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How Electroencephalography Serves the Anesthesiologist

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Abstract

Major clinical endpoints of general anesthesia, such as the alteration of consciousness, are achieved through effects of anesthetic agents on the central nervous system, and, more precisely, on the brain. Historically, clinicians and researchers have always been interested in quantifying and characterizing those effects through recordings of surface brain electrical activity, namely electroencephalography (EEG). Over decades of research, the complex signal has been dissected to extract its core substance, with significant advances in the interpretation of the information it may contain. Methodological, engineering, statistical, mathematical, and computer progress now furnishes advanced tools that not only allow quantification of the effects of anesthesia, but also shed light on some aspects of anesthetic mechanisms. In this article, we will review how advanced EEG serves the anesthesiologist in that respect, but will not review other intraoperative utilities that have no direct relationship with consciousness, such as monitoring of brain and spinal cord integrity. We will start with a reminder of anesthestic effects on raw EEG and its time and frequency domain components, as well as a summary of the EEG analysis techniques of use for the anesthesiologist. This will introduce the description of the use of EEG to assess the depth of the hypnotic and anti-nociceptive components of anesthesia, and its clinical utility. The last part will describe the use of EEG for the understanding of mechanisms of anesthesia-induced alteration of consciousness. We will see how, eventually in association with transcranial magnetic stimulation, it allows exploring functional cerebral networks during anesthesia. We will also see how EEG recordings during anesthesia, and their sophisticated analysis, may help corroborate current theories of mental content generation.

Keywords

electroencephalography, general anesthesia mechanisms, anesthesia monitoring depth

Introduction

The first observations of the effects of anesthetic agents on the EEG occurred soon after the development of clinical EEG, at the beginning of the 20th century.[1] Interest in this noninvasive tool for exploring brain activity, and measuring the effects of anesthesia, became rapidly evident. However, the complexity of the EEG signal and its interpretation, as well as its high sensitivity to various types of perturbations, prevented rapid development of routine clinical applicability within the anesthesia field. Its intraoperative use remained limited to a small number of specialized research teams. A resurgence of interest took place at the end of the 20th century, with the development of EEG-derived indices that were aimed at simplifying EEG interpretation during anesthesia. The advent of digitization and computerization of the signal permitted the definition of specific EEG parameters, whose evolution through the course of anesthesia was correlated to the intensity of the desired effects of anesthetic agents, such as the alteration of consciousness.[2] Using mathematical algorithms, the combination of those parameters gave birth to dimensionless indices of the depth of specific components of general anesthesia. Simultaneously, and particularly during the past 10 years, technological advances progressively, and more thoroughly, dissected the EEG signal. High-density EEG and channel multiplication improved space resolution, allowed identifying sources of activity, and provided a better topographical definition

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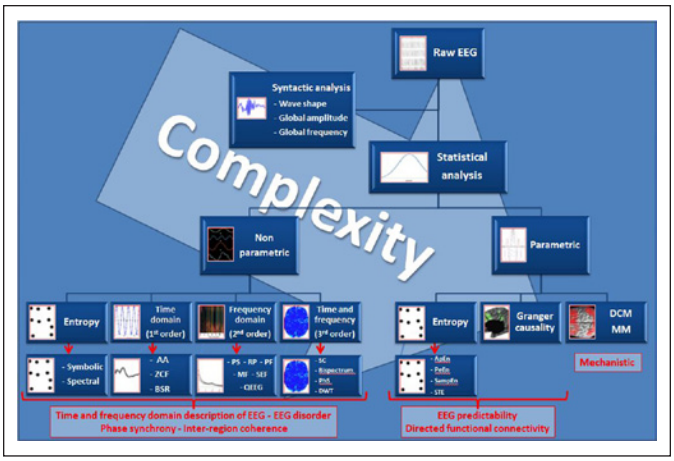

Figure 1. Summary of the approaches to EEG analysis as applied to anesthesia, and examples of derived parameters, as well as type of information provided by each kind of analysis. Derived from the classification by Rampil.[111] Besides syntactic analysis, which describes frequency, amplitude, and shape of the global signal, digitization of the EEG allows mathematical and statistical analysis. Nonparametric analysis extracts signal descriptors from time domain and frequency domain information, or from the estimated disorder into the signal. The parametric approach constructs statistical models that look at the ability of a given signal to predict another one.[111]
Abbreviations: Symbolic, symbolic entropy; Spectral, spectral entropy; AA, average amplitude; ZCF, zero crossing frequency; BSR, burst suppression ratio; PS, power spectrum; RP, relative power; PF, peak frequency; MF, median frequency; SEF, spectral edge frequency; QEEG, quantitative EEG; SC, spatial coherence; PhS, phase synchrony; DWT, discrete wavelet transform; ApEn, approximate entropy; PeEn, permutation entropy; SampEn, sample entropy; STE, symbolic transfer entropy; DCM, dynamic causal modeling; MM, meanfield modeling.

of anesthesia-induced changes. In addition, the detection of functional and effective interactions between brain regions defined the so-called functional and effective connectivity,[3] which is thought to play an important role in supporting higher order brain functions.[4]

Hence, besides increasing clinical interest with regard to monitoring of anesthetic drug effects, advanced EEG, alone or in combination with other techniques such as transcranial magnetic stimulation, has gained major importance in exploring the mechanisms of general anesthesia, with, consequently, implications for the understanding of the mechanisms of mental content generation. In this article, we will focus on those 2 specific aspects of advanced anesthesia-applied EEG.

Approaches to EEG Analysis of Current Use in the Anesthesia Field

The analysis of the EEG applied to anesthesia can be decomposed into different categories, according to the considered approach (Figure 1). The first descriptions of the anesthetic effects on the EEG were syntactic, or semantic, dealing with wave shape, amplitude, and global frequency. The progressive definition of time and frequency domain parameters led to a more detailed analysis of anesthesia-induced changes. As dose increases, anesthetic agents with hypnotic properties gradually modify the EEG, both in the time and frequency domain, and produce specific wave shapes. The description of EEG complexity through a time domain approach with parameters such as total power or zero crossing frequency is limited.[5] Hence, a more precise description has been sought for using a frequency domain approach. Induced changes in the frequency domain are classically considered to be biphasic,[1] at least for hypnotic agents that are presumed to act through the promotion of GABAergic inhibitory neurotransmission.[6] At low doses, EEG desynchronizes and accelerates to frequencies between 13 and 30 Hz. This is known as β activation. The EEG then slows down toward δ activity (0.5-4 Hz) and its amplitude decreases.[7] With propofol, a frequently used hypnotic agent, the observed slow waves resemble the slow waves of physiological sleep, but are spatially limited. At deeper stages, bursts followed by periods of flat signal occur, an EEG pattern known as burst suppression that can be quantified using the burst suppression ratio (proportion of the length of a signal epoch where the amplitude is below a specified voltage). Higher dosages of hypnotic agents are associated with isoelectricity.[5] Waxing and waning 12- to 15-Hz oscillations lasting for at least half a second, known as sleep-like spindles, can also be observed,[8] but their presence is not systematic.[7] Power in the γ range (>25 Hz)[9] displays variable modifications during anesthesia, depending on the hypnotic agent, the brain region, and the exact limits of the studied frequency band. With propofol, at intermediate doses, an increase in γ power has been described.[7] The alterations of first-order (time domain) and second-order (frequency domain) EEG parameters are not homogenously distributed over the scalp. Quantitative EEG (QEEG) studies have described the topographical distribution of frequency domain alterations during anesthesia,[9] showing a frontal predominance for most studied parameters.[10] For example, during propofol sedation, activity in the α range progressively disappears in the occipital part of the brain while progressively increasing in the frontal region. In addition, phase-amplitude relationships in the α and β range display reproducible modifications during consciousness-unconsciousness transitions.[11]

Several other parameters can be extracted from the dissection of the EEG signal into its frequency components, and from the estimation of the relative contribution of each component to the global signal, namely the power spectrum of the EEG.[5] Examples of such parameters are the peak frequency (the one with the highest power), the median frequency (50% of power is achieved by lower frequencies, and 50 % by higher ones), and the spectral edge frequency (a specified percentage of the power is achieved by lower frequencies, generally 90% or 95 %). Time and frequency domain description of the EEG can also be obtained through the use of discrete wavelet transform and eigenvector analysis.[12,13] It consists in deriving a number of coefficients that best correspond to time and frequency domain information contained in a signal epoch.

Higher orders of time and frequency domain analysis have also been studied during anesthesia, such as coherence,[9] a measure of synchronization between brain regions at a given

frequency range, bispectrum,[1] a measure of phase correlation between different frequency components, or phase synchrony.[14] The physiological significance of those parameters is still not known with certainty, but their changes over sequential transitions between different anesthestic stages are consistent and reproducible. The inter-region coherence in the gamma band may be modified during anesthesia,[15] while phase synchrony has been shown to increase in the θ, α, and γ frequency band during propofol-induced loss of consciousness.[7,16]

When administered to patients, some hypnotic anesthetic agents may produce different EEG patterns than those described above. For example, ketamine, although reducing α activity (8-13 Hz), induces high-amplitude rhythmic θ activity (4-10 Hz), polymorphic δ activity, and scattered β activity.[17] The α_2-adrenergic agonists such as clonidine or dexmedetomidine increase δ and θ power, as well as the activity in the spindle frequency range (12-15 Hz).[18] The observed differences between agents are certainly related to differences regarding their mechanism of action.

Another approach to EEG analysis during anesthesia consists in estimating the underlying disorder into the signal, a physical concept named entropy. Intuitively, one may easily understand that EEG disorder will be higher in an awake individual as compared with an anesthetized unconscious one. EEG entropy can be calculated by EEG amplitude (Shannon or symbolic entropy), or by power spectrum (spectral entropy).[2] The third type of entropy estimation is based on the prediction of future amplitudes according to previous ones, and hence estimates the stability of the system. During anesthesia, the EEG tracing is more predictable than during the awake state. This principle has been applied to calculate the approximate entropy,[19] the sample entropy,[20] and the permutation entropy.[21] All these 3 types of entropy are based on single channel recordings.

Besides parameters that describe the EEG in the time and frequency domain, or describe the complexity of a single electrode EEG signal, other types of analyses may extract supplementary information and add the dimension of interactions between brain regions. Contrary to the other types of entropy, symbolic transfer entropy looks at causality between signals recorded at different sites, and hence allows exploitation of directed functional connectivity between brain regions.[22] However, symbolic transfer entropy is an oversimplification of Granger causality analysis.[23] Granger causality establishes a statistical link between the activity observed in a specific region and the activity recorded previously in another region.[23] It has allowed evidencing directed functional connectivity alterations during propofol anesthesia.[14] Other methods such as dynamic causal modeling[3,23] and meanfield modeling,[24] add a mechanistic dimension to the exploration of connectivity. They necessitate the a priori construction of mechanistic models that describe the coupling among brain regions. The task then consists in identifying the model that best fit the recorded data.

As illustrated above, an in depth dissection of the EEG signal is able to provide a huge amount of information. This information may be of variable nature, ranging from numerical signal descriptors whose combination reflects a specific state of brain activity, to statistical maps describing spatial coherence or phase synchrony between or within brain regions, statistical maps describing functional connectivity, or mechanistic models. Evidently, the information driven from the EEG may serve either to measure anesthetic drug effects, or explore the mechanisms of anesthetic action on the brain.

Assessing Depth of Anesthesia Using EEG

The administration of anesthetic agents to patients aims at allowing them to tolerate unpleasant and painful interventions, while facilitating the surgical procedure and avoiding complications. This is achieved through several pharmacodynamic effects of anesthetic agents including, among others, an alteration of consciousness (the hypnotic effect of anesthesia), immobility (essentially achieved through muscle relaxation), and limitation of reactions to noxious surgical stimulation (or anti-nociception). Depending on anesthetic agent combinations, doses, and inherent properties, each pharmacodynamic component of anesthesia may be more or less pronounced. Changing the combination allows adapting anesthesia to circumstances. Hence, when referring to depth of anesthesia, one must be precise over the concerned pharmacodynamic element.[25,26] In that respect, being able to separately and specifically monitor each pharmacodynamic component of anesthesia, and modify anesthetic agent administration accordingly, would be ideal. Muscle relaxation can easily and reliably be assessed by peripheral neurostimulation and recording of muscle response, and is beyond the scope of this review. The other 2 main components of anesthesia, namely hypnosis and anti-nociception, may be approached through EEG recording and analysis.

The Hypnotic Component: Prevention of Intraoperative Awareness

The fear of unexpected intraoperative awareness, and the wish to prevent patients from experiencing such a traumatic event, has long prompted anesthesiologists to search for efficient prevention means. During anesthesia, the observation of common clinical alerts such as increased blood pressure, heart rate, tears, or movements is not sensitive and specific enough to achieve a reasonable degree of security. The reasons for this are myriad: pharmacodynamic effects of anesthesia interact with each other (eg, the level of hypnosis is influenced by the amount of noxious stimulation), the pharmacodynamic properties of anesthetic agents are variable, there exists interindividual variability in sensitivity to the effects of anesthetic agents, and patients often receive nonanesthetic medications with effects on clinical signs that are not related to the depth of one component of anesthesia or the other.[25] Furthermore, consciousness is likely influenced by, but not directly related to, autonomic system activity, dissociating these signs from consciousness mechanistically.

Considering its sensitivity to the effects of anesthetic agents, EEG was the first noninvasive recording to catch anesthesiologists' attention in that domain. Interpreting single or multiple channels raw EEG is not within easy reach of untrained clinicians, though with training this can be overcome. In addition, single time and frequency domain parameters often have poor prediction ability regarding depth of hypnosis,[27] prompting the idea of developing dimensionless indices whose value would correlate with depth of the hypnotic component of anesthesia.

Commercially Available Dimensionless Indices. The general principle governing construction of EEG-derived dimensionless indices is based on the extraction of parameters from the EEG whose value is known to be statistically correlated with anesthetic agent concentration and/or clinically assessed depth of hypnosis. These parameters then enter a mathematical algorithm whose output is a normalized index. The index is generally a number varying between 0 and 100, or a letter indicating anesthetic stage. Currently, at least 7 different indices of that type are available on the market, namely the Bispectral Index (BIS, Covidien plc, Dublin, Ireland), the M-Entropy (RE and SE, Datex Ohmeda Inc, GE Healthcare, Madison, WI), the Patient State Index (PSI, SEDline, Masimo Corp, Irvine, CA), the Cerebral State Index (CSI, Danmeter-Goalwick, Odense, Denmark), the Narcotrend (Arbeitsgruppe Informatik/Biometrie der Anästhesieim Klinikum Region Hannover Oststadt-Heidehaus, Hannover, Germany), the WAV_{CNS} (NeuroSense, NeuroWave Systems Inc, Cleveland, OH), and the aepEX (Medical Device Management Ltd, Essex, UK; Table 1). Several of these are generated through a patent-protected algorithm, whose details are not entirely divulged.

Historically, BIS was the first, and has been studied the most. Its calculation algorithm has evolved over time to ameliorate artifact rejection and reliability. It involves power spectrum, relative activity in the β frequency range, burst suppression activity, synchronized fast slow activity, and bispectrum.[28]

The spectral entropy of the EEG is calculated on the power spectrum, using the Shannon function. The calculation is performed over two different frequency bands to generate 2 different normalized numbers: the Response Entropy (RE; 0.8- to 47-Hz band), and the State Entropy (SE; 0.8- to 32-Hz band).[29] RE and SE are independent of the frequency and amplitude scales of the EEG signal. SE ranges between 0 and 91, is mainly based on cortical EEG activity, and is supposed to reflect the depth of the hypnotic component of anesthesia. In addition to EEG activity, RE takes account of facial EMG activity, which increases in case of non-counterbalanced noxious stimulation. RE ranges between 0 and 100, and is always higher or equal to SE. Its gradient with SE has been proposed to reflect the balance between nociception and anti-nociception during anesthesia.[30]

The PSI is derived from 4 EEG channels, and has been designed to be less dependent on anesthetic drug combination.[31] The PSI algorithm incorporates relative activity in specific frequency bands, interhemispheric coherence information, as well as anteroposterior frequency and phase relationships. It takes account of the frontal localization of power spectrum changes during anesthesia. The output of the algorithm is, again, a dimensionless number between 0 and 100.[32]

Cerebral State Index calculation involves relative α and β powers, the difference between them, and the importance of burst suppression.[33,34] The system automatically selects the best parameter to be used. Correspondence between CSI values and depth of the hypnotic component of anesthesia are well defined. The delay between EEG acquisition and index output is approximately 15 seconds.

The concepts governing the development of the Narcotrend were slightly different from the above-described indices. Six different visually recognizable EEG patterns were initially identified as corresponding to different sleep stages. They were further divided into a total of 15 different patterns evidenced during anesthesia. Each of these stages was then characterized by a set of EEG parameters, including spectrum, entropy, and autoregression. The output is a number between 0 and 100, as well as a letter corresponding to the anesthetic stage. This index seems to be more appropriate for propofol-based anesthesia than for anesthesia induced by volatile agents.

A wavelet analysis, which captures both time and frequency domain information on the EEG signal in the form of wavelet coefficients, is used to calculate the WAV_{CNS} (Wavelet-based Anesthetic Value for Central Nervous System monitoring).[12,13] The result is a 0 to 100 index with high stability in time during steady-state anesthesia and linear evolution during the transition from the awake state to isoelectricity. The reaction time of that index is shorter than the reaction time of BIS.

The aepEX uses a different approach. It necessitates the administration of 7-Hz auditory clicks to the patient through earphones. Middle latency auditory evoked potentials are extracted from the raw EEG using a moving averaging window. The index is then calculated based on the amplitude and latency of those evoked potentials,[35,36] knowing that amplitude decreases and latency increases with hypnotic depth.

Clinical Utility of EEG Indices During Anesthesia. The debate on the prevention of intraoperative awareness.

The use of EEG indices correlating with hypnotic anesthetic agent pharmacodynamic effects or anesthetic stages is appealing. From the beginning of their availability, a potential utility of those indices to prevent unexpected intraoperative awareness with explicit recall has been foreseen. Demonstrating such utility was not straightforward, and this was because of 3 main reasons (Table 2).

First, unexpected intraoperative awareness is a relatively rare event, with an overall estimated incidence of approximately 0.2%. Hence, large studies, preferably randomized control trials, were needed to demonstrate any potential benefit of using those monitors for prevention. Those studies are now available, and show conflicting results.[37-42] According to Avidan and Mashour,[43] an in-depth analysis of those studies leads to the conclusion that an EEG-driven administration of intravenous hypnotic anesthetic agents helps prevent unexpected intraoperative awareness with explicit recall, at least in patients at higher risk of experiencing such an event. However,

Table 1. Principal Commercially Available Monitors of the Depth of the Hypnotic Component of Anesthesia, With Parameters Entering Their Calculation Algorithm, and Reference Values.

Name	Involved Parameters	Range of Values	Classically Defined Thresholds	ADD (Seconds)
BIS	• Relative β activity • SFS activity • Quasi-flat activity • BS activity • Bispectrum	0-100	Wake state: >93 LOR: 80 RIV: 40-60	30-60
RE-SE	• Power spectrum • Shannon equation • RE: 0.8-47 Hz • SE: 0.8-32 Hz	RE: 0-100 SE: 0-91	RIV: <60	2-60[a]
PSI	• Power spectrum • IHC • APFPR	0-100	Wake state: > 90 Surgery: 40-50 Eyes opening: 80	50
CSI	• α and β ratio • α − β difference • Burst suppression	0-100	Wake state: 90-100 Drowsy: 80-90 Light sedation: 60-80 RIV: 40-60 Deep: 10-40 Very deep: 0-10	15
Narcotrend	• Spectral • Entropy • Autoregressive	0-100 Letter	Wake state: A, B0 Sedation: B1, B2 Light anesthesia: C0 to C2 General anesthesia: D0 to D2 Deep hypnosis: E0 to E2 Burst suppression: F0, F1	20
WAV_{CNS}	• Wavelet coefficients	0-100	Linear relationship between wake state and EEG iso-electricity	15-30
aepEX	• MLAEP latency and amplitude	0-99	Full wake state: 99 No brain activity: 0	0.144

Abbreviations: ADD, average delay between signal recording and index display on the screen; SFS, synchronized fast slow; BS, burst suppression; LOR, loss of responsiveness; RIV, recommended intraoperative value; RE, response entropy; SE, state entropy; IHC, interhemispheric coherence; APFPR, anteroposterior frequency and phase relationships; MLAEP, middle latency auditory evoked potentials.
[a]Increases for lower frequencies.

Table 2. Factors Limiting the Ability to Demonstrate Usefulness of EEG-Derived Indices for the Prevention of Unexpected Intraoperative Awareness With Explicit Recall.

Factor	Detail	Solution	Current Implication
Low incidence of UAER	0.2% overall	Large randomized control trials	More efficient for IV anesthesia No superiority over ETACM for inhaled anesthesia
Factors confounding interpretation of displayed value	• Electrical artifacts • Interindividual variability • Site of recording • Delay for value display • Hypothermia • Hypoglycemia • Cortical atrophy • Age • Seizures • Carotid clamping • Cerebral ischemia • Interactions • . . .	Artifact rejection Detailed definition of situations where interpretation is difficult Better models of interactions	Good knowledge of limitations for optimal use
Definition of loss of consciousness during anesthesia	• Consciousness • Connectedness • Responsiveness	Search for witnesses of the integrity of physiological substrates sustaining consciousness, connectedness, and responsiveness	Ongoing active research

Abbreviations: UAER, unexpected intraoperative awareness with explicit recall; IV, intravenous; ETACM, end-tidal anesthetic agent concentration monitoring.

when volatile anesthetic agents are used, monitoring their end-tidal concentration, which reflects concentrations attained in the brain, and setting low concentration alarms is at least as efficient at achieving the same goal. The difference between intravenous and volatile agents may be explained by a larger interindividual variability of the minimal effective concentration for intravenous agents compared with volatile agents.

Second, several confounding factors may impede the interpretation of EEG-derived indices, and may lead to erroneous conclusions regarding real depth of the hypnotic component of anesthesia. They include artifacts from surrounding electrical devices, interindividual variability in terms of baseline EEG characteristics, erroneous site of EEG recording, delay between EEG acquisition and value display,[44-46] and specific clinical conditions such as hypothermia, hypoglycemia, dementia, cortical atrophy, advanced age,[47] seizures, carotid clamping, and cerebral ischemia.[25] In addition, the effect of the interactions between anesthetic medications on the index value is often not much considered but is important. For example, an observed BIS value of 40 does not mean the same in the presence of high anti-nociceptive agent concentration and relatively low hypnotic agent concentration, or in the presence of the inverse.[48] In the latter, the patient may be at higher risk of reacting to noxious stimulation, and perhaps waking up, than in the first case. Other medications, such as ketamine,[49,50] nitrous oxide,[17] and muscle relaxants, may also paradoxically modify the index value.[51,52]

Third, there has long been confusion regarding the definition of consciousness or loss of consciousness during anesthesia. From an operational point of view, it seems reasonable to distinguish between different concepts that are relevant to anesthesia,[53] namely consciousness, connectedness, and responsiveness, which are often mixed up, even in the anesthetic literature.[54] Consciousness corresponds to subjective experience, connectedness to the awareness of the environment and of external stimuli (as opposed to experience triggered by internal thoughts, dreams, and imaginings), and responsiveness movement by the patient be it spontaneous or goal-directed behavior. During anesthesia, consciousness is not necessarily associated with connectedness, responsiveness, or even recall. Connected consciousness describes experience of surgery or external stimuli during anesthesia. Different physiological substrates and mechanisms sustain the presence or the absence of such abilities. As we will describe below, consciousness likely depends on the integrity of corticothalamic networks, while spontaneous responsiveness may depend on subcortical and spinal cord networks. The mechanisms underlying connectedness remain more obscure, but may depend on specific neuromodulators and corticothalamic circuits. Searching for specific signs of the integrity of each of them could help better detect the presence or absence of connected consciousness during anesthesia, and hence prevent patients from being conscious of their surgical procedure.

It appears that EEG-derived indices of the depth of the hypnotic component of anesthesia are far from being a panacea, and that improvements are needed to optimize their clinical use with regard to detection of unexpected intraoperative connectedness. At the present time, other clinical utilities may further justify their regular usage.

Other clinical utilities. No superiority of one type of monitor over the other has been evidenced. Insofar as they measure an effect of medications, they should allow individual titration, avoid episodes of overdosage,[55] and hasten recovery when the procedure has come to its end,[56] with less side effects. Although large randomized control studies have failed to corroborate such beneficial effects,[43] they were not controlling for interactions between anesthetic medications. If anesthesia is achieved using high doses of hypnotic agents and low doses of anti-nociceptive agents, one may expect that EEG-guided titration will be less efficient at limiting hypnotic agent consumption than in situations with tightly controlled anti-nociception.[57] Controlling for overdosage may prove important, since an association has been found between prolonged time with low EEG indices during anesthesia, and long-term outcome,[58-61] but not with absolute amount of anesthetic agent received. However, this may reflect an intrinsic sensitivity of the brain to the effect of anesthetic agents in vulnerable patients. Hence, cause and effect remain far from established. Nonetheless, the ease of titration may even be further improved in the future, when closed-loop administration systems will be available for routine use .[62-68]

The Future. As stated above, there is a need for a refinement in the detection of the presence or absence of connected consciousness during anesthesia. A necessary step for achieving this goal is a detailed understanding of anesthesia-induced alteration of consciousness, connectedness, and responsiveness,[53] and a better definition of endpoints when designing studies in that domain. Recent advances in EEG analysis may provide the means to develop specific monitors of cortical connectivity, and particularly of fronto-parietal feedback connectivity, which is thought to be a sign of consciousness, but not necessarily of connectedness.[69,70] High-density EEG, transcranial magnetic stimulation,[4] Granger causality,[23,71] symbolic transfer entropy,[22] permutation entropy,[21] and others might be the route to follow, but these techniques must be refined and/or simplified before used in daily practice. Monitoring connectedness is not accessible the same way, and evoked potentials could be an alternative in that case.[53] Finally, Purdon et al[11] have recently proposed a refined analysis of phase-amplitude relationships, and topographical distribution of power spectrum that identifies signatures of the presence or the absence of responsiveness during anesthesia.[11]

The Balance Between Noxious Stimulation and Anti-Nociception

In an attempt to better titrate anti-nociception individually, there is currently intense effort to develop specific monitors of this pharmacodynamic component of anesthesia.[72] Based on known repercussions of noxious stimulation (Figure 2), 4 types of parameters are investigated, namely signs of autonomic response

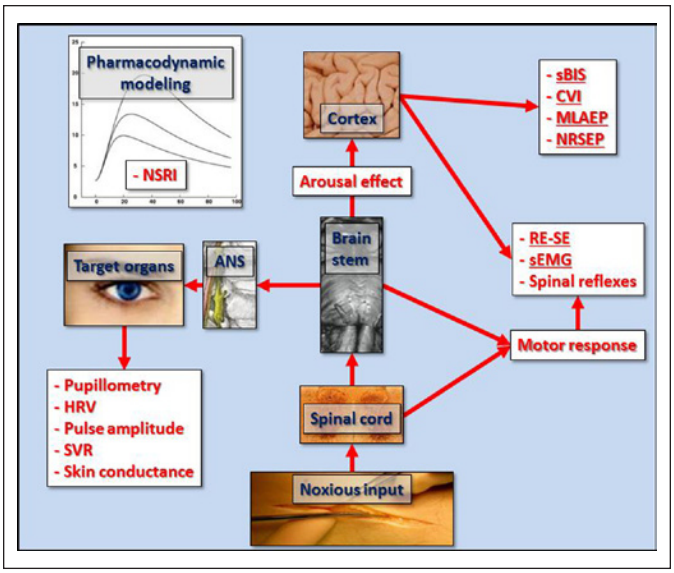

Figure 2. Principles of nociception balance monitoring. Underlined parameters are those obtainable through EEG recordings. Noxious input evokes a motor response emerging from the spinal cord and the brainstem, and leading to spinal reflexes and an increase in electromyographic (EMG) power. Noxious input to the cortex produces an arousal effect and an increase in EEG variability. Noxious input also has an impact on the autonomic nervous system and its target organs such as the pupils, and the cardiovascular system. Pharmacodynamic modeling allows designing theoretical indices that correlate with the probability of a patient response to noxious stimulation.

NSRI, Noxious Stimulation Response Index; ANS, autonomic nervous system; HRV, heart rate variability; SVR, skin vasomotor reflex; sBIS, Bispectral Index variability; CVI, Composite Variability Index; MLAEP, middle latency auditory evoked potentials; NRSEP, nociception-related somatosensory evoked potentials; RE-SE, gradient between response and state spectral entropy of the EEG; sEMG, variability of electromyographic activity.

to noxious stimulation, signs of withdrawal motor response, evoked potentials, and EEG variability. The first 2 types include parameters such as pupil diameter,[73] heart rate variability,[74,75] skin vasomotor reflex,[76] skin conductance,[77] spinal reflexes,[78,79] and indices combining heart rate and pulse amplitude.[80-84] These parameters have proven ability to appreciate the balance between noxious stimulation and anti-nociception to a certain degree, or being able to predict patient motor response to noxious stimulation, but their interpretation may sometimes be affected by confounding factors.[85-87] Other concepts use pharmacodynamic interaction modeling to derive theoretical indices of nociception, but do not involve physiological measurements (Noxious Stimulation Response Index, NSRI).[88,89]

Describing all these new indices in detail is beyond the scope of this review, because they are not related to the EEG. However, the latter may also provide information on nociception, either through the recording of evoked potentials, or through the study of EEG variability. Nociception-related somatosensory evoked potentials are sensitive to the noxious stimulation–anti-nociception balance,[90] but their recording is not easy in the electrically hostile environment of an operating theater. Middle latency auditory evoked potentials, and derived indices, may also provide information on the level of anti-nociception.[91] Their early variation in response to noxious stimulation, as compared to BIS, may simply be due to the arousal effect of noxious stimulation and shorter delay for index calculation. Recent interest has emerged regarding BIS and electromyographic (EMG) variability, or an index combining both parameters (the Composite Variability Index, CVI), at assessing the adequacy of anti-nociception during anesthesia.[92] Again, the idea behind it is the arousal effect of noxious stimulation, and hence its effect on BIS value, and the evocation of a motor reflex that would translate into an increase in EMG activity. BIS variability can be estimated using the standard deviation of BIS values recorded during the previous 3 minutes. EMG variability corresponds to the standard deviation of EMG power over the same period of time. CVI is a normalized index ranging between 0 and 100. The algorithm for its calculation has been designed according to the ability of subparameters to predict the occurrence of a somatic event (or patient movement) in response to noxious stimulation. This new tool still needs clinical validation with respect to the influence of muscle relaxation on its value, reliability of considering patient movement as a surrogate of inadequate anti-nociception, efficacy at guiding anti-nociceptive agent administration, and effect on outcome.[93] The last EEG-derived parameter proposed to assess anti-nociception is the aforementioned RE-SE gradient of Spectral Entropy.[94] The same restrictions as those described for CVI also apply to RE-SE, and particularly the effect of muscle relaxation.[49,95-97]

Functional Exploration of the Brain During Anesthesia Using EEG

Exploring Functional Connectivity

EEG studies have contributed to the considerable progress that has recently been made in the understanding of the mechanisms of anesthesia-induced alteration of consciousness.[6,98,99] The advantage of EEG over other techniques, is that it allows exploring functional effective connectivity, or causal influence, between brain regions rather than statistical dependencies in changes of indirect signs of regional brain activity.[23] From a holistic view, concepts have evolved toward dose-dependent targeted effects of hypnotic agents on brain functional assemblies sustaining consciousness. Following the demonstration that the cortex was affected by hypnotic agents at lower doses than subcortical structures,[100] and that higher order cortical association areas were more sensitive to that effect than lower order ones,[101] the first evidence of altered connectivity into thalamocortical networks sustaining consciousness came from high-density EEG studies combined with transcranial magnetic stimulation.[4] These findings were further confirmed by functional magnetic resonance imaging studies describing dose-dependent connectivity alterations into the Default Mode Network (DMN, involved in self-awareness), and in the Executive Control Network (ECN, involved in the awareness of the environment), while connectivity in lower order sensory networks was preserved.[102] Granger causality and dynamic

causal models applied to EEG recordings during anesthesia also confirmed the preferential inhibition of frontoparietal feedback connectivity, an element of consciousness networks,[22] while thalamocortical connectivity specific to those networks was shown to be preserved[3] at doses that induce unresponsiveness. That connectivity requires higher doses to disappear.[53] Contrarily, the nonspecific thalamocortical connectivity involved in cortical arousal is early inhibited.[103] In other networks, such as the lower order visual and auditory networks, functional connectivity, including thalamocortical connectivity, is relatively resistant to the action of hypnotic anesthetic agents,[102] but cross-modal interactions are altered. All these changes may occur through deregulation of subcortical thalamo-regulatory systems involving the putamen.[104]

Despite a current better definition of what happens during anesthesia, the exact sequence of events remains to be determined. The link with known effects of hypnotic agents on subcortical systems sustaining arousal or promoting sleep is still not known with precision.[6] Primary effects of anesthesia may occur at the cortical level with secondary effects on subcortical systems, but the inverse could also be true. Locally, cortical neuronal networks remain intact but become isolated from other brain regions,[105] and this could be the consequence of a direct effect of hypnotic agents on the cortex, or the consequence of an indirect effect on subcortical structures. On emergence from anesthesia, connectivity recovery does not seem to simply follow the inverse of what happens during induction of anesthesia.[103,106] These differential dynamics between induction and recovery remain to be precisely defined. Finally, the exact link between biochemical targets of anesthetic agents and observed functional effects is still in the dark.

The whole picture of functional alterations during anesthesia is therefore far from being entirely understood. For a better comprehension of these mechanisms, there is a need for additional studies that should ideally be designed according to the operational concepts of consciousness, connectedness, and responsiveness,[53] and investigate dynamic changes rather than steady states.

EEG and Theories of Consciousness

The reversibility of anesthesia, and the study of anesthesia-induced EEG modifications, is a unique tool for studying consciousness, and for corroborating or invalidating conceptual theories about that state. For example, the reversible breakdown of connectivity into corticothalamic networks during anesthesia[4] fits in the integrated information theory (IIT).[107] Like most respected theories of consciousness, IIT postulates that consciousness is generated by corticothalamic networks. Specialized cortical areas can distinguish among a large repertoire of information, and connections within and between those areas allows integration of information. The breakdown of connectivity during anesthesia, and the associated loss of consciousness reinforce the hypotheses of ITT. Another example is the global workspace theory (GWT).[108] GWT hypothesizes that specialized brain regions share their information into a global workspace. Attention then brings one element of that information or the other from the backstage to the front of the conscious scene. The discovery of frontoparietal connectivity alterations during anesthesia,[22] which is thought to represent a global workspace breakdown, provides support to GWT.[109] The third example is the theory explaining the ability of the brain to bind information into a single unified percept.[15] This binding would occur through a hierarchical processing of information from lower order neurons to higher order ones (convergence), from lower order cell assemblies to higher order ones (assembly), and at a global level (synchrony). Oscillations in the γ frequency range would be the landmark of synchrony. The suppression of γ oscillations during anesthesia would be responsible for the unbinding of information, and therefore for the loss of consciousness. All those theories constitute at least parts of the substrate of consciousness, but their unification is not yet within easy reach. Several features of consciousness still require formal theoretical explanations, and the ability to get access to their quantification and measurement.[110] Anesthesia and EEG will more than probably help progress in that domain.

Conclusions

As demonstrated in this review, EEG provides a huge amount of information to the anesthesiologist, either for routine clinical practice or for the understanding of the mechanisms of anesthesia. There is still a lot of work to be performed in both domains, for refining the way we provide anesthesia to our patients, avoid undesirable events, hopefully improve outcome, and understand what we do every day. EEG will be of great help to achieve these goals in the near future.

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