REVIEW ARTICLE

The EEG signal: a window on the cortical brain activity

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Basics

The EEG is today the main element allowing us to measure the depth of anesthesia or, more precisely, the level of hypnosis. This central role is explained by the easy and noninvasive nature of the monitor, and because the main hypnotic agents cause characteristic and dose-dependent changes in the signal it measures. The EEG is a representation of cerebral electrical activity (mainly cortical) over time. The tracing is a sum of excitatory and inhibitory postsynaptic activities. Axonal transmission contributes little to the signal. The recorded differences of potential come mainly from pyramidal cells, which have long dendrites oriented perpendicular to the cortical surface. This geometry allows the summing of millions of those differences of potential. When the cortex is quiet, the pyramidal cells are synchronized, and the EEG shows

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Summary

The accurate assessment of the depth of anesthesia, allowing a more accurate adaptation of the doses of hypnotics, is an important end point for the anesthesiologist. It is a particularly crucial issue in pediatric anesthesia, in the context of the recent controversies about the potential neurological consequences of the main anesthetic drugs on the developing brain. The electroencephalogram signal reflects the electrical activity of the neurons in the cerebral cortex. It is thus the key to assessment of the level of hypnosis. Beyond visual analysis, several monitoring devices allow an automated treatment of the electroencephalographic (EEG) signal, combining time and frequency domain analysis. Each of these monitors focuses on a specific combination of characteristics of the signal and provides the clinician with useful information that remains, however, partial. For a comprehensive approach of the EEG-derived indices, the main features of the normal EEG, in adults and children, will be presented in the awake state and during sleep. Age-related modifications accompanying cerebral maturation during infancy and childhood will be detailed. Then, this review will provide an update on how anesthetic drugs, particularly hypnotics, influence the EEG signal, and how the main available monitors analyze these drug-induced modifications. The relationships between pain, memory, and the EEG will be discussed. Finally, this review will focus on some specific EEG features such as the electrical epileptoid activity observed under sevoflurane anesthesia. The EEG signal is the best window we have on cortical brain activity and provides a fair pharmacodynamic feedback of the effects of hypnotics. However, the cortex is only one of several targets of anesthesia. Hypnotics and opiates, have also subcortical primary targets, and the EEG performances in the evaluation or prediction of noception are poor. Monitoring subcortical structures in combination with the EEG might in the future allow a better evaluation and a more precise adaptation of balanced anesthesia.
wide and slow complexes. Inversely, during cortical stimulation, these cells are desynchronized, and the tracing shows rapid oscillations and low-amplitude signal.

EEG activity, as a biorhythm, is influenced by age and environment, and shows circadian variations.

The amplitude of the EEG signal is 10–100 µV, thus 100 times weaker than that of an electrocardiogram.

Analysis of the EEG trace

Each of our states of awareness, awake, slow sleep, and deep sleep has its characteristic rhythm of EEG oscillation. The rhythmicity is a result of interactions between the thalamus and the cortex (1).

Visual analysis of EEG

The EEG tracing can be analyzed visually, without mathematical tools. It is a complex mixture of oscillations of different frequencies (calculated by the wave length, expressed in Hz (hertz), the number of waves per second). Historically, the first analysis of EEG consisted in a description of the main oscillations in terms of amplitude, form, and duration. Classically, this produces four types of waves in the frequency interval of 0–30 Hz (Figure 1).

- **Beta rhythm** (β), characterized by rapid oscillations of 13–30 Hz and around 30 µV amplitude, is the characteristic tracing of the awake alert subject who is actively thinking. This rhythm would result from cortico-cortical activity.

- **Alpha rhythm** (α), the first described historically, corresponds to that of a subject who is awake with eyes closed, relaxed, or meditating, with a frequency of 8–13 Hz and an amplitude of 30–50 µV. This tracing may be the result of the interaction of cortical and thalamic pacemakers (cortico-thalamic network).

- **Theta rhythm** (θ), is the rather slow frequency between 4 and 7 Hz, with an amplitude of 50–100 µV. This rhythm is observed in light sleep (stage 2) and may represent the inhibitory action of GABAergic interneurons affecting the cortico-thalamic network. It could be associated with limbic activity (memory and emotions).

- **Delta rhythm** (δ) has a slow frequency between 0.5 and 3–4 Hz, and a large amplitude (100–200 µV). This rhythm is observed in deep sleep and coma. It is generated by the cortex with no sensory input (cortico-thalamic dissociation).

- **Gamma rhythm** (γ), described recently, consists of very rapid oscillations above 30 Hz. This rhythm may be associated with consciousness; that is, the association of input from different cerebral areas to form a coherent concept. Reflecting the interconnection of cortico-cortical and cortico-thalamo-cortical networks (loop activity), this rhythm may be involved in the processes of perception.

Automated analysis of EEG

With the technology allowing the digitizing and analysis of these analog signals has come a more sophisticated analysis, both in time and in frequency domains (2).

**Time domain analysis**

The time domain analysis allows a measure of mean signal amplitude, frequency, and the burst suppression ratio (BSR), which represents the proportion of time the EEG trace is flat.

**Frequency domain analysis**

- **Spectral analysis** (Figure 2) is derived from the decomposition of light via a prism. It is based on a mathematical process called the fast Fourier transform (FFT), which separates a complex sinusoidal wave into a sum of simple wave forms of specific frequency and voltage. The result is a spectrum with, for the abscissa, a frequency scale in Hz, from which are plotted the spectral powers of each constituent oscillation. Various numerical parameters can be deduced from the spectral analysis of the EEG: the total spectral power, in microvolts², which is a measure of the overall signal variability; the spectral power of four constituent frequency bands according to the neuroelectrophysiological definition (δ, θ, α, β). The spectral power of the different bands is commonly expressed as a percentage of total power, which allows evaluation of the relative

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**Figure 1** Main constitutive waves of the EEG.
contribution of each band to the global variability of the signal. One can also determine the F95 (the frequency under which occurs 95% of total spectral power) and the F50 or median frequency (the frequency under which occurs 50% of total spectral power) are represented. General anesthesia is associated with an increase of slow oscillations (delta and theta), which results on the spectra, in a shift to the left of the F50 and the F95.

The bispectral analysis is a second level of analysis in the frequency domain. Preceded by an FFT, this process compares two by two the waveforms to find a third sinusoid (harmonic) that measures the degree of synchronization between the two waveforms, in terms of phase shift (lag). Having examined the pairs of waveforms, the degree of synchrony is calculated between the number of harmonics and the number of waveforms of the spectrum. Synchronization is near 0 when the subject is awake, that is, there is little synchrony between waveforms. The number rises with the increasing depth of anesthesia, similar to the way the EEG becomes more synchronous during coma.

Measure of entropy (approximate or spectral) or complexity. The principle is the following: if you compare successive segments of EEG, the variation from one to the next may be described by a mathematical model. The last segment in the series may obey or diverge from the model, more or less. If it follows the model, the regularity of the signal is high and the predictability is good: one can say the entropy and complexity are low. As individual segments vary from the general form of the series, complexity grows and regularity and predictability diminish. If the various EEG segments bear no relationship to one another, and analysis of a particular EEG segment does not allow prediction of the subsequent trace, entropy and complexity are maximal. It has been written that the entropy and desynchronization of the EEG increase during awareness or conscious thinking during anesthesia. Thus, these parameters are high during the awake state and diminish with deepening anesthesia.

**EEG-based monitoring devices**

The EEG varies in a dose-dependent fashion with the hypnotic agent. However, in some particular conditions, the raw EEG can be a misleading source when conducting anesthesia and evaluating anesthetic depth. This weakness is due in part to differing effects depending on the agent used (halogenated vs IV hypnotics, for example) and also to the difficulty in monitoring and analyzing the raw EEG while conducting the anesthesia. These problems lead to the development of more sophisticated EEG-based monitors, with performance enhanced by the use of algorithms which integrate parameters derived from spectral analysis of the raw signal. Among these monitors, the bispectral index (BIS; Covidien, Boulder, CO, USA), the spectral entropy (Entropy, GE Healthcare, UK), and the Narcotrend (Schiller, Switzerland) have been evaluated in children.

**Figure 2** EEG traces recording at baseline, and under general anesthesia and the corresponding spectra. The F95 (the frequency under which occurs 95% of total spectral power) and the F50 or median frequency (the frequency under which occurs 50% of total spectral power) are represented. General anesthesia is associated with an increase of slow oscillations (delta and theta), which results on the spectra, in a shift to the left of the F50 and the F95.
The bispectral index (BIS) (Figure 3)
The BIS is calculated from three sources: the spectral analysis (which permits calculation of the beta ratio), the bispectral analysis (which basically makes an estimation of the synchronization between pairs of traces), and the temporal analysis including the periods of flat EEG or nearly flat EEG. So, the three parameters in the BIS algorithm are as follows:

- the ‘synchfastslow’, or degree of synchronization, a parameter derived from the bispectral analysis of the EEG – this increases with depth of anesthesia.
- The beta ratio, the percentage of rapid beta frequencies measured by spectral analysis of the EEG, predominating during light sedation.
- The BSR, or proportion of flat or almost flat EEG during deep sleep.

These three factors are weighted according to the level of the BIS value. Thus, for a BIS above 60 (sedation), the beta ratio is favoured, whereas during surgical anesthesia (60–40) the BIS predominates and under deep anesthesia (BIS < 40) the BIS varies linearly with the BSR. In addition, the XP version of the BIS measures and subtracts the electromyograph (EMG) contribution to those parts of the EEG which are included in the calculation.

The Entropy
The measure of spectral entropy is made from an analysis of the frontal EEG. The calculation is based on a public algorithm that estimates predictability and regularity of the signal. The entropy monitor produces two numerical measurements, which differ by the frequency interval at which they are calculated (3,4):

- The value of state entropy or SE varies from 0 (flat EEG) to 91 (awake) and is calculated on a frequency interval of 0–32 Hz reflecting the classical EEG oscillations.
- Response entropy or RE is calculated on the interval of 0–47 Hz, thus going beyond the EEG frequency to include, in theory, the range of the EMG oscillations and the subclinical muscular contractions, which may indicate insufficient depth of anesthesia or insufficient analgesia (muscular activity in response to noxious stimulus).

- In addition, the entropy calculation includes a temporal factor of percentage of time with flat or nearly flat EEG in deep anesthesia.

The Narcotrend
Commercialized in 1981, this monitor is based on spectral analysis of the frontal EEG and produces a classification A to F with three subclasses. They are derived directly from a calculation of the spectral power of each band, delta, theta, alpha, and beta (5).

Class A and B correspond to awake state; D to E represent surgical anesthesia; and F corresponds to burst suppression. In parallel, to permit comparison with other monitors, the Narcotrend produces a value on a scale of 100 to 0 of increasing anesthetic depth.

Of these three monitors, the BIS, because of its longer time on the market, has been the most extensively studied one in children. All three include a scale from 100 (awake) to 0 (deeply anesthetized). The scale is constructed to decrease in value as the EEG regularizes and slows. The three monitors are insensitive to products that do not induce these typical EEG changes. The BIS does have one added tool, the beta ratio, which provides a more accurate evaluation of the signal with higher frequencies. This may explain its sensitivity to periodic epileptoid features.

Regarding the Entropy monitor, the State Entropy values tend to evolve like the BIS, with however a target interval, which probably needs to be adjusted (6). It should be noted that the Entropy does include the EMG factor, as additional information, but for the moment its utility is not demonstrated.

The Narcotrend has been used mainly in Germany. Because of the difficulty in calibration, its use is less appealing. However, it is the only one with a pediatric algorithm. Its changes seem parallel to those of the BIS.

Main characteristics of the normal EEG

EEG in adults
In the awake subject, the main frequency is the beta rhythm (>13 Hz) with low amplitude (10–20 μV). With eye closing, there is an immediate enrichment with alpha (8–13 Hz) waves of slightly higher amplitude (20–40 μV). When the subject becomes tired and tends to fall asleep, the alpha rhythm disappears and is replaced by slower and more ample oscillations called
theta (4–7 Hz, 40–80 µV). During deep sleep, the EEG waves are slower (< 3 Hz and 100–120 µV).

In the awake subject, some pathological factors such as hypocapnia, hyponatremia, hypocalcemia, hypothyroidism, hypothermia, hypoxia, and hypoglycemia may cause a slowing of the EEG.

**Specific features of the pediatric EEG**

The age-dependant EEG changes reflect the process of cerebral maturation, in particular the neuronal myelination (7). (Figure 4)

In the awake state, some EEG parameters evolve from birth to adolescence. Basically, the newborn’s EEG is rich in slow oscillations; the dominant frequency of the EEG increases progressively with age, as the amplitude of oscillations diminishes. This maturation is quite rapid in the first year of life and progresses more slowly thereafter.

*Developmental stages in detail:*

- **From birth to 2 months:** Sleep spindles appear.
- **From 3 to 5 months:** Parieto-occipital sinusoidal activity appears, announcing alpha rhythm, with increasing frequency: from 4–6 Hz initially to 8–9 Hz by the age of 3.
- **In the normal child aged 3 years and older:** The alpha parieto-occipital rhythm, initially discreet and slow (8 Hz), with high voltage and asymmetry. Theta rhythm is abundant, diffuse, and mixed with alpha in the posterior leads and predominates. Slow waves appear, grouped in bursts, and become rhythmic at 2–3 Hz.
- **From 3 to 10 years:** Alpha rhythm becomes more important and abundant, with voltage up to 60 µV, with an increasing reactivity; theta waves become rare in the occipital leads and are seen more clearly in parietal and posterior-frontal areas. Slow waves disappear, although they are seen occasionally in certain individuals in posterior leads.
- **At this age, hyperpnea (hyperventilation) induces the appearance of slow and generalized hypersynchrony, from posterior to anterior. This phenomenon is practically universal at 3–5 years of age, but becomes less pronounced with maturation.**

- **From 10 to 14 years:** Certain patterns become more clear: ample alpha rhythm, limited abundant theta, and slow patterns becoming less evident or more organized as posterior slow waves.
- **From 14 to 19 years:** Alpha rhythm predominates with reduced voltage to adult levels (50 µV), theta becomes more discreet, and posterior slow waves disappear. Asymmetry diminishes from its prior prominence in the very young.
- **After 19 years:** The tracing is that of the adult, although there may remain some theta activity. Posterior slow waves have generally disappeared.

**EEG and Anesthesia**

Effects of hypnotics

The GABAergic anesthetics have EEG effects similar to that of physiologic sleep, with the exception of those seen in deep anesthesia (burst suppression or flat EEG).

In general, the effects of these agents can be summarized as follows: the effects are proportional to the potency of the GABA stimulation, which is responsible for cortical inhibition. Classically, the effect is described as biphasic, with initial stimulation followed by inhibition (8) (Figure 5).

- **At subanesthetic doses** (early sedation), the IV and inhaled hypnotics induce rapid oscillations (mainly beta).
- **At anesthetic dose**, there is an increasing amplitude of the signal with a decreasing frequency. Rapid alpha and beta waves diminish as slow theta and delta waves supervene. This is measured as an increase in total spectral power, dependent mainly on oscillation amplitude, and associated with a shift to the left (slower frequencies on the spectrum) of F50 and F95.
- **At supra-anesthetic doses** or more precisely, under very deep anesthesia, most of the hypnotics induce a subtotal inhibition of EEG electrical activity. The tracing is nearly isoelectric with short salves of slow activity (burst suppression), which disappear with further deepening of anesthesia (flat EEG).
Benzodiazepines, used as sedative agents, show only the first part of the previously described EEG changes (sedation). Benzodiazepines decrease alpha activity and increase beta, with EEG effect reflecting blood levels of the drug. Quantitative EEG parameters have been shown to provide continuous, objective reproducible, and sensitive measures of the central nervous system effects of benzodiazepines as anticonvulsant activity (9). Changes in amplitude in 11.5–30 Hz frequency band of the EEG (beta) is a relevant measure of the affinity and the intrinsic efficacy of midazolam at the central GABA–benzodiazepine receptor complex (10).

Ketamine and nitrous oxide are NMDA receptor antagonists that have modest EEG effects far different from those of the GABA agonists. They are known to activate the electroencephalogram, despite their sedative effects (11). They increase rapid beta waves, and under certain conditions increase the BIS value; however, most of the time the addition of nitrous oxide or ketamine under general anesthesia does not change the value of the EEG-derived parameters (12).

Compared to the racemic ketamine, the S + ketamine seems to have a more potent effect, associated with an increase in slow EEG waves when used at high doses (13).

Xenon is associated with an increase in fast oscillations at low doses (Fe:30%) (14), while increase in slow waves may appear at high concentrations (Fe 70%) (15).

Interaction of EEG and muscle relaxants
Muscle relaxants have no direct action on the EEG; however, the suppression of waveforms coming from possible contraction of cranial muscles under the EEG electrodes might interfere with the measurement. These are rapid oscillations 20–80 Hz and can influence the calculations in a portion of automated EEG analysis, with their upper limit of 30–40 Hz. Supporting this is the observation that in the adult under light propofol anesthesia, the BIS value diminishes with use of muscle relaxants (16). In children under light levels of propofol anesthesia, this effect may be seen, but not under sevoflurane anesthesia (Figure 6) (17).

In the adult under light sevoflurane anesthesia (1.2%), administration of muscle relaxant (95% depression of T1) does not change the BIS reading, but may inhibit the increase in BIS seen during tetanic stimulation. The explanation of this is not clear, perhaps deafferenting sensitive muscle or suppression of EMG effect on EEG is the cause (18).

Effects of narcotics
High doses of narcotic agents may cause a slowing with large amplitude waveforms and without burst suppression. These effects are only seen with high concentrations, well above those used for routine balanced anesthesia. In their ordinary dose, these agents do not influence the EEG to a noticeable degree (Figure 7). The weakness of this effect is also tied to the intensity of the painful stimulus (balance of activation related to pain and inhibition related to narcotic).

In terms of reaction to pain, the narcotic agents reduce the EEG changes during painful stimulus, which testifies indirectly of their efficacy. Because of this relatively minor effect on the EEG, all EEG-based
monitors of depth of anesthesia are poorly sensitive to narcotics.

**EEG and pain**

In a schematic sense, pain causes EEG activation in the deeply asleep patient, similar to a startle, with decrease in slow delta and augmentation of fast alpha and beta. This depends on the type of stimulus and on the degree of pain (articular > muscular > cutaneous) (19). In the anesthetized patient (with hypnotics), the same response is observed, similar to a startle, and is diminished by the increasing depth of anesthesia or by increasing the dose of analgesic agent. This activation of rapid frequencies in response to pain is the basis of the decision algorithms that generate a higher BIS score and indicate a lack of analgesia.

The value of the EEG or an EEG-derived parameter in predicting movement attributed to a painful stimulus under anesthesia depends on the profile of the relationship between the anesthetic agent and the EEG parameter: thus, if the concentration being examined lies in the horizontal portion of the dose–response curve, the relationship will be weak, but if it lies in the steep part, the predictive value will be better. This explains why the BIS is more predictive during propofol infusion than under sevoflurane anesthesia. The motor response to each hypnotic agent, which is mediated by cortical and spinal mechanisms, is in proportion to the agent’s specific cortical, subcortical, and spinal actions (spinal effects of sevoflurane are more marked than for propofol) (20). These (dissociated) effects have been demonstrated in an elegant study by Velly based on simultaneous recording of cortical and subcortical (thalamic) EEG in anesthetized subjects under sevoflurane and propofol. They found that the cortical inhibition preceded the subcortical and that the features of the cortical EEG allowed prediction of loss of consciousness, but inversely, the subcortical recording predicted the reaction to laryngoscopy (21).

Under balanced anesthesia, in the child as in the adult, the BIS does not predict response to painful stimulus with accuracy, because the narcotics used in balanced anesthesia have little EEG effect. Furthermore, if the BIS reaction to nocepsive stimulus indicates insufficient analgesic or hypnotic anesthesia levels, the opposite is not true. In fact, in children under sevoflurane (Fe 2.5% in O2-N2O, 50-50) in steady state, a skin incision induces a pupillary reflex

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**Figure 6** Effects of myorelaxants on the bispectral index in children, anesthetized with propofol (left) and sevoflurane (right). From (17) and personal data.

<table>
<thead>
<tr>
<th>Propofol concentration (μg·ml⁻¹)</th>
<th>BIS</th>
<th>PROPOFOL</th>
<th>BIS</th>
<th>SEVOFLURANE</th>
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**Figure 7** Effect of alfentanil (20 μg·kg⁻¹) on heart rate (HR), bispectral index, state entropy (SE), and response entropy (RE) in children anesthetized with sevoflurane. From (57) and personal data.

- Curarisation decreases the BIS only under low concentrations of propofol (Cp = 2 et 3 μg·ml⁻¹)
- Under sevoflurane anesthesia, curarisation does not influence the BIS

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(dilatation, via subcortical pathways) in all patients, while the BIS remains unchanged (22).

### EEG and recall

Episodes of intraoperative recall occur in children and perhaps more frequently than in adults (about 1%) (23,24). In addition, 10–20% of children describe dreams during anesthesia (25). Such dreaming in adults is thought to be associated with a higher risk of recall, and their occurrence reminds us that the anesthetized brain is not inactive.

There is no study in children on the use of EEG or its derived parameters to diminish the frequency of recall. The explicit character of recall requires cortical activity, which is theoretically inhibited by low doses of hypnotics. Such an effect is measurable by BIS, and in adults, a value of 40–60 is thought to be a good target range for suppressing recall; however, the usefulness of the BIS monitor for preventing awareness is still debated (26,27).

Implicit recall is more complex, and the factors that influence it are being studied in adults. Some studies show ability to learn and remember words by subcortical pathways, even under sedation and general anesthesia deemed adequate by BIS. The significance of such episodes including their cause and deleterious effects is unknown. The cortical EEG is not of interest in these studies, because the processes are mainly subcortical and are inhibited only by deeper levels of anesthesia than that required to inhibit explicit recall. The cortical vs subcortical relationship of each agent would dictate the utility of cortical monitoring, and the possible effects of narcotics on subcortical learning, particularly under stressful conditions, further complicates the picture.

### EEG and anesthesia for the child

Studies of the pediatric EEG under anesthesia are few and focus mainly on paroxysmal epileptoid phenomena. In spite of this short bibliography, one may postulate that the action of anesthetic agents on the EEG above the age of 1 year are comparable to those in older patients, although the concentration to attain a specific effect may be correlated with age. In this idea, the evolution of the EEG tracing under propofol infusion in the child from age 3–10 illustrates the different profiles previously described in the adult (28) (Figure 8). In this context, the main spectral parameters (F50, F95, and delta ratio) are correlated with plasma concentration during continuous infusion. In addition, in the child anesthetized with halothane or sevoflurane, one sees the various profiles described in the adult (29). It is interesting to note that in the child aged 4–12 years, the resting awake spectral power is higher than in the awake adult (because of greater amplitude of the waveforms), with a similar distribution of the various waves (Figure 9). These observations are also seen under anesthesia; the spectral parameters (F50, F95, delta ratio, and total spectral power) are correlated with endtidal sevoflurane concentrations.

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**Figure 8** EEG changes during propofol anesthesia in children. (Personal data). In children receiving IV propofol (bolus of 6 mg/kg during 6 min), the EEG trace shows slow oscillations up to the occurrence of burst suppression periods. The corresponding spectrum shows a shift of the F50 and SEF to the left (slow frequencies). During recovery, when the child opens his eyes, the EEG trace and the corresponding spectrum are close to those recorded at baseline.
Davidson (30) found in the child aged 2–12 years a decrease in spectral power and an increase in F90 (not F95) during awakening from anesthesia; however these variations were not found in the young infant (<6 months). In the child over the age of one, expired sevoflurane concentration associated with a specific BIS value (=50) (FeBIS50) decreases as age increases (31,32). This inverse relationship of FeBIS50 to age is dissociated from the relationship of minimal alveolar concentration required to inhibit movement response to skin incision (MAC) to age, which theoretically does not change from 6 months to 12 years (33). This dissociation is related to the nature of MAC (movement in response to noxious stimulus) and reflects the level of subcortical (brainstem and spinal cord) inhibition that is not measured by the BIS. In the same vein, the BIS value at one MAC sevoflurane rises as the age of the child falls (34), suggesting again that MAC is not a good predictor of hypnotic power of a halogenated agent. A bias because of the BIS algorithm, calculated on adult traces, is unlikely because pediatric EEG’s specificities should lead to opposite results (EEG slower and BIS lower as the child is young).

A similar effect of age is found for propofol infusion: for a given BIS level (BIS 50 for example), a higher concentration is needed in the child compared to the adult (35) in whom this target concentration actually decreases with greater age.

Comparative EEG effects of propofol and sevoflurane

These are the two main agents used for anesthesia in children and adults. They both produce clinical effects of rapid induction and emergence from anesthesia, with excellent cardiovascular tolerance. With this similarity of clinical effect, quite different EEG profiles are seen. During induction, while similar dynamic clinical events are occurring, the EEG profiles of the two agents differ markedly. With propofol, the EEG demonstrates progressive slowing associated with falling BIS values, until intubation, while during the same events the EEG with sevoflurane shows a paradoxical and biphasic progression (see further) (36). In steady-state measurements, further deepening of anesthesia with propofol inhibits the cortex more and more, until burst suppression (progressive lowering of BIS). One sees this same slowing with sevoflurane until just over 3% Fe (1.2 MAC) after which there is acceleration of the EEG frequencies with appearance of epileptoid signs, first isolated and then periodic (2 MAC) (37).

Electrical epileptoid effects of sevoflurane

EEG changes specific to sevoflurane anesthesia

Sevoflurane induction and deepening of anesthesia follow a similar pattern to that described above, with one
exception: during ‘rapid’ induction with 7–8% sevoflurane in O₂-N₂O (50:50), the EEG shows a brief increase in beta activity occurring around the loss of eyelash reflex (30–60 s after beginning induction), which is rapidly followed by sudden slowing down to <2 Hz delta activity maximal at the end of the second minute of induction, and then acceleration to delta predominance (2–4 Hz) until pupils are constricted and central. The bispectral index monitor (BIS) also shows a higher index number at central pupils than during the middle of induction, where slowing down is maximal (36). Some subjects show episodes of burst suppression with deeper anesthesia (higher endtidal sevoflurane and longer duration of anesthesia). Basically, EEG oscillations at 2 MAC sevoflurane are faster than at 1.5 MAC (38), and they seem to be faster under sevoflurane than under propofol at equipotent doses.

**Epileptiform activity under sevoflurane**

Describing electrical epileptiform activity is complex and differs among authors. An example of this activity is presented in relation to deepening anesthesia during sevoflurane induction in Figure 10.

Spikes are the earliest elements to appear, usually during delta oscillations (spike-wave). They may be simple or complex (spike with >2 positive or negative deflexions, multiple spike-waves, or multiple spikes) or in periodic discharge (rhythmic polyspikes) leading to periods of epileptiform discharges or frank electroencephalographic seizure. These elements may appear in a background of slow (delta) activity or burst suppression. Generally, major seizure manifestations (periodic discharge or frank seizure activity) are observed under deep anesthesia around the occurrence of burst suppression, sometimes accompanied by tonic-clonic movements, but most often without clinical signs. Abnormal fluctuation in BIS or entropy parameters caused by EEG epileptoid changes may be observed (Figure 10).

In adults, during induction with sevoflurane, risk factors for the occurrence of epileptiform EEG activity were hyperventilation (39), female sex, short delay of onset of anesthesia, and high alveolar sevoflurane concentrations (40). In children during sevoflurane induction (8% in O₂-N₂O, 50-50), Vakkuri (41) described epileptiform discharges in 88% of children under controlled ventilation. The speed of induction seems to play a major role: incremental induction (2–4–6% of sevoflurane) is associated with lower incidence of epileptiform discharges when compared to rapid induction (6% of sevoflurane) (42). Under steady-state conditions in adults, Jaaskelainen and Sato found seizure-like activity in all patients at >1.5 MAC sevoflurane in 100% O₂ (38,43). Under steady-state conditions, the relationship between expired sevoflurane concentrations and EEG-derived parameters such as the BIS follows a typical profile with a dose-dependent decrease from 0% to 3% and then a rise of the EEG-derived parameter from 4% to 5% of expired concentration of sevoflurane. This paradoxical increase in the BIS may be explained by a look at the raw

![Figure 10](image-url)
EEG showing polyspikes at 4% and 5%. In children studied in steady-state conditions, the minimal alveolar concentration of sevoflurane associated with major epileptoid signs in 50% of patients was calculated using the Dixon method, at 4.3% (1.7 MAC), in 100% of O2. The adjunction of 50% N2O or a bolus of alfentanil seems to have a protective effect (44).

EEG and anesthesia of the infant: some questions

Although the EEG effects of anesthetic agents on patients older than 2 years are similar to those observed in adults, there are unsolved questions for the infant. In fact, most studies of the automated EEG in the infant under anesthesia show results quite different from those in an older child. In the infant, the Fe sevoflurane necessary to reach a steady-state BIS 50 is higher than in a child over 2 years: 1.55% vs 1.25%, and the evolution of the BIS during awakening shows an ‘on-off’ pattern instead of the progressive change seen in older patients (32). Caudal anesthesia causes a diminution of BIS in the child over 2 years at 1.5% sevoflurane, but this effect is not seen in the infant (45). In addition, the differences in BIS seen using halothane vs sevoflurane, at equivalent MAC over the age of 2, are not seen in the infant (46). The EEG of the infant shows episodes of burst suppression (bursts of activity alternating with electrical silence) more frequently than older children (30). These episodes persist up to the clinical wake-up and differ from the older patient who, under deep anesthesia, has prolonged periods of flat EEG. In a similar vein, during sevoflurane anesthesia, cortical neuronal inhibition, evaluated either at a BIS = 50 or with a BSR > 50%, occurs at lower concentrations in the younger infant than in the child. (30). These results emphasize a pharmacodynamic cerebro-cortical difference in the infant, suggesting the earlier appearance of neuronal inhibition, in contrast to a later appearance of subcortical inhibition, as measured by MAC. Presently, the regular and ‘blind’ use of an automated EEG monitor in the infant under the age of 1 requires more clinical and EEG investigation, to define its usefulness in this population. These studies are all the more important given the possible greater susceptibility of this age group to the toxic effects of general anesthetics, extrapolated from animal studies (48–50). As an opening thought in this consideration, one may consider the occurrence of burst suppression in more than 50% of pediatric patients under 2 years of age during routine anesthesia practice, and the fact is that in newborns, these episodes are particularly frequent and prolonged (51).

The limits of the EEG, in monitoring depth of anesthesia

As previously described, the EEG provides information mainly limited to cortical brain activity. Using cortical and subcortical recordings of EEG in patients undergoing neurosurgery, Velly et al. have demonstrated that quantitative parameters derived from cortical EEG but not from the subcortical EEG were able to predict consciousness vs unconsciousness. Conversely, quantitative parameters derived from the subcortical EEG but not from the cortical EEG were able to predict movement in response to laryngoscopy (21). They conclude that in humans, unconsciousness mainly involves the cortical brain, but that suppression of movement in response to noxious stimuli is mediated through the effect of anesthetic agents on subcortical structures. This has important implications for predicting movements with EEG-derived parameters. It is likely that refinements in algorithms for analyzing the EEG will improve our ability to detect consciousness or unconsciousness. But the risk of movement in response to noxious stimulation will probably be much more difficult to assess because it is under the control of brain structures not monitored by the EEG.

On the other hand, Mourisse et al. (20,52) demonstrated that the blink reflex (brainstem function) is more sensitive to sevoflurane than BIS (forebrain function), while tetanic stimulus-induced withdrawal reflex (spinal cord) is less sensitive than BIS. These authors concluded that anesthetics may act differently according to the effect site. Up to now, there are very few pediatric data investigating the relative effect of anesthetics on cortical and subcortical sites. A simple way to consider this issue could be to compare the ratio between surgical MAC and a given target of cortical EEG, that is, a BIS value of 50; this was done by Davidson et al. (31), who have demonstrated an age-related discrepancy between MAC and EEG suppression with a less active EEG relative to MAC gradually as the child grows from one to 12 years; these authors concluded that the relationship between the two differs with brain maturation. Recently, using noninvasive devices, we assessed cortical (BIS derived from EEG) and subcortical (pupillary reflex) response to noxious stimulus in prepubertal children vs young adults. Our data suggested that sensitivity to sevoflurane of some subcortical structures (i.e. mesencephalic control of pupillary reflex dilatation) is lower in children than in older subjects. Interestingly, we found some children with a BIS under 10, and still showing a significant pupillary response to noxious stimulation. These find-
ings suggested that prepubertal children anesthetized with sevoflurane may keep subcortical reactivity to noxious stimulus despite the major cortical inhibition attested by EEG.

Taken together, all these data support Kissin’s view that ‘the search for a reliable index of anesthetic depth should be transformed into a search for separate indices of different components of anesthesia’ (53). So we need an index allowing assessment of subcortical activity, and this activity may be considered at multiple levels, for instance diencephalic, mesencephalic, brain stem. In fact, most of them are based on the investigation of autonomic responses to nociceptive stimulation. Among the emerging clinical devices, we can mention those that assess vascular sympathetic response (skin conductance) (54), cardiac and vascular sympathetic response (Surgical Stress Index) (55), parasympathetic cardiac response (antinociception index) (56), and finally the pupillometry, which is based on the assessment of the pupillary reflex dilatation induced by nociceptive stimulation and seems a more sensitive index than hemodynamic parameters (22).

Conclusions

The EEG is a measurable biorhythm influenced by the internal and external environments of the subject, demonstrating circadian variation and changing with age. The sensitivity of this signal to physiologic and pharmacologic changes, and its oscillatory nature, make it a good subject of mathematical analysis of various types in measuring changes of state of consciousness. Thus the EEG signal, as a pharmacodynamic window on the cerebral cortex, is presently the basic element in evaluation of anesthetic depth, even if the automated mathematical algorithm only quantifies the degree of cortical inhibition (slowing and synchronization) induced by anesthetic agents.

Cerebral maturation is measured as a progressive acceleration of the EEG pattern. In general terms, the pediatric EEG has specific characteristics according to age, but after 2 years, the changes induced by anesthesia are quite similar to those in the adult. Nonetheless, there is a dose dependency related to age.

The two main hypnotic agents used in children, sevoflurane and propofol, show different EEG effects, particularly under deep anesthesia. At higher concentrations, sevoflurane induces significant epileptoid activity, the possible deleterious effect of which remains to be determined.

Over the age of 2, the changes in the EEG in the maturing pediatric population have little influence on the BIS profile compared to that of the adult. However, for a given level of cortical inhibition, children require a higher concentration of anesthetic agent than adults. The pharmacologic implication that the child is less sensitive to anesthetic agents emphasizes the interest in an effective monitoring of central effects of anesthetics in this population.

During infancy, the EEG profile under anesthesia differs markedly from that of the older child. These differences are the subject of numerous current studies, evaluating the effects of anesthetic drugs, in view of concerns raised by animal studies demonstrating a toxic effect of these same agents on the developing brain.

The EEG gives us a useful pharmacodynamic window on the cortical effects of the anesthetics. However, it provides information mainly limited to cortical brain activity. As anesthetics act on both cortical (conscious processes) and subcortical (nonconscious processes) structures, we need indices that investigate subcortical processes, for instance by assessment of autonomic responses to nociception.

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References

EEG in pediatric anesthesia

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