Effects of noxious stimulation on the electroencephalogram during general anaesthesia: a narrative review and approach to analgesic titration

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Summary

Electroencephalographic (EEG) activity is used to monitor the neurophysiology of the brain, which is a target organ of general anaesthesia. Besides its use in evaluating hypnotic states, neurophysiologic reactions to noxious stimulation can also be observed in the EEG. Recognising and understanding these responses could help optimise intraoperative analgesic management. This review describes three types of changes in the EEG induced by noxious stimulation when the patient is under general anaesthesia: (1) beta arousal, (2) (paradoxical) delta arousal, and (3) alpha dropout. Beta arousal is an increase in EEG power in the beta-frequency band (12–25 Hz) in response to noxious stimulation, especially at lower doses of anaesthetic drugs in the absence of opioids. It is usually indicative of a cortical depolarisation and increased cortical activity. At higher concentrations of anaesthetic drug, and with insufficient opioids, delta arousal (increased power in the delta band [0.5–4 Hz]) and alpha dropout (decreased alpha power [8–12 Hz]) are associated with noxious stimuli. The mechanisms of delta arousal are not well understood, but the midbrain reticular formation seems to play a role. Alpha dropout may indicate a return of thalamocortical communication, from an idling mode to an operational mode. Each of these EEG changes reflect an incomplete modulation of pain signals and can be mitigated by administration of opioid or the use of regional anaesthesia techniques. Future studies should evaluate whether titrating analgesic drugs in response to these EEG signals reduces postoperative pain and influences other postoperative outcomes, including the potential development of chronic pain.

Keywords: analgesia; arousal; electroencephalogram; general anaesthesia; monitor; noxious stimulation

Editor's key points

- Nociception-induced changes in the EEG include beta arousal, delta arousal, and alpha dropout patterns.
- This review focuses on the above EEG patterns, and discusses potential implications for analgesia management and insights for future research.

Noxious stimulation influences the EEG

It is expected that patients undergoing surgery with general anaesthesia should neither experience nor remember the
Current state of analgesia monitoring in the operating theatre

Using EEG-derived information from a patient undergoing surgery is becoming more and more common to help navigate general anaesthesia. With some exceptions, available EEG-based monitors focus on the hypnotic component of anaesthesia. This is done by tracking the changes from low-amplitude, high-frequency activity during wakefulness to high amplitude, low frequency activity during anaesthesia levels adequate to perform surgery. The most widely used indices are the Patient State Index (PSI); Sedline, Masimo, Irvine, CA, USA), the bispectral index (BIS; Medtronic, Dublin, Ireland), and the state and response entropy (SE/RE, GE Healthcare, Helsinki, Finland). By design, these monitoring systems do not explicitly focus on EEG changes caused by noxious stimulation. Because these systems are designed to measure the relative high frequency EEG power, they are reasonably sensitive in detecting beta arousal after noxious stimuli, but less sensitive for detecting the changes in lower frequency activity that can occur with stimulation (e.g. delta arousal or an alpha dropout).

Studies using processed EEG indices are summarised in Table 1. Previous research with the BIS demonstrated a failure to detect noxious stimuli during volatile anaesthesia, whereas a specific focus on EEG alpha band features was successful. The challenge for developing a more holistic EEG-based monitoring system is to include algorithms that can detect all the different patterns of EEG changes induced by noxious stimulation. Most commercially available pain monitoring systems do not use EEG parameters. Instead, they include heart rate variability, modelled drug and opioid concentrations, the polysynaptic spinal withdrawal reflex, plethysmographic pulse wave amplitude, and the heartbeat interval, or a multivariate model from EEG, BIS, blood pressure and other factors. Recently the nociception level (NoL) index has been developed which amalgamates several different dimensions of autonomic function, and was shown to improve intraoperative analgesic titration and cardiovascular stability.

The minority of EEG-based monitoring systems that explicitly aim at evaluating the analgesic component are: the Brain Anaesthesia Response monitor (BAR; Cortical Dynamics Ltd, North Perth, Australia), the composite variability index (CVI) from the bispectral index (Medtronic), and the qNOX (Quantum Medical, Barcelona, Spain), which uses the ratios between the energies of the EEG signal in different frequency ranges to track noxious stimulation. It was calibrated to nail-bed pressure as a noxious stimulus, but seems to work for stimuli such as laryngeal mask airway insertion, a stimulus known to also trigger beta arousal. Hence, it may be comparable with the response entropy index. The BAR, based on neural field modelling, uses autoregressive and moving averages to estimate separate hypnotic and analgesic components. If we are to design a holistic EEG monitoring system, we have to understand all the different responses triggered by noxious stimuli, and then implement tools that can detect them. A thorough monitoring of the raw EEG or the density spectral array (DSA) regarding the possible types of reaction to a noxious stimulation adds no more costs or risks to the patient because the EEG information is available and should be used for intraoperative decision-making anyway.

It can help the anaesthesiologist to identify and react to the different reaction types by adjusting analgesia, hypnosis, or both, as it can help the scientific community further understand the situations the different reactions occur. Therefore the EEG-based approach to monitor reactions to noxious stimulation may provide a relevant addition to anaesthesia monitoring as it positively answers the questions that are relevant to a useful application.
# Studies investigating the influence of noxious stimulation on the processed EEG

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Continued
### EEG responses to general anaesthesia and to surgical stimulation

As is comprehensively described elsewhere, sufficient concentrations of propofol or an inhalation ether change the patient’s EEG from a low-amplitude, high-frequency pattern (the so-called ‘desynchronised’ EEG) to one that looks similar to that of slow wave sleep and some comas – namely, a high-amplitude, slower-frequency pattern, with dominant EEG activity in the delta and alpha ranges. We have to recognise that these transitions are non-linear. For example, during anaesthesia induction, episodes of paradoxical excitation (beta range) of the frontal EEG beta range may be observed.

Similarly, at excessively high doses of anaesthetic medication the EEG does not result in higher and higher amplitudes but eventually decreases in amplitude and finally becomes discontinuous. Low EEG amplitude at both ends of the dose relationship is another example as to how representing surgical anaesthesia on a single axis numeric scale is a gross oversimplification. Many anaesthesiologists use a multidimensional mental model for different clinical goals; for example, although unconsciousness and analgesia may be synergistic, the pain/analgesia axis can often be considered independently of the arousal/hypnosis axis (Fig. 1) for pharmacologic decision-making (i.e. does this patient need more disruption of cortical processing or more analgesia?). It is also being increasingly realised that a variety of other factors such as age, patient cognition, and co-morbidities can influence intraoperative EEG patterns.

It might be assumed that surgical stimulation acts to ‘wake the patient up’ by overwhelming the pharmacodynamic effects of hypnotic drugs and causing premature arousal, which would result in EEG features towards those relating to consciousness (lower amplitude EEG, less delta waves, more beta waves). However, noxious stimulation under general anaesthesia can also trigger atypical changes in the EEG that do not follow this classical arousal pattern. In the following sections we describe the proposed mechanisms of the different responses to noxious stimulation. We show three tables to summarise the work that has been done on this subject. Tables 1 and 2 present results from studies that deal with the EEG reaction to noxious stimuli in patients or volunteers by either describing changes in the processed EEG (Table 1) or in the raw EEG (Table 2). Furthermore, Table 3 contains information from studies conducted with animal models.

#### Beta arousal

The observation of an acceleration in the EEG after painful stimulation (beta arousal) was described in the very earliest days of EEG clinical research.

#### Mechanisms of beta arousal

Although it is difficult to draw definitive conclusions regarding the underlying neurobiology that triggers these changes in the EEG during surgical anaesthesia, there is evidence that points toward an increase in cortical activity – and the concomitant increase in beta wave EEG power – that marks progression towards either a dream-like state or wakefulness. The neuroanatomy and neurophysiology of the beta arousal response are quite well understood. In 1949, Moruzzi and Magoun demonstrated that beta arousal could be replicated by electrical stimulation of the ascending reticular activating...
system that regulates transitions between sleep and wakefulness. Since then, a large literature has burgeoned, showing in some detail, that noxious stimulation acts to increase aminergic and cholinergic neuromodulators in the brain stem to depolarise the thalamus and thus inhibit the hyperpolisation-dependent slow wave thalamicocortical oscillations in the EEG. Aminergic systems are important mediators of beta arousal in the EEG. Clinical studies have shown that a beta-adrenergic receptor blockade helps to block arousal reactions after the stimulus of tracheal intubation. More recently these results were replicated in a large group of patients undergoing a more clinically routine fentanyl and desflurane or propofol anaesthesia regimen (aiming for a BIS of 40–55; i.e. the index range recommended to perform surgery). Loss of alpha activity was associated with

**Delta arousal**

During modern ‘balanced anaesthesia’ techniques, typically involving opioids, neuromuscular block, along with propofol anaesthesia, volatile gas anaesthesia, or both, beta arousal is somewhat mitigated because opioids act synergistically with hypnotic drugs to obtund EEG responses to the stimulus. In the previously mentioned work by Kochs and colleagues, patients receiving 66% nitrous oxide were placed into low (0.5 MAC) and high (1.0 MAC) isoflurane groups. EEG delta power increased with incision. The increase was stronger in the low MAC group (+181%; electrode F3) than in the high MAC group (+44%; frontal and occipital electrodes). Alpha power decreased by about half in both groups. The main effect was seen frontally. Although all these patients received nitrous oxide, delta arousal to noxious stimulation can appear in its absence. Hartley and co-workers have shown that even the mild stimulus of intravenous cannulation increased delta waves in children receiving sevoflurane monoanaesthesia. Kiyama and Takeda reported a similar relative increase in delta and loss of alpha EEG responses to incision, which were completely prevented by pre-existing epidural blockade. More recently these results were replicated in a large group of patients undergoing a more clinically routine fentanyl and desflurane or propofol anaesthesia regimen (aiming for a BIS of 40–55; i.e. the index range recommended to perform surgery). Loss of alpha activity was associated with

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**Fig 1.** Schematic concept of hypnotic and analgesic drug titration. (a) Relation between calculated index values of processed electroencephalographic (EEG) monitors and the exemplary EEG traces for the different states. (b) The desired target range of general anaesthesia should prevent the patient from awareness (hypnotic management) and pain (analgesic management) without overdosing. (c) Different main classes of typical EEG patterns as induced by different doses of the hypnotic and analgesic drugs.
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an increase in delta power in many patients at the initiation of surgical stimulation. These observed delta arousals may be limited to a certain frequency range, because although delta power may increase to a stimulus, the power in the sub-delta range can decrease. This finding may contradict the term ‘paradoxical’ arousal, because it describes a stimulus-induced shift towards faster frequencies, which does not seem ‘paradoxical’ at all.

Influence of type of surgery

Although the clinical relevance of the delta arousals remains uncertain, the source of the noxious stimulation has some influence on the type of arousal response. Bischoff and colleagues showed that the delta amplitude increase was more pronounced for laparotomy (body cavity surgery) than mastectomy (body surface surgery). The increase in delta power during laparotomy was most pronounced at frontal (F3) positions with 245%, in contrast to only 45% at occipital positions (O1). Morimoto and colleagues observed a similar profound increase in (frontal) delta waves (see Fig. 2 in their paper) when they reported a decrease in BIS value with abdominal irrigation. This increase in slow waves can be markedly reduced by opioids, but not by increasing concentrations of the inhalation anaesthetic. Other research groups using other indices have also observed this (frontal) decrease in the processed EEG index.

Mechanisms of delta arousal

Delta waves are understood to represent synchronous synaptic input onto cortical cells as occurs during sleep and anaesthesia. This hyperpolarisation can release cortical cells from their sensory input, and when occurring in combination with decreased cortical activation by the ascending reticular activating system, delta waves develop. The link from these findings to the paradoxical response to noxious stimulation is not known, and may be related to specific drugs used and type of stimulation. It would seem that visceral pain pathways are more likely to stimulate the specific mesencephalic centres that cause cortical delta waves. Using similar techniques to those used by Moruzzi and Magoun, Kaada and colleagues found that high-frequency stimulation of the mid-brain reticular formation can induce theta and delta waves in about a third of the experiments.

The addition of nitrous oxide to volatile anaesthetics seems to transiently augment delta power, and it is speculated that N-methyl-d-aspartate receptor blockade by nitrous oxide has the effect of hyper-synchronising oscillations. Conversely, the co-administration of remifentanil during higher doses of

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propofol anaesthesia decreases delta power and increases alpha power.81

Although originally termed delta arousals,51,54,73 these delta responses may not necessarily represent progression towards the restoration of consciousness. Neuroanatomical information from the coma and sleep literature provides some insight into the source of these delta power increases. Intermittent rhythmic delta activity is non-specific and seen in various comas of mild severity, but can also occur in normal subjects.62 In contrast, continuous high-voltage delta activity typically develops with substantial lesions involving tracts carrying subcortical arousal information and can be localised or generalised depending on the extent of the lesion. Although intermittent rhythmic delta activity is associated with mild stimulation in some patients, during natural sleep it is not unusual to see benign and non-specific rhythmic delta activity restricted to frontal leads, typically in lighter stages of sleep.63 Fig. 2b illustrates the proposed mechanism of delta arousal.

**Alpha dropout**

The development of a steady-state alpha oscillation during general anaesthesia is primarily driven by hypnotic drugs interacting with underlying patient factors. For volatile anaesthetics, the alpha power is typically maximal in the moderate dose range, with diminished alpha power observed at both lower concentrations (<0.5 MAC) and at higher concentrations (where the EEG might be dominated by delta activity, discontinuities, or both). A sudden episodic loss of frontal alpha power is a relatively common response to noxious stimulation. Opioids can prevent or recover an alpha dropout.79 These observations have given rise to the concept that (frontal) maximal alpha power is a reasonable biomarker for the titration of intraoperative opioids.85 Hagihira and colleagues74 looked at the effect of abdominal surgery in patients anaesthetised with isoflurane or sevoflurane (0.7–0.8 MAC). They gave a bolus of fentanyl either 5 min before incision (looking at EEG at incision and 5 min after) or 5 min after incision (and looked at EEG 5 and 10 min after incision). They observed a decrease in EEG features in the alpha band after incision, which then recovered with subsequent fentanyl administration; in contrast, if fentanyl was given before incision to provide sufficient analgesia, the prominent alpha oscillatory activity did not decrease with incision.76 Mackay and colleagues86 looked at pre- vs post-stimulus changes in alpha power and burst suppression in response to two stimuli (intubation and incision) with three levels of fentanyl. Loss of alpha power was more pronounced in the low opioid (1 μg kg⁻¹) group. These studies highlight the capability of adequate analgesia management to prevent the stimulus induced decrease in EEG alpha power and hence possibly prevent pain-triggered arousal events.

**Mechanisms of alpha dropout**

In animals it has been shown that noxious stimuli act to depolarise the thalamus via the effects of ascending aminergic and cholinergic input on the reticular nuclei of the thalamus. EEG alpha rhythms may be associated with the activity of thalamic pacemaker neurones, the intrinsic oscillatory rhythm of neurones in the thalamic relay nuclei, and their interactions with cortical areas.77 The increase in frontal alpha power and the development of the frontal alpha spectral peak, that is the anteriorisation of alpha power, is a well-observed phenomenon during general anaesthesia.78 Modelling work relates the high frontal alpha power during propofol to simple, low-dimensional, synchronised oscillations in thalamocortical loops,58 and hyperpolarised thalamic calcium current-induced bursting activity. Hence, the loss of alpha power induced by a noxious stimulus may reflect increased
complexity of communication between thalamus and cortex, because the depolarised thalamus switches from its hyperpolarised burst-firing mode to a more continuous firing mode. This is manifest as loss of alpha power in the EEG signal, a reaction analogous to a partial beta arousal.

Curiously — as described in the previous section — this can occur in the presence of a strong, or even increased slow oscillation, which is clear evidence that it is possible to achieve cortical, slow, up–down states that are independent of the thalamus. A down state presents a hyperpolarised membrane potential of the neurones and an up state reflects a more depolarised state, that is periods of sustained firing of neurones and quiescent episodes. Because these EEG responses can occur separately, it clearly demonstrates the dependence of alpha oscillations on the thalamus but also the independence of delta oscillations from the thalamus. This alpha dependence on the thalamus manifests itself in a few types of coma that show alpha-dominant rhythms. Examples include those induced by barbiturate or benzodiazepine overdose, some anoxic encephalopathies (typically these cases have a predominance of low alpha activity, 7–8 Hz, and sometimes referred to as alpha–theta coma), and specific sub-tentorial vascular infarcts rostral to the pons that spare the thalamus. Stimulation cannot change these alpha-dominant patterns, suggesting that the thalamus is effectively uncoupled from its depolarising input arising from the pons and other brain stem nuclei. The described mechanisms of alpha dropout are highlighted in Fig. 2c.

Clinical consequences

As a component of anaesthesia monitoring, the changes in the EEG coincident with a noxious stimulus have been hitherto somewhat neglected. A major consideration during anaesthesia care is to suppress the responses to noxious stimulation. Autonomic responses are clearly related to various perioperative cardiovascular complications, but it remains to be determined if pure EEG nociceptive responses have significant long-term clinical consequences.

Nevertheless, the practitioner should be aware of the possibility of a delta arousal as a response to body cavity noxious stimulation, as this phenomenon causes EEG indices to falsely suggest that hypnotic dose is excessive, and hence might trigger an erroneous response on the part of the anaesthesiologist to decrease the hypnotic drugs. Clearly this is potentially a major problem for any putative closed-loop anaesthesia/analgesia drug control device. For this reason, new EEG monitors should be able to quantitatively track the details of the changes in low (delta) and moderate (alpha) frequency power in the spectrogram so the clinician can respond appropriately.

The other immediate consequence of the nociceptive EEG effects is to guide intraoperative opioid titration. A good argument can be made for opioids to be titrated to maximise EEG alpha power — and avoid alpha dropouts — in the face of surgical nociceptive input (see example in Fig. 3). According to recent theories, a maximised alpha power would indicate an
adequate level of anaesthesia, that is a state of idling communication between thalamus and cortex that minimises the reaction to a noxious stimulus. Whether this practice results in improved intraoperative autonomic stability and less postoperative delirium,85 pain, and immune suppression has yet to be evaluated in large clinical trials.85 In order to appropriately use EEG alpha power as a potential marker of anaesthesia quality,10 it is important to personalise the EEG pattern. Some patients with neurodegeneration,38 previous stroke,36 or sleep disorders95 may have less alpha power than expected. Furthermore, patients of older age36,45,96,97 and cognitive impairments62 will intrinsically have less absolute frontal EEG alpha power. To account for these individual differences, calibration and correction algorithms are necessary. Besides a general adjustment according to patient age, cognitive status, etc., preoperative baseline EEG recordings for each patient may be useful. Alternatively, the patient’s maximal frontal alpha power could be determined after the patient is in a steady state of unconsciousness before surgical stimulation begins.

Conclusions
EEG reactions to noxious stimuli during general anaesthesia indicate an incomplete blockade of stimulus information entering the central nervous system. Awareness and quantification of these observed EEG reactions might help guide intraoperative clinical decisions by optimising analgesic drug administration separate from anaesthetic titration. The clinician should be aware that noiceptive-induced changes in EEG can be quite variable, and include patterns of beta arousal, delta arousal, and alpha dropout. These EEG changes are often best treated by increased analgesia (opioids, or establishment of regional local anaesthetic blocks) rather than by increased hypnotic drugs. However, at present we have insufficient information to determine if this approach is associated with preferred patient outcomes, and no large randomised trials to test whether nociception-EEG guided manipulation of drug dosage confers widespread beneficial effects.

Authors’ contributions
Planning: PSG, JWS
Writing of the manuscript: PSG, MK, DH, JWS
All authors participated in manuscript revision.

Funding
James S. MacDonnell Foundation (award number 22002046, PSG).

Declarations of interest
The authors declare that they have no conflicts of interest.

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Handling editor: Tony Absalom