Hypothermia Amplifies Somatosensory-evoked Potentials in Uninjured Rats

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Abstract: Temperature fluctuations significantly impact neurological injuries in intensive care units. As the benefits of therapeutic hypothermia continue to unfold, many of these discoveries are generated by studies in animal models undergoing experimental procedures under the influence of anesthetics. We studied the effect of induced hypothermia on neural electrophysiological signals of an uninjured brain in a rodent model while under isoflurane. Fourteen rats were divided into 2 groups (n = 7 each), on the basis of electrode placement at either frontal-occipital or primary somatosensory cortical locations. Neural signals were recorded during normothermia (T = 36.5 to 37.5°C), mild hypothermia (T = 32 to 34°C), and hyperthermia (T = 38.5 to 39.5°C). The burst-suppression ratio was used to evaluate electroencephalography (EEG), and amplitude-latency analysis was used to assess somatosensory-evoked potentials (SSEPs). Hypothermia was characterized by an increased burst-suppression ratio (mean ± SD) of 0.58 ± 0.06 in hypothermia versus 0.16 ± 0.13 in normothermia, $P < 0.001$ in frontal-occipital; and 0.30 ± 0.13 in hypothermia versus 0.04 ± 0.04 in normothermia, $P = 0.006$ in somatosensory. There was potentiation of SSEP (2.89 ± 1.24 times the normothermic baseline in hypothermia, $P = 0.02$) and prolonged peak latency (N10: 10.8 ± 0.4 ms in hypothermia vs. 9.1 ± 0.3 ms in normothermia; P15: 16.2 ± 0.8 ms in hypothermia vs. 13.7 ± 0.6 ms in normothermia; $P < 0.001$), whereas hyperthermia was primarily marked by shorter peak latencies (N10: 8.6 ± 0.2 ms, P15: 12.6 ± 0.4 m; $P < 0.001$). In the absence of brain injury in a rodent model, hypothermia induces significant increase to the SSEP amplitude while increasing SSEP latency. Hypothermia also suppressed EEGs at different regions of the brain by different degrees. The changes to SSEP and EEG are both reversible with subsequent rewarming.

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Hypothermia has been suggested as a means for neuroprotection after cardiac arrest,[1,2] traumatic spinal cord injury,[3] stroke,[4] cardiac surgery,[5] and brain trauma.[6] At the same time, it is also known that hyperthermia can exacerbate neural injury, shown in some animal[7] and clinical studies.[8]

In the development of neuroprotective strategies for acute brain injury, there has been an increasing need to move basic research findings to the clinical setting through translational research or preclinical studies that involve whole-animal preparations under some form of anesthetic. Although a large number of studies have focused on demonstrating the benefits of hypothermic intervention after neural injury in animal models and humans, the effect of temperature changes in a noninjured brain in vivo remains unclear. Anesthetics have direct effects on the neural response to experimental injuries and interventions. Several studies have dealt with the effect of temperature on neural activity, but the presence of multiple confounding factors, including different surgical procedures such as cardiopulmonary bypass,[9] varying anesthetics, rate of cooling, and depth of temperature change, have led to mixed results.

The uninjured brain's response to hypothermia has been studied using neuroimaging[10]; however, imaging techniques can only describe the indirect changes that occur in the brain after neuronal activation, whereas electrophysiological recordings provide direct measures of underlying neuronal activation. In this study, we use a rat model to determine the effects of temperature changes on neural activity in a standard procedure under isoflurane as the anesthetic without any form of neural injury. Specifically, we investigated changes to both spontaneous [electroencephalography (EEG)] and evoked neural activity [somatosensory-evoked potentials (SSEPs)] at clinically relevant temperature ranges: mild hypothermia (32 to 34°C) and mild hyperthermia (38.5 to 39.5°C).

MATERIALS AND METHODS

Fourteen adult male Wistar rats were used for this study. The animal protocol used in this study was

approved by the Animal Care and Use Committee at the Johns Hopkins University School of Medicine.

Electrode Implantation

One week before the experiment, the rats were implanted with epidural screw electrodes (Plastics One, Roanoke, VA). In the first group (n = 7), the electrodes were placed over the frontal (F1, F2:6 mm anterior and ± 3 mm lateral to bregma) and occipital (O1, O2: 7.5 mm posterior and ± 3 mm lateral to bregma) regions of the rat "10-20 system,"[11,12] with a reference at the center (Cz: 1.5 mm posterior to bregma at the midline). In the second group (n = 7), the electrodes were placed over the forelimb and hindlimb regions of the bilateral primary somatosensory cortex (S1FL: 1 mm posterior and ± 3.8 mm lateral to bregma); HL: 2 mm posterior and ± 1.5 mm lateral to bregma) as described previously (Fig. 1).[13,14]

Experimental Procedure

On the day of the experiment, the rats were anesthetized by a tight-fitting facemask (Kent Scientific Corporation, Torrington, CT) using 1.5% isoflurane in 1:1 N_2/O_2 by a standard precision anesthesia vaporizer (Penlon Sigma Delta, Penlon Ltd., Abingdon, Oxon, UK) for the entire experiment. The anesthetic depth at the prescribed concentration of delivered volatile anesthetic was consistent in reproducing a tranquil but cardiopulmonarily stable animal. This concentration of isoflurane has been used in prior studies with the same experimental anesthesia model when median nerve stimulation is applied.[13–15] Adequate oxygenation and acid-base balance was verified by arterial blood gas measurements as in previous experiments with or without cardiac arrest.[11,13,14,16] Recent studies from the National Academies Institute for Laboratory Animal Research Journal et al have also suggested that the most appropriate isoflurane dose level was 1.5%, yielding stable mean arterial pressure and heart rate values comparable to those observed in the animal's conscious state.[17,18] We recognize the limitation of using a facemask for anesthesia and potential interanimal variability. However, in our experiments, we observe very little signal (EEG or SSEP) variability between animals given a set isoflurane level.

The rats were placed on a heating pad, and the temperature was continuously measured using a semiautomated temperature-monitoring system (Mon-a-Therm 6510, Mallinckrodt Medical Inc., St Louis, MO). To record evoked somatosensory cortex activity, the median nerves were stimulated by needle electrodes that were connected to a stimulus generator with direct current stimulation using pulses that were 6 mA in amplitude and 200 μs wide at a frequency of 0.5 Hz.[13,14] The stimulation was performed on 1 side at a time in an alternating manner. A stimulation current of 6 mA was chosen for median nerve stimulation as this was the current required to induce "supramaximal" stimulation in the vast majority of our rats. Data were sampled at a frequency of 6.1 KHz for SSEPs and 305 Hz for EEG using the Tucker Davis Technologies (TDT, Alachua, FL) System 3 data acquisition system.

Temperature Modulation and Recording Protocol

Rat temperature was recorded from a rectal probe. After the rats were stabilized at normothermic temperature (36.5 to 37.5°C), baseline EEG and SSEPs were recorded for 15 minutes. The rat was then cooled down to the hypothermic range (32 to 34°C) by external systemic cooling using a fan and alcohol-water mist spray.[11,16] In all rats, the transition to hypothermia was achieved within 15 minutes. The temperature was allowed to stabilize within the hypothermic range before reaching a thermo-steady state.[16] Finally, the rats were gradually warmed up to the hyperthermic range (38.5 to 39.5°C) over a period of 60 to 75 minutes (~15 min/°C) using an infrared lamp (Thermalet TH-5, model 6333, Phyritemp, NJ), and signals were recorded for 15 minutes after stabilization of the temperature around 39°C. The rats were allowed to cool down to normal temperature before they were returned to the cage. All rats used in this study survived the experiment.

Quantification of EEG Burst Suppression

Burst-suppression (BS) is defined as an EEG pattern where high-amplitude δ (0.5 to 4 Hz) and/or θ (4 to 7 Hz) waves, often with high-frequency components,

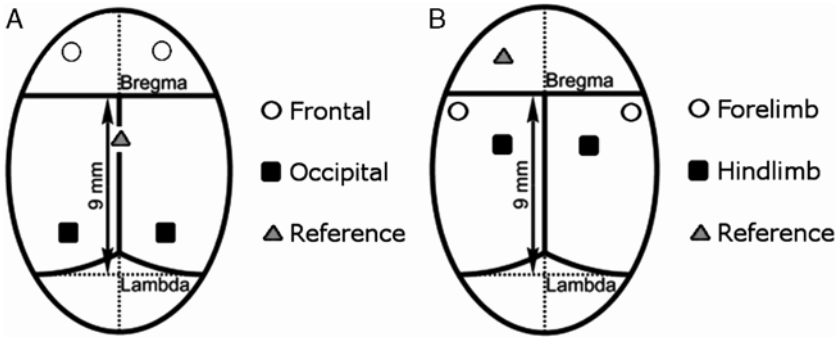

FIGURE 1. Schematics of the electrode placement locations on the rat brain for recording EEG and median-nerve–evoked potentials. Montage (A) shows placement of the electrodes for EEG recordings over the frontal-occipital regions and (B) shows the electrode positions on the primary somatosensory forelimb and hindlimb regions for evoked potential recordings.

are interspersed with relatively inactive periods that occur in an irregular stochastic manner. The most common time-domain parameter used to quantify the bursting phenomenon is the burst-suppression ratio (BSR),[19] which represents the percentage of time for which the EEG remains suppressed. Suppression is defined as periods longer than 0.5 seconds during which the EEG amplitude typically does not exceed ± 10 μV. BSR was calculated as the duration of suppression as a fraction of segment length. An amplitude threshold between ± 10 to 25 μV was selected for the detection of suppression stretches based on the baseline EEG amplitude. BSR was computed for minute-long windows and then averaged over the duration of the recording in each temperature phase. Monopolar EEG signals from all 4 channels were low-pass filtered before processing with a fourth-order Butterworth filter at a cutoff frequency of 50 Hz to cut off the 60 Hz noise and high-frequency noise. Before analysis, the raw signals were examined to identify segments/channels with electrical noise or motion artifacts.

Amplitude-latency Analysis of SSEPs

Bipolar SSEPs were computed using the difference of the contralateral forelimb and hindlimb channels implanted on each cerebral hemisphere. The average of every 30 sweeps was mean-corrected and the first 5 to 25 msec of each 150 msec waveform was used for further processing. SSEP peaks were identified using an automated peak detection algorithm in user-defined windows of interest to determine peak-to-peak amplitudes and peak latencies. The interpeak latency was taken to be the difference between the first negative and the first positive peak. Amplitude calculations were normalized to the mean amplitudes at normothermia for comparison. We focused on capturing the changes to the amplitudes during hypothermia and hyperthermia for each rat as each rat had a variable amplitude baseline during normothermia.

Statistical Analysis

Statistical analysis was performed using MedCalc for Windows, version 11.2.1.0 (MedCalc Software, Mariakerke, Belgium). The normality of the EEG-derived and SSEP-derived parameters was verified using the Kolmogorov-Smirnov test. All data are presented as mean ± SD. As signals from each rat were recorded during different temperature phases, differences were evaluated using repeated measures analysis of variance. The *P*-values were Bonferroni corrected and $P < 0.05$ was considered significant.

RESULTS

Hypothermia Leads to Reversible EEG Burst Suppression

The EEG (here refers to spontaneous brain activity without stimulation) in both groups showed continuous activity with low BSRs (on average < 10% in somatosensory and < 20% in frontal-occipital) during normothermia. With the onset of hypothermia, the EEG showed characteristic BS patterns with variable burst durations and interburst intervals (Fig. 2). Frontal-occipital regions had 58 ± 8% suppression, and the primary somatosensory areas had an average BSR of 30 ± 12% (Fig. 3). Upon rewarming, the EEG waves fused to continuous waveforms. Mild hyperthermia did not show significant differences in BSR when compared with normothermia (Fig. 3).

Temperature Dependence of the SSEP

The rat's SSEP is characterized by a triphasic waveform with a negative peak around 10 ms (N10), which is equivalent to the commonly observed N20 potential in human, followed by a positive peak around 15 ms (P15; Fig. 4).

Marked changes in the peak amplitudes and latencies of the evoked potentials were observed in response to changes in temperature (Fig. 5). SSEPs demonstrated a sharp increase in N10 to P15 peak-to-peak amplitudes

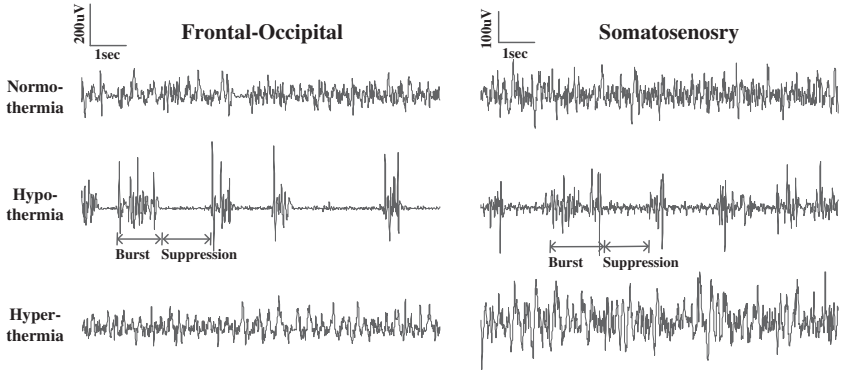

FIGURE 2. Representative EEG traces during the different temperature phases of the experiment in the frontal/occipital and primary somatosensory regions. Induced hypothermia results in a burst-suppression pattern, with periods of high-amplitude activity interspersed with periods of relative quiescence. The continuous nature of the EEG waveform is restored upon gradual rewarming to the mild hyperthermic range.

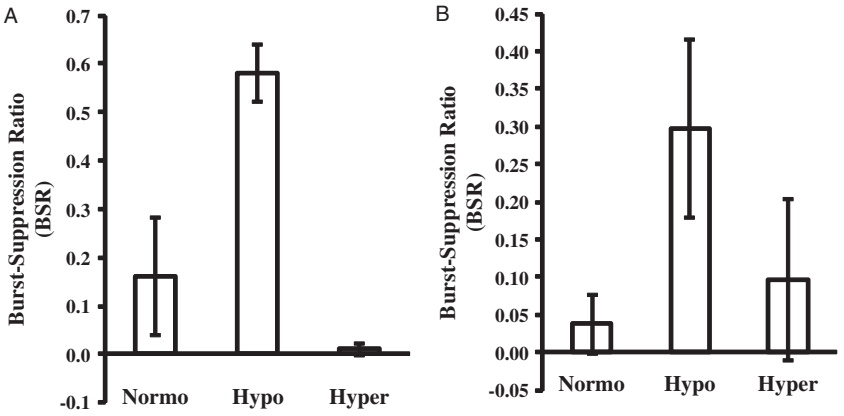

FIGURE 3. Summary of the burst-suppression ratio (BSR) in the frontal-occipital (A) and somatosensory regions (B) during normothermia, hypothermia, and hyperthermia, respectively. This increase is reversible, and the burst-suppression levels decrease to around normothermia levels during mild hyperthermia (A: normo-hypo $P = 0.002$, normo-hyper $P = 0.06$; hypo-hyper $P < 0.001$; B: normo-hypo $P = 0.006$, normo-hyper $P = 0.41$; hypo-hyper $P = 0.06$).

(2.89 ± 1.24 times normothermia baseline in hypothermia, $P = 0.02$) accompanied by a transmission delay of the obligate potentials. The N10 and P15 latencies were delayed on average by 18% to 19% during hypothermia (N10: 10.8 ± 0.4 ms; P15: 16.2 ± 0.8 ms) compared with normothermia (N10: 9.1 ± 0.3 m; P15: 13.7 ± 0.6 ms; $P < 0.0001$). Moreover, the N10 to P15 interpeak latency is also prolonged during hypothermia (5.4 ± 0.6 ms) compared with normothermia (4.6 ± 0.4 m; $P = 0.005$).

Upon warming to the mild hyperthermia, SSEP amplitudes fluctuated around baseline values (1.29, ± 1.14 times normothermia baseline, $P = 1.0$), whereas a decrease in latencies was observed, indicating faster impulse conduction in the underlying somatosensory pathway (N10: 8.6 ± 0.2 ms; P15: 12.6 ± 0.4 ms; $P < 0.001$).

No significant decrease in the N10 to P15 interpeak latency was observed in hyperthermia (3.8 ± 0.8 ms; $P = 0.11$).

DISCUSSION

This study demonstrates the effects of induced mild hypothermia (32 to 34°C) and mild hyperthermia (38.5 to 39.5°C) on EEG and SSEPs in a rodent model without neural injury in the setting of spontaneous circulation using isoflurane as the anesthetic. Although negligible BS was observed during normothermia, the suppression increased significantly during hypothermia. The observed increase in BS can either be attributed to hypothermia-induced metabolic suppression or may result from the hypothermic potentiation of isoflurane-induced metabolic suppression.[20] We have previously shown that there is more bursting in animals subjected to hypoxic-ischemic injury during hyperthermia compared with normothermia possibly due to an increased metabolic rate.[21]

The prolongation of SSEP latencies in hypothermia and faster conduction during hyperthermia has been reported in several studies.[22,23] In our study, both the N10 latency and the N10 to P15 interpeak latency are delayed. It is known that the rising slope of N10 is most likely generated by the thalamocortical radiation,[24] with the subsequent components of the evoked response (the N10 to P15 waveform and beyond) speculated to be the result of corticocortical interactions.[24] The delay in N10 is therefore indicative of a conduction delay at the subcortical level of transmission, and the increase in the N10 to P15 interpeak latency suggests that corticocortical networks are also slowed down.

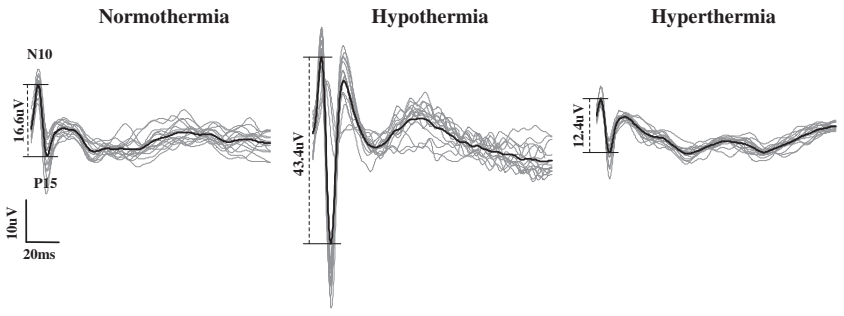

FIGURE 4. Representative somatosensory-evoked potential traces during normothermia, hypothermia, and hyperthermia. The lighter waveforms are 30-sweep bipolar averages obtained during the 15-minute recording, with the average for the entire recording block superimposed as the dark waveforms.

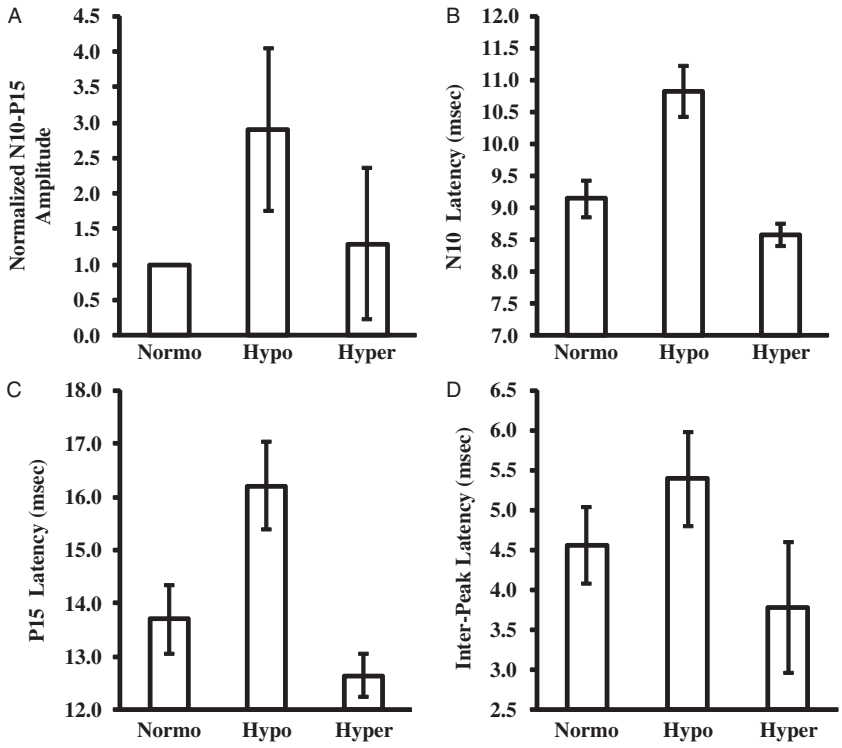

FIGURE 5. N10 to p15 peak-to-peak amplitudes and corresponding peak latencies of the somatosensory-evoked potentials (SSEPs) during normothermia, hypothermia, and hyperthermia, respectively. A, Marked increase in SSEP amplitudes during hypothermia (normo-hypo $P = 0.02$, hypo-hyper $P = 0.02$) and no significant difference between hyperthermia and normothermia amplitudes; (B) and (C) indicate that the peak latencies are increased during hypothermia and reduced during hyperthermia (N10: normo-hypo $P < 0.001$, hypo-hyper $P < 0.001$, normo-hyper $P = 0.02$; P15: normo-hypo $P < 0.001$, hypo-hyper $P < 0.001$, normo-hyper $P = 0.04$); (D) shows the corresponding trend in interpeak latencies (normo-hypo $P = 0.005$, hypo-hyper $P = 0.001$, normo-hyper $P = 0.11$).

The effect of hypothermia on SSEP amplitudes remains unclear and unpredictable.[25] It has been well established that increases in concentrations of halogenated anesthetics such as isoflurane suppresses SSEPs.[22,26] Further, hypothermia is known to downregulate cerebral metabolism.[27] In accordance with this, we would expect a suppressed cortical SSEP during hypothermia; however, a 2- to 4-fold increase in amplitude was observed. The counter-intuitive increase in SSEP amplitudes observed in our study points toward a hypothermia-mediated regulation of cortical activity. Although we are not able to explain the exact mechanism of hypothermic potentiation by this experiment alone, we speculate that hypothermia reduces the basal tone of cortical firing that acts synergistically with the diminished activity of inhibitory cortical interneurons to produce a hyperexcitable state[28,29] in the cortex. This "hyperexcitable" state may lead to a larger evoked response upon the arrival of an afferent stimulus to the cortex. As isoflurane-induced BS does not affect thalamic sensory processing,[30] the amplified response upon stimulation may be due to the synchronous recruitment of a larger number of thalamocortical and/or cortical neurons.

Technical errors such as EEG artifacts or noise would likely only have very minimal impact on our consistently observed SSEP amplitude increase. Assuming that these artifacts or noise occur in a random manner, any effects would be averaged out in our data analysis. The fact that we consistently observed this amplitude increase and that differences were very significant led us to believe that this is a very real observation. Furthermore, we evaluated SSEPs during spontaneous circulation, as described in the clinical study by Lang et al,[31] which also described a higher SSEP amplitude during hypothermia. This is in contrast to prior clinical findings in models of cardiopulmonary bypass surgery, where hypothermia is known to suppress the somatosensory response.[32] The difference in the effects of hypothermia may be due to the presence of spontaneous pulsatile circulation.

Our study shows that both spontaneous and evoked neural responses are sensitive to changes in temperature. Although mild hyperthermia may not cause any significant changes to the EEG in the noninjured brain, hypothermia may act synergistically with isoflurane and suppress the tone of basal cortical activity, leading to electroencephalic suppression. As the afferent volley from the thalamus reaches the cortex, a larger population of cortical neurons is recruited, leading to a more synchronized, and hence amplified, SSEP. This also indicates that the synergistic effect of hypothermia and isoflurane is not functionally equivalent to the effect of increasing the

anesthetic concentration alone, which would have resulted in the suppression of cortical SSEPs. A potential limitation in this study is that we randomized the temperature manipulation methods using hypothermia first for all rats without verifying the effect if the sequence of procedures were switched.

As we undertake more translational studies with animals subjected to anesthetics in conjunction with experimentally induced injuries and further modify how we deliver hypothermia, it is critical that we develop a firm grasp of the uninjured brain's response to temperature modulation paradigms to fully understand the impact of our interventions. Although experiments are typically undertaken with a concomitant control group, the analysis of data is always focused on the intervention, and results are interpreted with no in-depth focus of the response in the control group. In this study, we provide observations that neuroelectrophysiological responses are clearly altered in uninjured animals, and we hope that a full appreciation of these changes will help us design better experiments and guide us to a more precise interpretation of the data that are generated.

From a clinical practice consideration, these observations further highlight the temperature-dependent nature of EEGs and SSEPs, as these signals are frequently studied in conjunction with anesthetics in operating rooms and intensive care units for assessing neurological function, diagnosis, and prognosis.

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