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Isoflurane Blunts Electroencephalographic and Thalamic–Reticular Formation Responses to Noxious Stimulation in Goats

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Background: **Anesthetics, including isoflurane, depress the electroencephalogram (EEG). Little is known about the quantitative effects of isoflurane on EEG and subcortical electrical activity responses to noxious stimulation. The authors hypothesized that isoflurane would depress the results of EEG and subcortical response to noxious stimulation at concentrations less than those needed to suppress movement. Furthermore, determination of regional differences might aid in elucidation of sites of anesthetic action.**

Methods: **Ten goats were anesthetized with isoflurane, and minimum alveolar concentration (MAC) was determined using a noxious mechanical stimulus. Depth electrodes were inserted into the midbrain reticular formation and thalamus. Needle electrodes placed in the skull periosteum measured bifrontal and bihemispheric EEG. The noxious stimulus was applied at each of four anesthetic concentrations: 0.6, 0.9, 1.1, and 1.4 MAC.**

Results: **At an isoflurane concentration of 0.6 MAC, the noxious stimulus activated the midbrain reticular formation, thalamic, and bifrontal–hemispheric regions, as shown by decreased high-amplitude, low-frequency power. For all channels combined (mean ± SD), total (−33 ± 7%), delta (−47 ± 12%), theta (−23 ± 12%), and alpha (−21 ± 6%) power decreased after the noxious stimulus ($P < 0.001$); beta power was unchanged. At 0.9 MAC, total (−35 ± 5%), delta (−42 ± 7%), theta (−35 ± 8%), and alpha (−23 ± 11%) power decreased after the noxious stimulus ($P < 0.001$); beta power was unchanged. At 1.1 MAC only one site, and at 1.4 MAC, no site, had decreased power after the noxious stimulus.**

Conclusions: **Isoflurane blunted EEG and midbrain reticular formation–thalamus activation response to noxious stimulation at concentrations (1.1 MAC or greater) necessary to prevent movement that occurred after noxious stimulation. It is unknown whether this is a direct effect or an indirect effect *via* action in the spinal cord. (Key words: Anesthetic mechanisms; spinal cord; pain.)**

THE electroencephalogram (EEG) has been used with limited success as a monitor of depth of anesthesia for several decades.[1] Recently, bispectral analysis of EEG has had some success in monitoring depth of anesthesia,[2,3] although how specific anesthetics quantitatively affect the EEG response to noxious stimulation is unclear. Noxious stimulation is the hallmark of a surgical procedure and is the primary reason anesthesia is necessary for surgery. Anesthetics generally have biphasic effects on EEG, as manifested first by activation and desynchronization, followed by increased slow-wave activity, decreased fast-wave activity, burst suppression, and finally isoelectricity.[4] When a noxious stimulus is applied to a lightly anesthetized human or animal, EEG may desynchronize, *i.e.*, low-amplitude, fast-wave activity predominates, although increased high-amplitude, slow-wave activity has also been described.[5–8] These previous studies either used a combination of anesthetics or did not determine quantitative effects.[5–8] Subcortical structures, such as the midbrain reticular formation (MRF) and thalamus, are known to be critical processing points in the centripetal transmission of peripheral stimuli.[9] Previous work by Angel[10,11] documented that anesthetics depress the afferent transmission of stimuli from the thalamus to the cerebral cortex.

Recent evidence suggests that the spinal cord is the site at which volatile anesthetics suppress movement that occurs after noxious stimulation.[12,13] Some anesthetic end-points (amnesia, unconsciousness) occur presumably as the result of anesthetic action in the brain and are relatively more sensitive to volatile anesthetics than is immobility. This is shown by the 50% or greater

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reduction in anesthetic concentration needed to achieve amnesia and unconsciousness, compared with immobility.[14] We hypothesized that isoflurane would blunt the EEG desynchronization response (in cortical and subcortical structures) to noxious stimulation at anesthetic concentrations less than those that blunt the movement response. The use of depth electrodes in the MRF and thalamus also permitted determination of significant regional differences, if any, in the response to noxious stimulation.

Methods

The local institutional animal care committee approved this study. Ten female goats (48.2 ± 11.2 kg, mean ± SD) were anesthetized by mask with isoflurane and their tracheas were intubated. End-tidal isoflurane was determined using a calibrated agent analyzer. A rumen tube was passed through the esophagus to drain rumen contents. A peripheral intravenous catheter was placed for administration of lactated Ringer's solution. A catheter was placed in a femoral artery for measurement of blood pressure and withdrawal of blood for determination of hematocrit, glucose, and blood gases. Glucose was infused as needed to maintain plasma glucose at 60–100 mg/dl. Ventilation was adjusted to maintain arterial carbon dioxide at 37 ± 6 mmHg and partial pressure of arterial oxygen (Pa_{O_2}) at more than 200 mmHg. Temperature was measured from the rectum and maintained at 37.1 ± 0.9 °C using a heating lamp. A craniotomy was performed to gain access to the brain.

Minimum alveolar concentration (MAC) of isoflurane was determined. In brief, the end-tidal isoflurane was equilibrated for 15 min and an A clamp (Pony 3202; Adjustable Clamp Company, Chicago, IL) was applied to a dew claw on the hind limb. The clamp was moved back and forth (at approximately 1 Hz) for 60 s. This clamp delivered a force of approximately 0.5–0.6 N/mm^2.[15] A positive response was gross, purposeful movement, such as turning of the head toward the stimulus or a pawing motion of the extremities, excluding withdrawal of the stimulated limb. Stiffening, swallowing, and chewing were considered negative responses. Depending on the response, the isoflurane was increased or decreased by 0.2% and equilibrated for 15 min, and then the stimulus was applied again. Two end-tidal isoflurane concentrations were found that just permitted and just prevented movement. The MAC was the average of these.

Anesthesia was maintained with isoflurane, and after administration of pancuronium (0.1–0.15 mg/kg and 0.1 mg/kg every 1 to 2 h), the head was placed in a stereotaxic frame and secured with ear bars and a mouth piece. Six stainless steel (copper in one goat) electrodes (28 gauge, covered with polyurethane except for the distal 2 mm) were passed into the midbrain region, with three on either side of the midline. The targets were the caudal MRF (5 mm lateral to the midline, 5 mm superior to the horizontal interaural line, and 3 mm rostral to the vertical interaural line), the rostral MRF–caudal thalamus interface (5 mm lateral, 5 mm superior, 10 mm rostral), and the rostral thalamus (5 mm lateral, 5 mm superior, 22 mm rostral).[16] Four platinum needle electrodes (E-2; Grass Instruments, West Warwick, RI) were placed in the periosteum overlying the skull in the occipital and frontal areas bilaterally, with a ground electrode placed in the scalp. Impedances of the bifrontal–hemispheric electrodes were less than 2 kOhm. The depth electrodes had slightly higher impedances and were generally less than 5 kOhm. Ten channels were recorded: ipsilateral and contralateral cerebral cortex and bifrontal cortex, ipsilateral and contralateral MRF, ipsilateral and contralateral thalamus, bilateral caudal–rostral MRF, and thalamus (figs. 1 and 2; recording montage). The electrodes were connected to a Grass, model 8-10E, EEG machine (Grass Instruments, Braintree, MA), and the signals were amplified and fed into a personal computer, where they were digitized (12-bit resolution at 250 Hz) using a commercial program (PolyViewPro; Grass Instruments, Braintree). The amplifiers filtered the signals (low: 1 Hz; high: 70 Hz; the data were further filtered off-line at 35 Hz; see Statistical Analysis). The EEG was recorded continuously. Using each animal's MAC, the end-tidal isoflurane was equilibrated for at least 15 min at 0.6, 0.9, 1.1, and 1.4 MAC, and the noxious stimulus was applied to the dew claw on the hind limb for 1 min. The order of the MAC levels was alternated from study to study to minimize any time effects on a particular MAC level.

At the conclusion of the experiment, electrolytic lesions were made (6–8 V [DC] for 30–40 s). The animals were killed with potassium chloride and the brains were removed and fixed in 10% formalin and 1% potassium ferricyanide. The brains were frozen and sectioned with a microtome (50 μm) and the recording sites were determined.

Statistical Analysis

The data for each channel were not normally distributed and are presented as the median with twenty-fifth

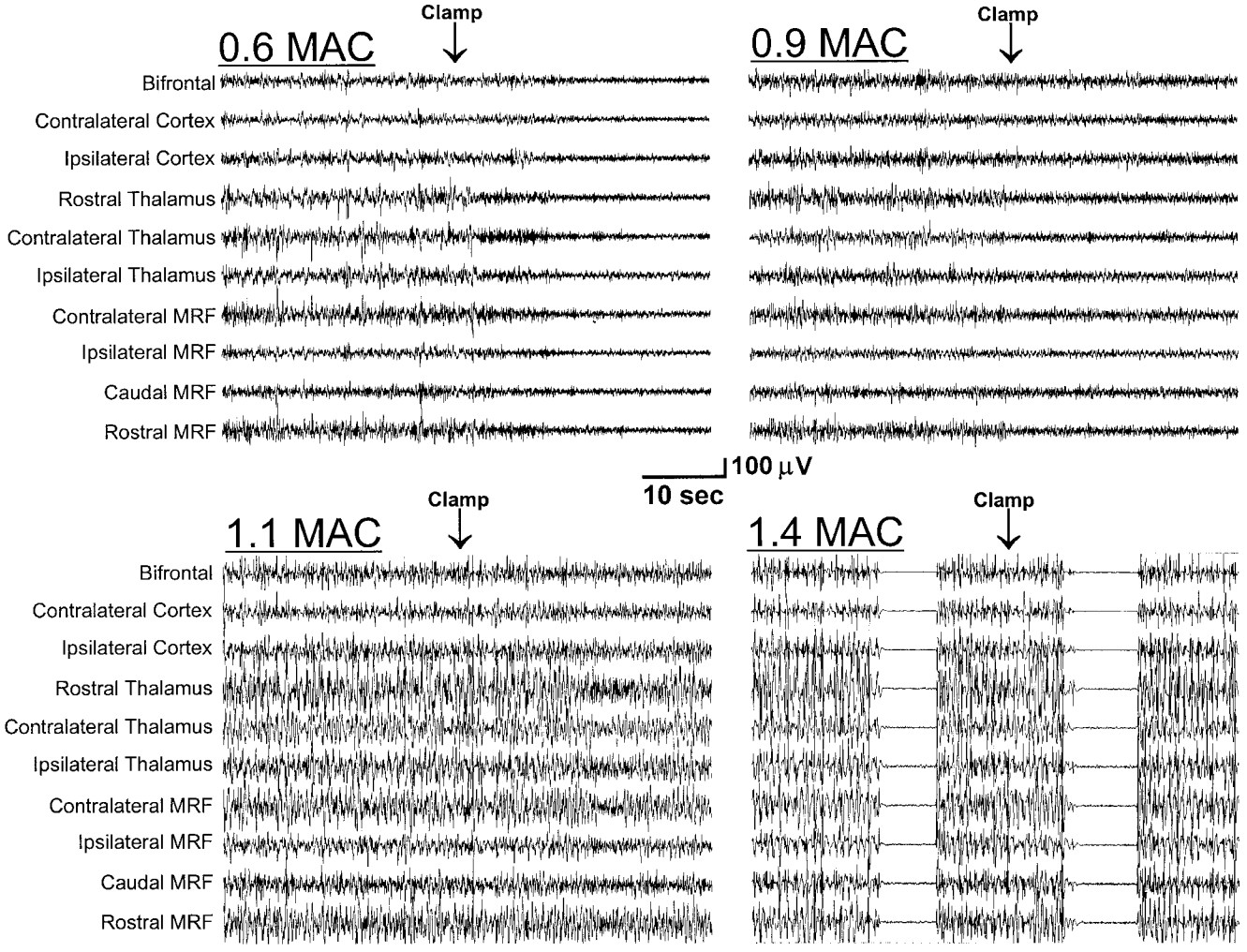

Fig. 1. Example of the raw electroencephalogram and electrical activity of the thalamus and midbrain reticular formation that shows the loss of low-frequency, high-amplitude (delta, theta, alpha) activity when the noxious stimulus was applied at 0.6 and 0.9 minimum alveolar concentration (MAC) isoflurane. At 1.1 and 1.4 MAC, the noxious stimulus did not alter the electrical activity. At 1.4 MAC, this animal had periods of isoelectricity, although this was not seen in any other animal. The MAC in this animal was 1.5% end-tidal isoflurane.

to seventy-fifth percentiles and the range (figs. 2–5). The summary data for all channels combined were normally distributed and are presented as the mean ± SD (fig. 6). The raw signals were visually inspected and the artifacts deleted before analysis (< 1% of raw data). The electrical activity data for each channel were analyzed using the PolyViewPro software. The raw data were filtered at 1Hz–35Hz. Total power and power in the delta (1–3 Hz), theta (3–8 Hz), alpha (8–13 Hz), and beta (13–35 Hz) ranges were determined. The EEG data were analyzed for 1 min before and 1 min during the application of the noxious stimulus, using 4-s consecutive epochs of time. The power in these epochs was averaged over each 1-min period. The means of the prestimulus and poststimulus data were compared using the Friedman test for repeated-measures analysis of variance of nonparametric data to detect overall differences; a paired *t* test was used to determine differences between the pre- and poststimulus data at each anesthetic concentration. To correct for multiple comparisons, $P < 0.0125$ was considered to be significant. The percent change in power after the noxious stimulus for each frequency range (all channels combined) was analyzed using repeated-measures analysis of variance. To determine the extent to which the depth electrodes measured electrical activity from structures far away (*e.g.*, cortex), correlation coefficients

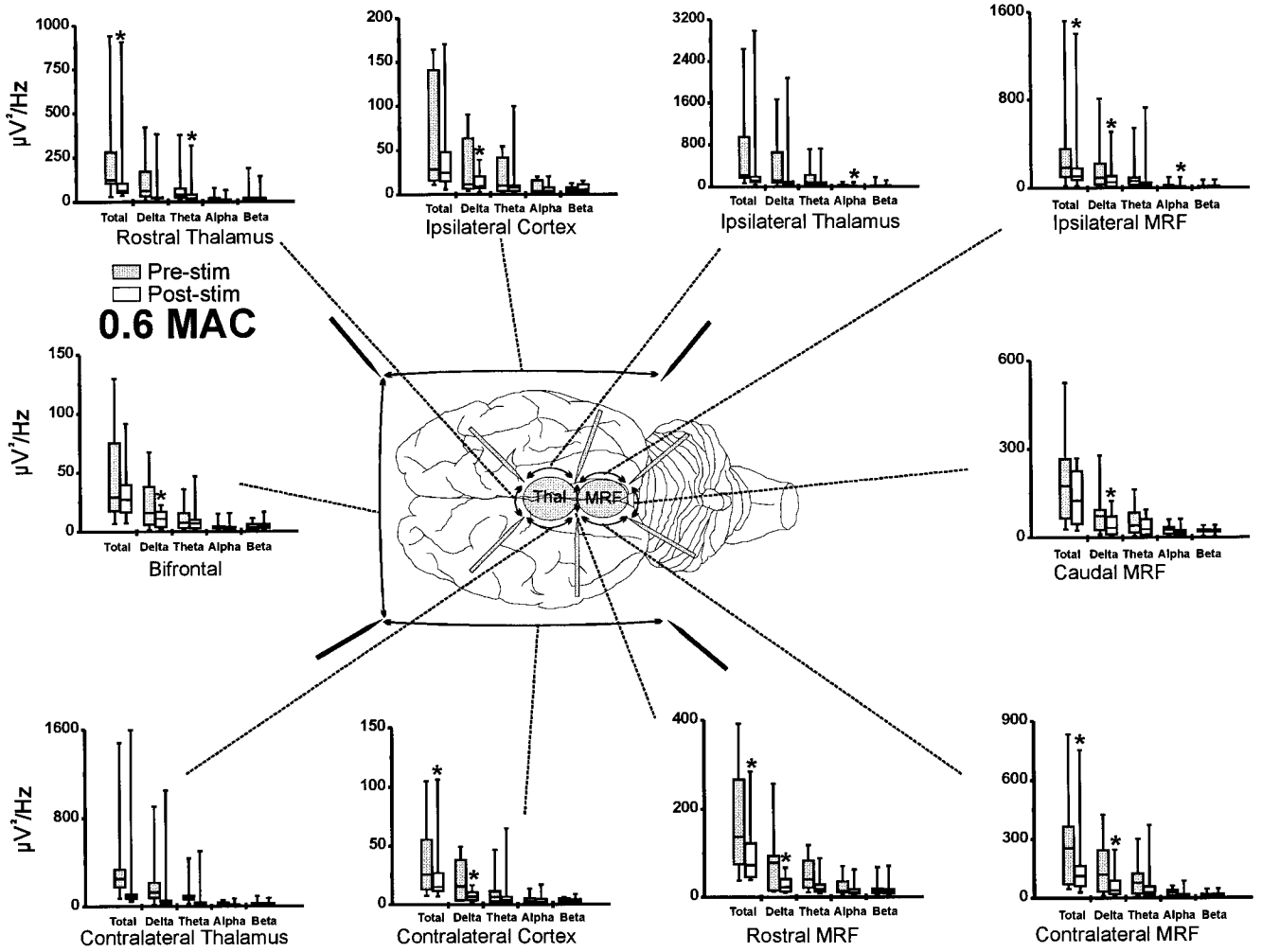

Fig. 2. Population data for all recording sites at 0.6 minimum alveolar concentration (MAC) isoflurane. There was a significant decrease in one or more of total, delta, theta, and alpha power in most sites. *$P < 0.0125$ prestimulus value compared with poststimulus value. (*Inset*) Shows the recording montage. The black electrodes represent the needle electrodes placed in the periosteum, and the gray electrodes represent the depth electrodes. Ten channels were recorded using pairs of electrodes (bipolar) denoted by the arrows. Note that the Y scales differ among the various graphs. The line through the box represents the median. The box bottom and the box top represent the twenty-fifth and seventy-fifth percentiles, respectively. The data range is shown with the error bars. MRF = midbrain reticular formation.

(r) for each animal were obtained by cross-correlation of single 1-min segments from simultaneous recordings of all sites (see table 1 for specific sites correlated).

Results

The isoflurane MAC was 1.3 ± 0.2%. At the lesser isoflurane concentrations (0.6, 0.9 MAC), the noxious stimulus caused the EEG to shift from a slow-frequency, large-amplitude pattern to a fast-frequency, low-amplitude pattern in all channels. An individual example is shown in figure 1. No change was seen at 1.1 or 1.4 MAC. The data for all animals at 0.6 MAC (fig. 2) indicated a significant decrease in one or more of total, delta, theta, and alpha power in 9 of 10 sites after application of the noxious stimulus; beta power was unchanged. At 0.9 MAC (fig. 3), a similar decrease occurred; however, only a slight, statistically significant change was noted in total and theta power of ipsilateral cortex at 1.1 MAC (fig. 4), and no brain area was affected at 1.4 MAC (fig. 5). Because each site had similar responses and any differences were likely to be small and subtle, no specific

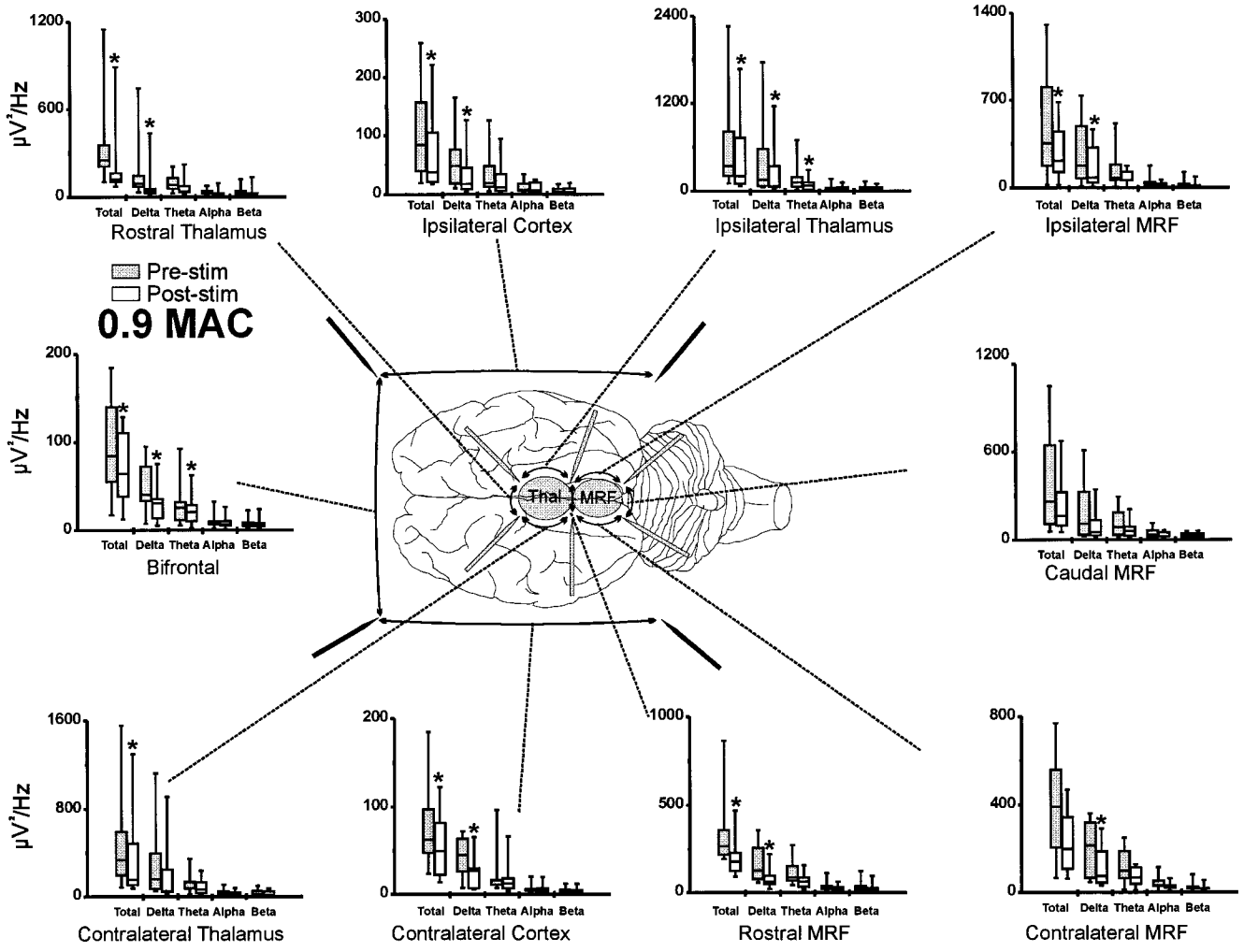

Fig. 3. Population data for all recording sites at 0.9 minimum alveolar concentration (MAC) isoflurane. There was a significant decrease in one or more of total, delta, theta, and alpha power in most sites. *$P < 0.0125$ prestimulus value compared with poststimulus value. Note that the Y scales differ among the various graphs. The line through the box represents the median. The box bottom and box top represent the twenty-fifth and seventy-fifth percentiles, respectively. The data range is shown with the error bars. MRF = midbrain reticular formation.

comparisons were made among the various sites. The data for all channels combined (fig. 6) showed that, at 0.6 and 0.9 MAC, there was a significant decrease in total, delta, theta, and alpha power after the noxious stimulus was applied, ranging from $-21 \pm 6\%$ to $-47 \pm 12\%$, $P < 0.001$. At 1.1 and 1.4 MAC, no significant power changes were found. Beta power was unaffected at any anesthetic concentration. Thus, the desynchronization was the result of loss of low-frequency power and not the gain of power from higher frequencies.

The cortical EEG was poorly correlated with the electrical activity recorded from the thalamus and MRF (table 1). Correlation was slightly better among the subcortical sites. These data suggest that each pair of depth electrodes recorded activity primarily from nearby structures.

Serial brain sections confirmed that the depth electrodes were located in the region of the caudal MRF–superior colliculus, the MRF–thalamic interface, and the rostral thalamus.

Discussion

The main finding of our study was the change in the EEG pattern with application of the noxious stimulus at the lower isoflurane concentrations. Isoflurane concen-

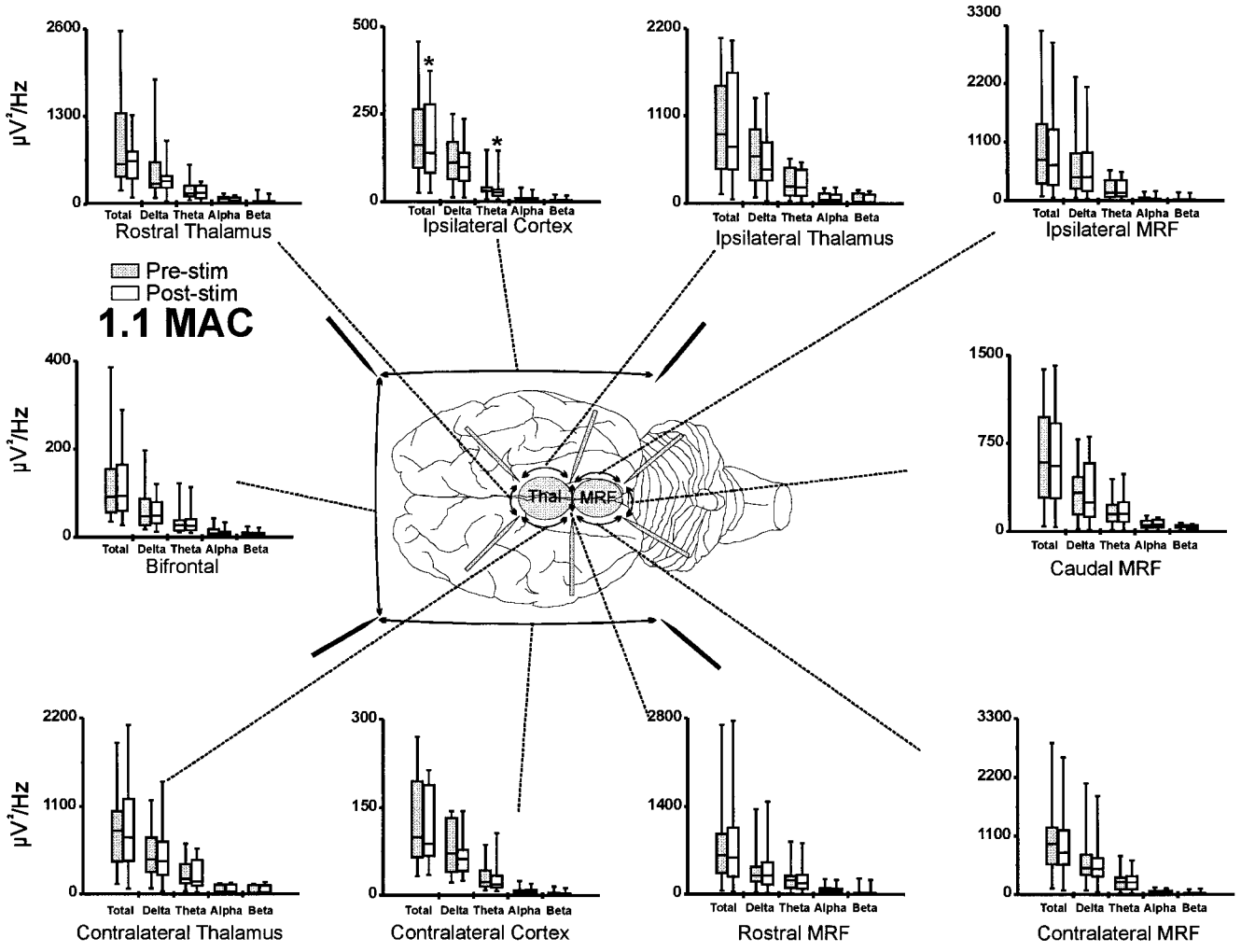

Fig. 4. Population data for all recording sites at 1.1 minimum alveolar concentration (MAC) isoflurane. Total and theta power decreased in ipsilateral cortex. *$P < 0.0125$ prestimulus value compared with poststimulus value. Note that the Y scales differ among the various graphs. The line through the box represents the median. The box bottom and box top represent the twenty-fifth and seventy-fifth percentiles, respectively. The data range is shown with the error bars. MRF = midbrain reticular formation.

trations more than 1 MAC blunted the EEG response, such that the EEG remained in a slow-wave, high-amplitude pattern, which is considered to be characteristic of deep anesthesia using inhaled anesthetics.[4] This response was seen in the cerebral cortex and in the MRF and thalamus. It is appealing to speculate that isoflurane blunts the response by interfering with the transmission of noxious stimuli through the thalamus, MRF, and other subcortical structures. In fact, anesthetics decrease afferent transmission through the thalamus, as shown by Angel.[10,11]

It is interesting to note that isoflurane affected the EEG and thalamic–reticular formation responses to noxious stimulation between 0.9 and 1.1 MAC. Recent studies suggest that the movement response is ablated by anesthetic action in the spinal cord.[12,13] The finding that the same isoflurane concentration was needed to abolish movement and the EEG response that occurred after a noxious stimulus raises the intriguing possibility that isoflurane might exert part of its blunting effect on the EEG and subcortical response by indirect action on the spinal cord. Little work now exists to establish or refute this possibility; however, differential delivery of anesthetics to the brain and spinal cord might shed some light.

Some animal studies that investigated the EEG response to noxious stimulation showed the classic activation pattern seen in the current study. Kowalczyk[17]

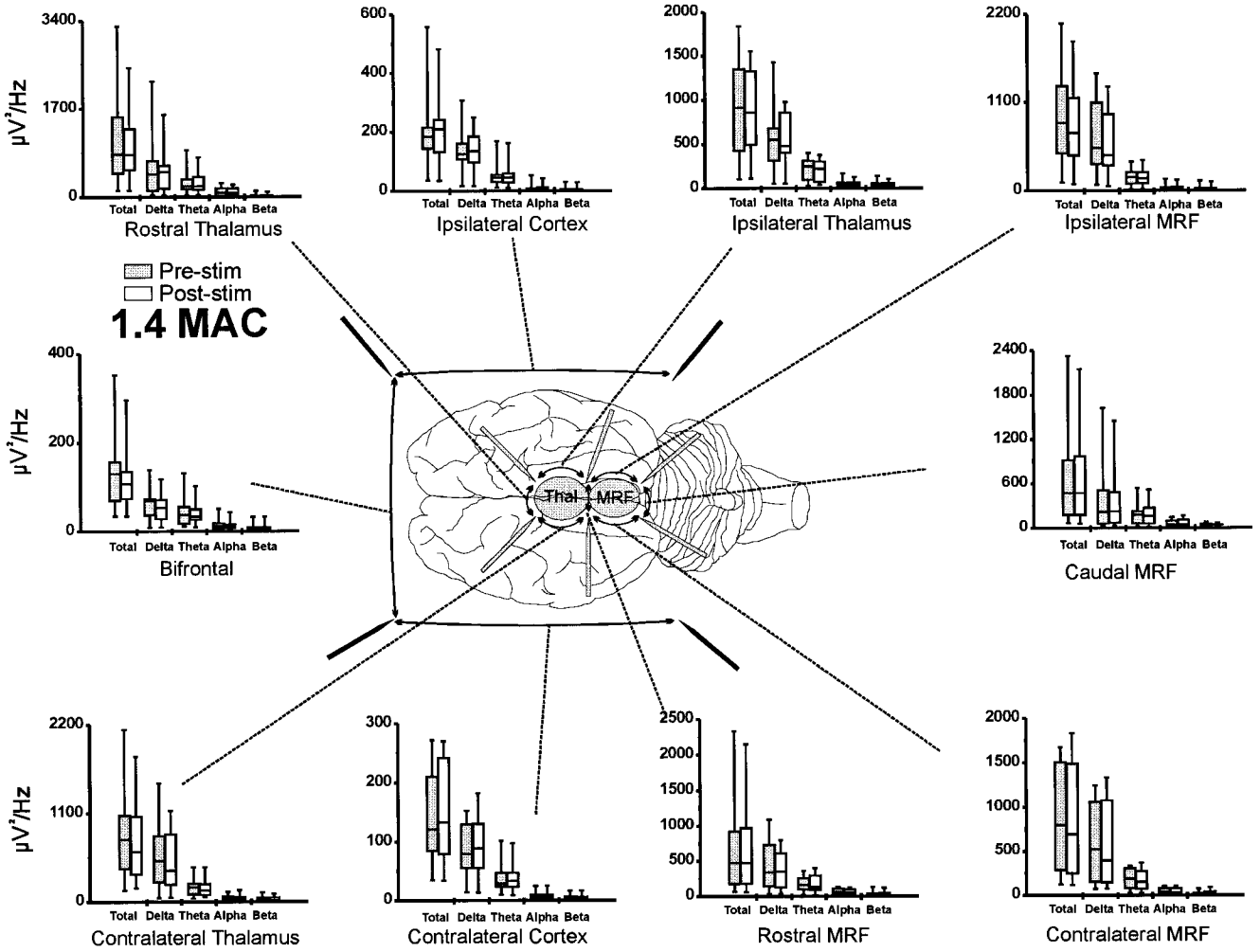

Fig. 5. Population data for all recording sites at 1.4 minimum alveolar concentration (MAC) isoflurane. None of the sites had a significant change in power in any of the frequency ranges. Note that the Y scales differ among the various graphs. The line through the box represents the median. The box bottom and box top represent the twenty-fifth and seventy-fifth percentiles, respectively. The data range is shown with the error bars. MRF = midbrain reticular formation.

placed electrodes into the sensorimotor cortex, ventroposterolateral thalamus, periaqueductal gray, and MRF of rabbits. After recovery, a noxious thermal stimulus was applied to the skin of the awake animal, and the EEG shifted toward a high-frequency, low-amplitude pattern. This response was abolished by morphine. In thiopental-anesthetized dogs, electrical stimulation of the sciatic nerve activated the EEG (shift to low amplitude, high frequency) at low, but not high, thiopental plasma concentrations.[5] In a similar study, halothane depressed the EEG activation response to sciatic nerve stimulation.[6] In these latter two studies, quantitative effects were not sought.

Wilder-Smith *et al.*[18] evaluated EEG responses in humans to laryngoscopy during thiopental or propofol anesthesia with nitrous oxide. Delta activity decreased with a shift to higher frequencies. Propofol appeared to depress the EEG more, as shown by the lack of response to the noxious stimulation of laryngoscopy.

Bischoff *et al.*[8] determined EEG changes to surgical stimuli during isoflurane–nitrous oxide anesthesia for hysterectomy and mastectomy. They described a "paradoxical arousal" phenomenon, whereby there was a shift to lower frequencies with noxious stimulation. This contrasts with the prevailing theory that a shift toward lower frequencies signifies deepening anesthesia. It is unclear why paradoxic arousal occurs. Some theorized that the underlying EEG pattern, which is dependent on the

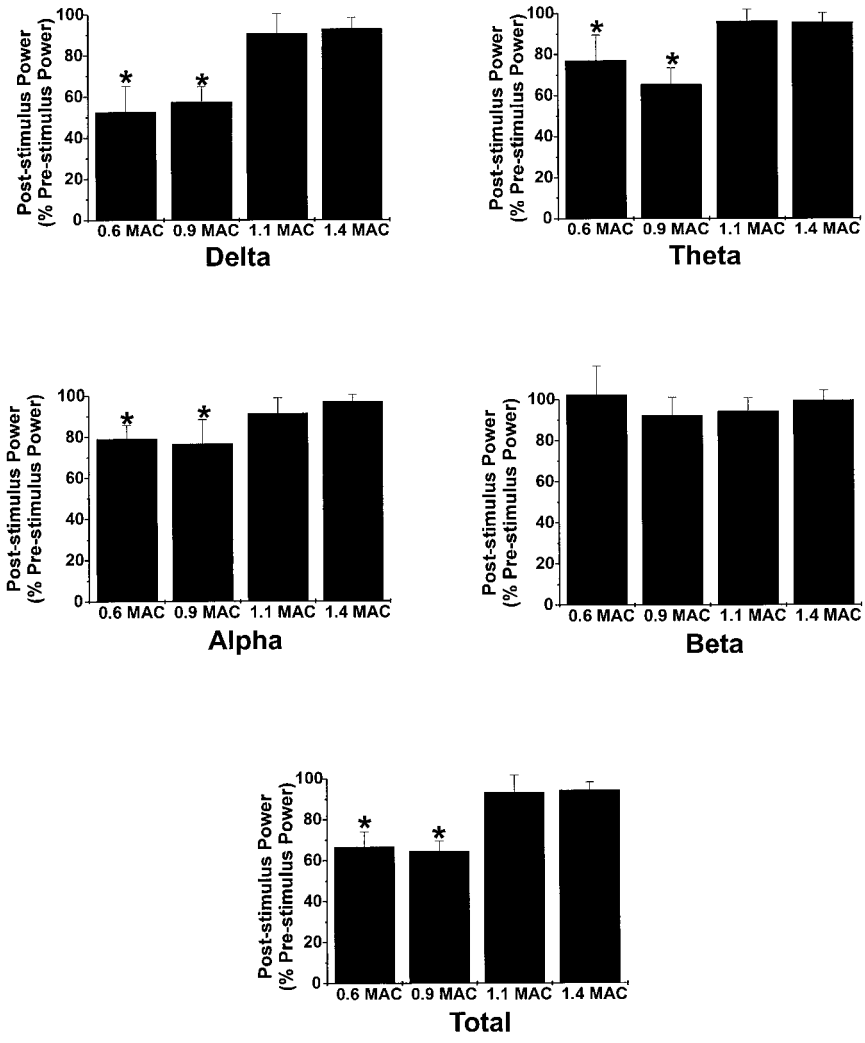

Fig. 6. The poststimulus power as a percent of prestimulus power is shown for total, delta, theta, alpha, and beta power (all channels combined) at each isoflurane concentration (mean, SD). Power decreased significantly at 0.6 and 0.9 minimum alveolar concentration (MAC) for total, delta, theta, and alpha frequency ranges. At 1.1 and 1.4 MAC, no significant change occurred. *$P < 0.001$ compared with prestimulus power.

anesthetic depth, is a factor that affects paradoxical arousal.[18] However, in the current study, a range of isoflurane concentrations was used, and paradoxic responses were not seen at any concentration. Another possible factor is the site of stimulation, with deep visceral noxious stimulation giving rise to a paradoxic arousal pattern and superficial noxious stimuli resulting in the classic EEG activation pattern.[18,19] Some authors described "shifting" that occurred during the transition from an "awake" to an "anesthetized" pattern.[20] This transitional pattern occurs in a very narrow anesthetic concentration range. In the current study, it is likely that the noxious stimulation caused an immediate change, thereby bypassing a "shifting" pattern.

Although we found that isoflurane depressed the EEG response to noxious stimulation at more than 1 MAC, some found that the cerebral cortex is still responsive to other stimuli. Schwartz *et al.*[21] demonstrated that pancuronium, when given to dogs that were deeply anesthetized with isoflurane (≈3%), increased the amount of time the EEG was isoelectric. Previous studies showed that muscle afferent information activated the EEG.[22,23] Lanier *et al.*[22] found that pancuronium, by preventing movement in response to noxious stimulation, could prevent the associated muscle afferent activity and subsequent EEG changes. It is unclear why, at more than 1 MAC, muscle afferent activity, but not noxious information, would be transmitted. Anesthetic action at the spinal cord might be a factor because dorsal horn cells with joint afferent input are relatively resistant to anesthetics, whereas dorsal horn cells with noxious inputs are sensitive.[24] In a related study, Eappen and Kissin[25] determined that hypnotic and anesthetic requirements for

Table 1. Correlation Coefficients (r) among Cortical and Subcortical Sites

	Bifrontal Cortex	Contralateral Cortex	Rostral Thalamus	Caudal MRF
Contralateral thalamus	0.06 ± 0.06	0.12 ± 0.14	0.25 ± 0.18	0.15 ± 0.07
Ipsilateral thalamus	0.09 ± 0.07	0.20 ± 0.15	0.36 ± 0.25	0.11 ± 0.08
Contralateral MRF	0.08 ± 0.04	0.14 ± 0.13	0.22 ± 0.13	0.48 ± 0.21
Rostral MRF	0.07 ± 0.04	0.11 ± 0.15	0.36 ± 0.15	0.28 ± 0.16
Ipsilateral MRF	0.04 ± 0.03	0.17 ± 0.15	0.19 ± 0.17	0.30 ± 0.16
Caudal MRF	0.09 ± 0.05	0.08 ± 0.05	0.26 ± 0.10	—
Rostral thalamus	0.16 ± 0.03	0.11 ± 0.11	—	—
Ipsilateral cortex	0.34 ± 0.24	0.62 ± 0.27	0.10 ± 0.07	0.06 ± 0.05
Contralateral cortex	0.37 ± 0.24	—	—	—

One-minute segments of the electrical activity measured at each site from each animal were correlated with segments from various other sites. Not all possible combinations are shown. N = 10 for each r. Note the poor correlation between any one cortical site and any one subcortical site. This suggests that the electrical activity measured from the subcortical sites arose primarily from nearby structures (thalamus, MRF). The correlation among the subcortical sites is slightly better. The correlation among the cortical sites is best, suggesting that the cortical electrodes were measuring similar volumes of brain tissue.

MRF = midbrain reticular formation.

thiopental decreased after intrathecal bupivacaine, suggesting that anesthetic blockade in the spinal cord could indirectly affect the brain.

We recorded subcortical sites (thalamus, MRF) to determine whether these structures had altered patterns after noxious stimulation. We chose these two areas because they are considered to be critical to the transmission of afferent information,[9] including that arising from noxious stimulation. The MRF is part of the reticular activating system and appears to be important to consciousness.[9] The depth electrodes in the current study were in, or near, the MRF and thalamus, and therefore recorded the electrical activity of those two areas. Electrical activity from structures further away, such as other subcortical sites or even the cortex, also contributed to the measured potentials. However, measured voltage from point sources would decrease inversely with the square of the distance from the electrode to the source.[26] The poor correlation of the cortical EEG with the thalamic–MRF electrical activity also suggests that the depth electrodes recorded activity mostly from nearby structures (thalamus–MRF). Nonetheless, we might have missed subtle regional differences, and the relatively small number of animals studied probably limited the statistical power of this study. Last, our use of a 1–35 Hz bandpass might have missed activity at higher frequencies ($>$ 35 Hz) and in the subdelta ($<$ 1 Hz) range.

In summary, at sub-MAC isoflurane concentrations, noxious stimulation activates cortical and subcortical structures (thalamus–MRF), but at concentrations exceeding MAC, isoflurane abolishes this response. It is unknown whether this is a direct effect or partly caused by an indirect effect in the spinal cord.

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