reduced too much during an experiment to overcome potential anesthetic effects, the animal might feel pain. Because of the pharmacological actions of each anesthetic agent, we expect that the temporal pattern of the response would be similar with different doses, but the signal should exhibit differences in amplitude based on dose.

Additional pharmacological approaches are needed to establish the neuronal groups generating gamma, FO, and VFO bursts, the specific effect of anesthetics, and their significance on somatosensory processing. Such studies must consider the possible role of gap junctions on the generation of high-frequency oscillations, as previously suggested (8). Because significant evoked responses are observed under certain anesthetics, typically claimed as good agents, at least some sensory
processing must be occurring at a lower level, and the characteristic ERP of each anesthetic might be used as a parameter to control depth of anesthesia.

Using the components of the ERPs, we show important differences across anesthetic and behavioral (sleep/wake) states; these signatures could be used as markers for neural state. Thus spatial mapping experiments that use electrical, NMR, or optical techniques must consider anesthetic-dependent signals, especially when comparing stimulation protocols. Relationships between metabolism and activity have shown that synaptic activity is directly correlated with metabolic demand (24). Thus imaging techniques that rely on metabolic indicators will be influenced by the type of anesthetic used, especially if metabolism, neuronal vascular coupling, or mean neuronal activity is affected.

Because the signal-to-noise ratio of fast optical signals is small, many optical imaging studies require many hundreds or thousands of averages to adequately observe the signal. These studies typically require long recording sessions because long interstimulus intervals are needed. However, these studies often use isoflurane, urethane, pentobarbital sodium, or other anesthetics that significantly suppress the evoked response. Faster imaging signals may be seen with less recording time if agents that do not suppress the ERP, such as ketamine/xylazine or propofol, are used (29).

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