ELSEVIER

Revalidation FOR ANAESTHETISTS RCA Revalidation matrix
Matrix codes: 1E06, 2A04, 3J02

BJA Education, 20(5): 166–172 (2020)

doi: 10.1016/j.bjae.2020.01.004
Advance Access Publication Date: 20 February 2020

Role of electroencephalogram oscillations and the spectrogram in monitoring anaesthesia

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Learning objectives

By reading this article, you should be able to:

- Explain the limitations inherent to using only indices to monitor the anaesthetic state of patients.
- Describe the EEG oscillations that can be used to track commonly encountered states of sedation.
- Identify EEG oscillations that can be used to track commonly encountered states of general anaesthesia.
- Recall that EEG oscillations change systematically as a function of the anaesthetic drug class, anaesthetic dose and patient age.

Key points

- Each anaesthetic drug class is associated with unique EEG oscillations.
- The spectrogram is a frequency-dependent representation of the EEG.
- Intraoperative EEG monitoring may require the use of both the unprocessed EEG and its spectrogram.
- The unprocessed EEG and its spectrogram can be used to target states of anaesthesia precisely.
- The use of unprocessed EEG and its spectrogram to infer brain dysfunction is an active area of investigation.

General anaesthesia is a drug-induced reversible state of unconsciousness; amnesia; analgesia; immobility; and stability of the autonomic, cardiovascular, respiratory and thermoregulatory systems.[1] Anaesthetic drugs are routinely given and adjusted empirically based on pharmacokinetic and pharmacodynamic properties and physiological variables, such as changes in heart rate or arterial pressure. This

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Accepted: 20 January 2020

empirical approach to drug dosing may result in inadvertent over- or underdosing of anaesthetic drugs. Overdosing of anaesthetic drugs is associated with adverse cardiovascular and respiratory effects and delayed recovery, whilst underdosing is associated with unintended intraoperative awareness and post-traumatic stress disorder. Personalised strategies for precisely targeting and maintaining states of anaesthesia are expected to directly improve anaesthetic care delivery.[2]

The EEG can be used as part of a personalised strategy for improving anaesthetic care.[1] The biophysics underlying the large-scale voltage fluctuations that are measured as EEG is beyond the scope of this article. The EEG can be used to non-invasively link brain neurophysiology to altered states of arousal.[1,2] Numerous studies have reported on the relationship between EEG oscillations and the behavioural states of general anaesthesia.[1,2] EEG-based anaesthetic state monitoring is, in theory, a principled strategy for achieving personalised anaesthetic care. However, the use of the unprocessed EEG and its spectrogram during anaesthesia is not a standard practice.[2] The spectrogram displays the frequency content of the unprocessed EEG time series as they change over time. Frequency is plotted on the y-axis, time on the x-axis and power is indicated in colour. The spectrogram allows for interpretability of EEG signals and an improved ability to track EEG oscillations over time.

Since the 1990s, we have been able to track the state of anaesthesia using indices (0–100) computed from the EEG and displayed on brain monitoring devices.[2] With the induction of general anaesthesia, these indices usually change from high values that indicate the awake state to lower values that indicate states of anaesthesia.[2] Therefore, indices displayed by these monitors fundamentally obscure potentially important EEG oscillations by reducing the complexity of the EEG to simple numeric values. A corollary to monitoring the anaesthetised brain solely with an index would be monitoring the cardiovascular system using just the heart rate whilst disregarding the underlying heart rhythm. Further, unlike the heart rate, the neurobiological underpinnings of EEG indices are ambiguous. Lastly, the algorithms and EEG features that are used to compute the indices displayed are proprietary, making their assumptions and oversights inaccessible for clinical decision-making.

The reliability of these index-based brain-monitoring devices has been called into question in numerous clinical scenarios. Using the isolated forearm technique, Schuller and colleagues recently demonstrated that BIS™ (Medtronic, Minneapolis, MN, USA) indices decreased to values that are consistent with general anaesthesia in awake and cognitively intact volunteers that were paralysed with rocuronium.[3] This finding suggests that the BIS algorithm ascribes high 'awake' prediction weights to EEG β (13–33 Hz) oscillations. (Muscle artefacts contaminate the EEG in β frequency ranges.) Therefore, the relative absence of β oscillations in awake and cognitively intact patients that received a neuromuscular blocking agent (NMBA) resulted in indices that were consistent with a state of general anaesthesia.[3]

The 5th National Audit Project on accidental awareness during general anaesthesia reported that the vast majority of accidental awareness under general anaesthesia (AAGA) occurred with neuromuscular block, and that the majority of patients with AAGA suffered significant distress.[4] Not surprisingly, distress and paralysis at the time of AAGA appear to be essential in developing long-term psychological sequelae, such as post-traumatic stress disorder.[4] This finding is particularly important, given that indices imprecisely suggest unconsciousness in patients that have been paralysed using an NMBA, but they remain conscious.[3] Results from large RCTs also suggest that BIS-index-based monitoring was less effective at reducing the incidence of AAGA compared with patients in whom end-tidal anaesthetic monitoring was used to guide management.[5,6] Further, anaesthetic state monitoring of paediatric patients and anaesthetic drug-class combinations remains imprecise.[2] Given the inherent limitations of index-based anaesthetic state monitoring strategies, principled strategies that significantly improve upon index-based approaches are needed. Commercially available anaesthetic state monitors that compute and display the EEG spectrogram in real time may enable the ability to more precisely monitor a patient's state of anaesthesia.

Prevention of awareness under general anaesthesia is a tractable problem if strategies used to monitor the level of arousal use neurophysiological-based markers that relate directly to the putative molecular and circuit mechanisms through which anaesthetic drugs alter the level of arousal.

EEG changes systematically with anaesthetic drug class

Neural oscillations are the most prominent feature of EEG. Each anaesthetic drug class produces distinct oscillations.[1] These oscillations can be related to the circuit mechanisms of drug action, and growing evidence suggests that anaesthetic-induced neural oscillations can be used to infer depth of anaesthesia.[1,2] In the following sections, we summarise EEG-based markers that are associated with the major anaesthetic drug classes.

EEG oscillations of sevoflurane

Sevoflurane, a derivative of diethyl ether, is extensively used in current clinical practice. The molecular targets of sevoflurane include γ-aminobutyric acid A ($GABA_A$) receptors, glycine receptors, two-pore potassium channels and N-methyl-D-aspartate (NMDA) receptors, amongst many others.[7] The i.v. anaesthetic propofol, which acts primarily at $GABA_A$ receptors, is associated with characteristic EEG changes that closely approximate those of sevoflurane.[8–10] This finding suggests a shared molecular and systems-level mechanism for the unconscious state induced by these drugs, and explains the success associated with monitoring the states of anaesthesia induced by these drugs with a conceptually similar approach.[9] Figure 1 illustrates the EEG oscillations associated with sevoflurane sedation and general anaesthesia.

Sedation

Sevoflurane can be given to achieve a sedated state. During the sedated state, the EEG shows increased β oscillation power.[1] Beta oscillations are also associated with propofol sedation and with sleep medications that enhance inhibitory postsynaptic currents through $GABA_A$ receptor.[1,11] A model to explain β oscillations suggests that a modest increase in $GABA_A$ decay time and conductance causes low threshold spiking interneuron anti-synchrony that patterns pyramidal cell spiking into a β rhythm.[12] Sedation is also associated with

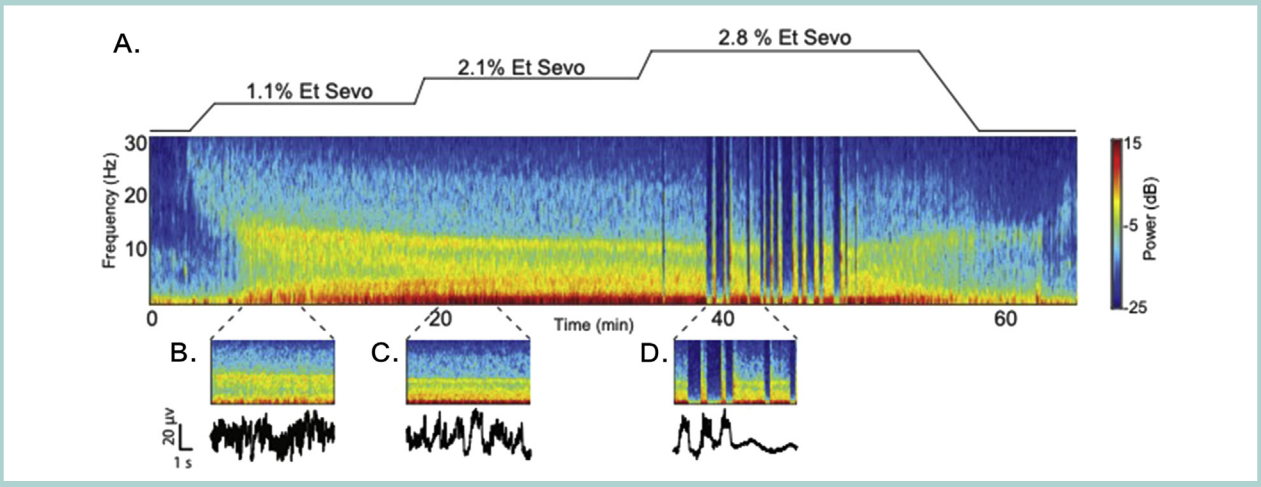

Fig 1 Spectrogram of a healthy volunteer subject that received graded increase of sevoflurane. (A) End-tidal sevoflurane concentration and corresponding frontal EEG spectrogram. The spectrogram shows that the EEG changes systematically as a function of the anaesthetic concentration. The drug-concentration-dependent EEG changes can be clearly appreciated on the spectrogram. (B) At an end-tidal sevoflurane concentration of 1.1%, the EEG shows increased slow-δ (0.1–4 Hz) and β (13–33 Hz) oscillations (top panel). This dynamic is better appreciated on the spectrogram compared with the EEG time series (bottom panel). (C) At a 2.1% end-tidal concentration of sevoflurane, the EEG shows that slow-δ is further increased in power. The broadband β oscillations associated with sevoflurane 1.1% become tightly constrained to a narrow α (8–12 Hz) frequency band. In addition, θ (4–8 Hz) oscillations are increased in power (top panel). The increase in θ oscillations results in the appearance of evenly distributed power from slow-δ to α frequency bands. This dynamic is better appreciated on the spectrogram compared with the EEG time series (bottom panel). (D) Further increases in the anaesthetic concentration can result in burst suppression. This state is characterised by alternations between isoelectricity and brief bursts of EEG activity. On the spectrogram, periods of inactivity are represented as discontinuities on the spectrogram (top panel). This dynamic can also be appreciated on the EEG time series (bottom panel). Et, end tidal; sevo, sevoflurane.

an increase in slow-δ oscillations (0.1–4 Hz). However, the increase in slow-δ oscillations associated with the sedative state may be underappreciated on clinical monitors because of hardware limitations.

General anaesthesia

During general anaesthesia with sevoflurane, the EEG shows increased α (8–12 Hz) and slow-δ oscillation power.[9] This dynamic also closely approximates the EEG of general anaesthesia with propofol.[9] Alpha oscillations are likely to originate from a mechanism similar to that proposed for the β oscillations. An increase in $GABA_A$ decay time and conductance results in cortical α oscillations and enhanced rebound spiking of thalamic relay cells, strengthening the intrinsic α oscillatory dynamic of the thalamus. The net result is reciprocal thalamic–cortical α oscillation coupling.[13] Mechanisms to explain the slow-δ oscillations are being investigated. However, slow-δ oscillations may be associated with an alternation between 'on' states, in which neurones are able to fire, and 'off' states, in which neurones are silent.[9] Different from propofol, sevoflurane general anaesthesia is also associated with increased frontal θ (4–8 Hz) oscillation power.[1,9] The increase in θ oscillation power creates a distinctive pattern of distributed EEG power from the slow-δ oscillation through to the α oscillation range.

Further increases in the anaesthetic concentration result in burst suppression.[1] Burst suppression consists of alternations between isoelectricity and brief bursts of electrical activity.[1] Burst suppression is not associated with normal behavioural states, and anaesthetic drugs are typically titrated to burst suppression to treat refractory status epilepticus and increased intracranial pressure. Intraoperative burst suppression has recently been associated with postoperative delirium.[14] Whether the association between burst suppression and delirium is causal and modifiable, or is non-causal, is an open question.

EEG oscillations of ketamine

Ketamine acts principally by binding to glutamate binding sites on NMDA receptors and non-NMDA receptors.[15] Ketamine also interacts with opioid, monoaminergic, cholinergic, nicotinic and muscarinic receptors.[15] Figure 2 illustrates the EEG oscillations associated with ketamine.

General anaesthesia

During general anaesthesia with ketamine, the EEG shows a characteristic γ burst pattern, in which γ oscillations alternate with periods of slow oscillations.[16] Ketamine is likely to exert its primary effect as a general anaesthetic by blocking excitatory glutamatergic inputs to both inhibitory interneurones and pyramidal neurones.[17] It is conceivable that the γ burst pattern parallels burst suppression (high drug concentration). This is because unresponsiveness to salient stimuli persists after dissipation of the γ burst pattern.[16] Immediately after γ burst dissipation, the EEG shows increased θ and γ oscillation power and decreased α–β oscillation power.[16] EEG oscillations that differentiate the sedative state from the non-γ burst general anaesthetic state have not been formally characterised. The increase in β and γ (>33 Hz) oscillation power during ketamine-induced states of anaesthesia may explain why EEG-based indices often report high values in patients receiving ketamine.

Dissociative state

Ketamine can be given to achieve a dissociative state, in which patients are responsive to salient stimuli or verbal commands. During the dissociative state, the EEG shows increased θ oscillation power and decreased α–low β

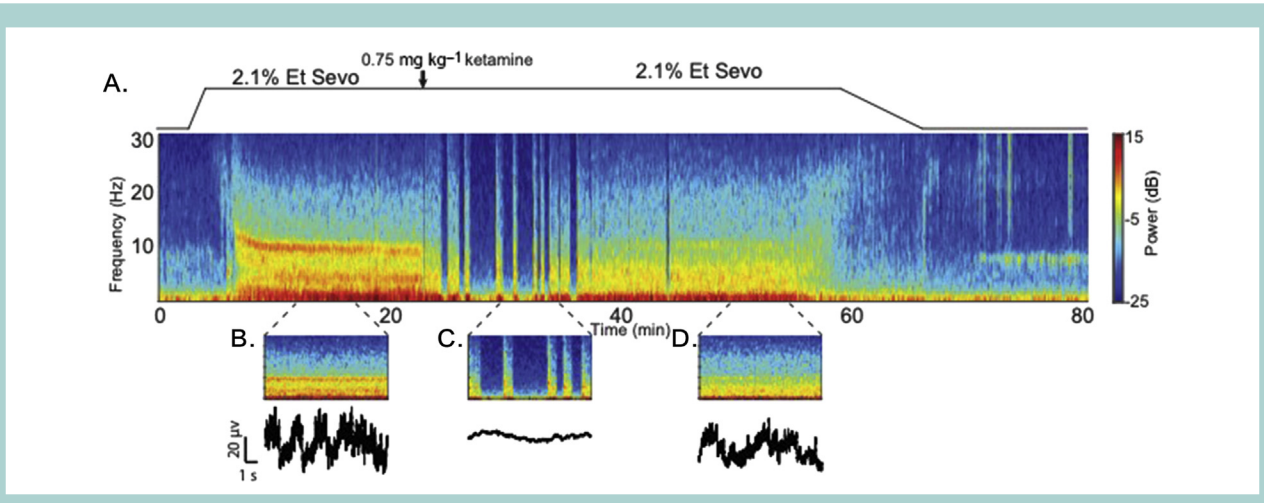

Fig 2 Spectrogram of a healthy volunteer subject that received a rapid induction of sevoflurane followed with an adjunctive dose of ketamine. (A) End-tidal sevoflurane concentration and corresponding frontal EEG spectrogram. The spectrogram shows that the EEG changes systematically as a function of the anaesthetic concentration. The drug-concentration-dependent EEG changes can be clearly appreciated on the spectrogram. (B) At an end-tidal sevoflurane concentration of 2.1%, the EEG shows that slow-δ (0.1–4 Hz), θ (4–8 Hz) and α (8–12 Hz) oscillations are all increased in power. The increase in θ oscillations results in the appearance of evenly distributed power from slow-δ to α frequency bands. This dynamic is better appreciated on the spectrogram compared with the EEG time series (bottom panel). (C) Giving an adjunctive dose of ketamine can result in burst suppression. This state is characterised by alternations between iso-electricity and brief bursts of EEG activity. On the spectrogram, periods of inactivity are represented as discontinuities on the spectrogram (top panel). This dynamic can also be appreciated on the EEG time series (bottom panel). (D) Giving an adjunctive dose of ketamine is typically associated with a decrease in δ (1–4 Hz), θ and α oscillation power (top panel). This state is also associated with a broadband increase in β oscillation power (13–33 Hz). These changes may explain why EEG-based indices often report high values in patients receiving ketamine. This dynamic is better appreciated on the spectrogram compared with the EEG time series (bottom panel). Et, end tidal; sevo, sevoflurane.

oscillation power (12–20 Hz).[18] This ketamine-induced EEG dynamic may be a consequence of ketamine blocking excitatory glutamatergic inputs to inhibitory interneurones.[15] Theta oscillations may appear in the absence of γ oscillations at the doses of ketamine used for analgesia.[19] We note that oscillatory dynamics that can be used to monitor ketamine analgesia are not explicit.

EEG oscillations of sevoflurane plus ketamine

Clinicians routinely give the drug-class combination of an inhaled anaesthetic (i.e. sevoflurane) to maintain unconsciousness and ketamine for analgesia as part of a balanced general anaesthetic technique. During the sevoflurane-plus-ketamine anaesthesia, the α oscillations typically associated with sevoflurane are reduced in power, and there is an increase in β oscillation power.[11,20] The δ oscillations associated with sevoflurane are also reduced in power.[11,20] This is likely because an adjunctive dose of ketamine excites neurones with intrinsic spiking frequencies below low β (12–22 Hz) to higher-frequency spiking. This finding is also conserved for propofol-plus-ketamine anaesthesia. Hayashi and colleagues examined the effect of ketamine on propofol-induced α oscillations, and they found that ketamine increased the peak frequencies of α oscillations from α to β frequencies.[21] It is important to note that an adjunctive dose of ketamine may result in EEG burst suppression. Figure 3 illustrates the EEG oscillations associated with sevoflurane-plus-ketamine general anaesthesia.

EEG oscillations of dexmedetomidine

Dexmedetomidine is an anaesthetic adjunct typically given as a sedative. Dexmedetomidine acts by binding α_{2a} adrenergic receptors on neurones projecting from the locus coeruleus.[1,22] Dexmedetomidine may also directly modulate non-adrenergic neurones in the thalamus and basal forebrain to alter the level of arousal.[1,22] Figure 4 illustrates the EEG oscillations associated with dexmedetomidine.

Sedation

Dexmedetomidine is typically given to achieve a sedated state. During the sedated state, the EEG shows increased slow-δ oscillations, increased spindle oscillations (13–16 Hz), increased occipital θ oscillations, and decreased β oscillations.[1,23] The spindle oscillations associated with dexmedetomidine have a transient frequency and time-domain morphology. This is similar to the spindle oscillations that define non-rapid eye movement Stages I–II of sleep.[1] Dexmedetomidine spindles are likely to originate from the thalamocortical mechanisms that have been described for sleep spindles.[23] Although dexmedetomidine is associated with increased slow-δ oscillations, this increase is smaller than the increase in slow-δ oscillations associated with general anaesthesia.[1,23] The close neurophysiological similarity between dexmedetomidine and natural sleep has been postulated as a mechanism to explain the reduced incidence of delirium associated with dexmedetomidine.[1]

EEG oscillations change systematically with ageing

In addition to changing systematically with anaesthetic class, the characteristic EEG changes of patients under general anaesthesia change systematically with age. This suggests that anaesthetic-induced neural oscillations are

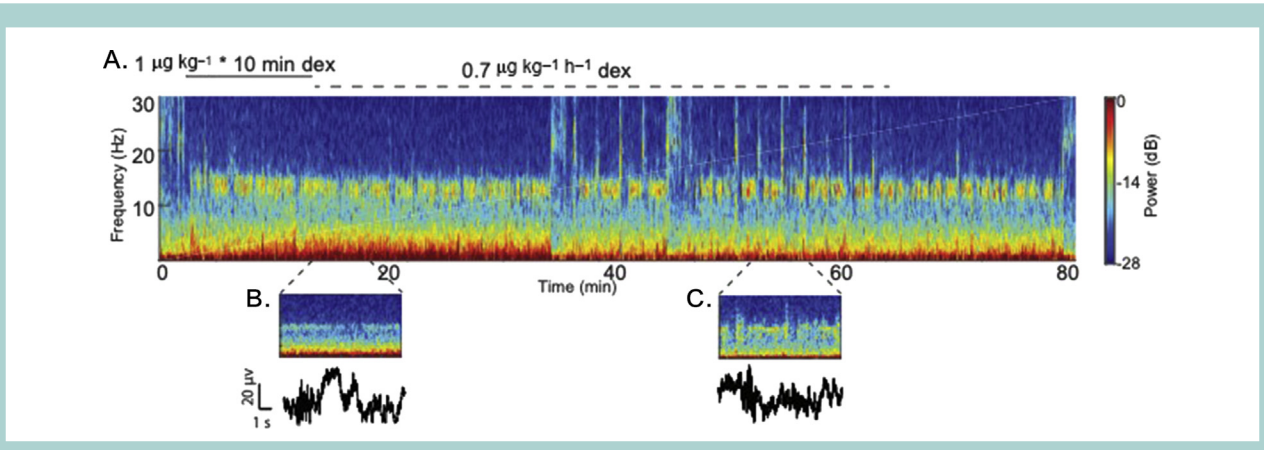

Fig 3 Spectrogram of a healthy volunteer subject that received a loading dose of dexmedetomidine followed by an infusion. (A) Dexmedetomidine dose and corresponding frontal EEG spectrogram. The spectrogram shows that the EEG changes systematically as a function of the anaesthetic concentration. The drug-concentration-dependent EEG changes can be clearly appreciated on the spectrogram. (B) After the loading dose of dexmedetomidine, the EEG shows that slow-δ (0.1–4 Hz) and spindle (13–16 Hz) oscillations are increased in power. Dexmedetomidine spindle oscillations have transient- frequency- and time-domain morphology. This dynamic is better appreciated on the spectrogram compared with the EEG time series (bottom panel). (C) During the maintenance infusion of dexmedetomidine, the EEG shows that slow-δ oscillations are decreased in power (top panel). This dynamic is better appreciated on the spectrogram compared with the EEG time series (bottom panel). dex, dexmedetomidine.

generated from mechanisms that depend on cellular properties, such as ionic currents, myelin integrity and synaptic density. However, the precise mechanisms underlying these age-dependent changes are unclear. We note that the EEG of children between 0 and 3 months of age, anaesthetised with sevoflurane or propofol as the primary agent, shows only slow-δ oscillations.[24,25] With increased age, slow-δ and α oscillations are reduced in power, and α oscillation power in adults older than 60 yrs may appear nearly absent. In addition, significant interindividual variations in the EEG power of patients of approximately the same age have been described. The clinical significance of these interindividual variations, which may be related to the cognitive and physical function status, remains unclear. Figure 5 illustrates that EEG oscillations change systematically as a function of age.

Implications for monitoring the state of anaesthesia

The unprocessed EEG and the spectrogram can be used to monitor the level of arousal in patients receiving general anaesthesia and sedation. Many of the current EEG brain function monitors have been configured to display both the unprocessed EEG and the spectrogram. Therefore, it is

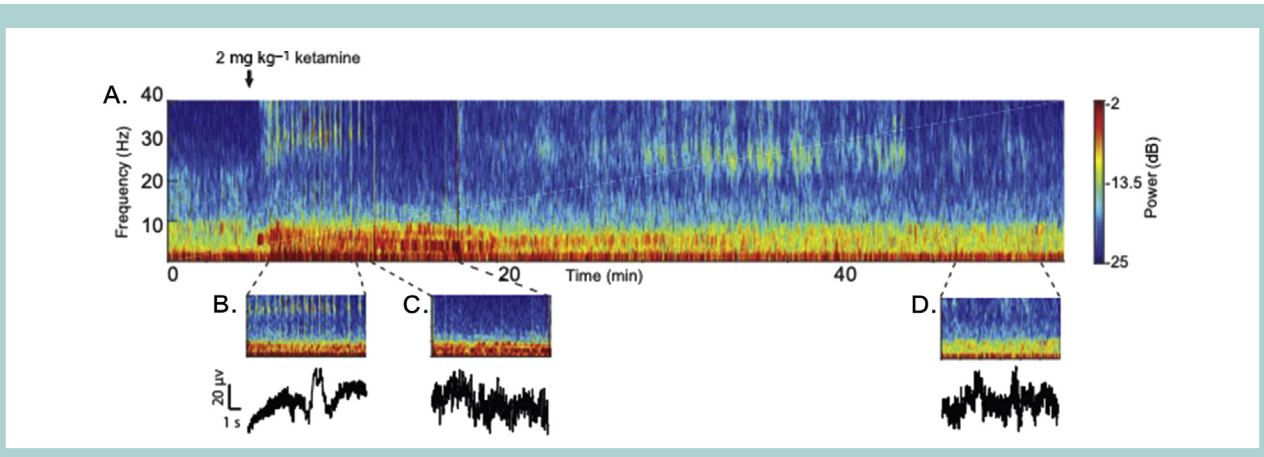

Fig 4 Spectrogram of a healthy volunteer subject that received a bolus dose of ketamine. (A) Ketamine bolus (2 mg kg^{-1}) time and corresponding frontal EEG spectrogram. The spectrogram shows that the EEG changes systematically after giving ketamine. (B) After a bolus of ketamine, the EEG shows a characteristic γ burst pattern, in which γ oscillations alternate with periods of slow oscillations. The γ burst state may represent a profound state of disrupted information processing. This dynamic can be appreciated on the spectrogram (top panel) and the EEG time series (bottom panel). This state is also associated with θ (4–8 Hz) oscillations. (C) The γ burst state is followed by an unresponsive anaesthetic state that is predominantly associated with θ oscillations. This dynamic can be appreciated on the spectrogram (top panel) and the EEG time series (bottom panel). (D) Theta oscillation power is reduced during the ketamine dissociative state during which responsiveness to verbal commands can be elicited.

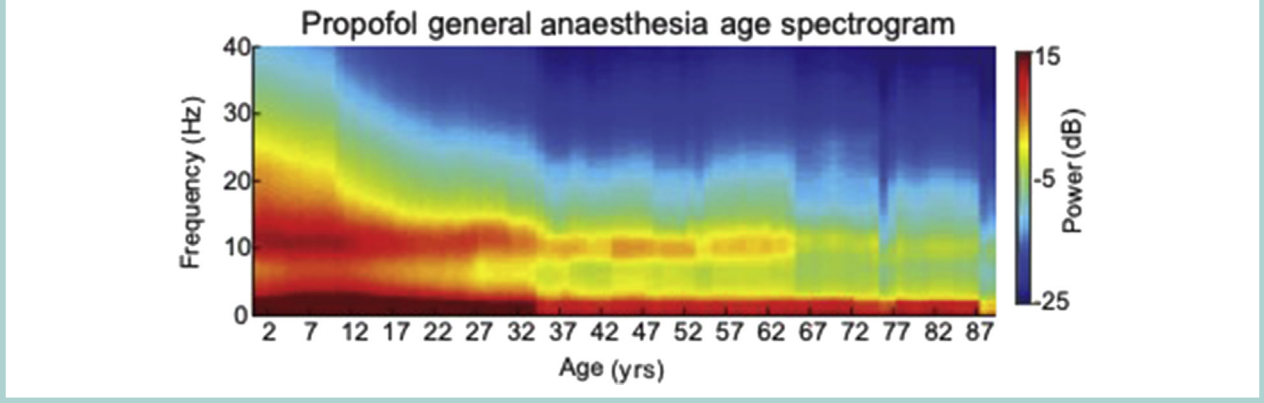

Fig 5 An age-varying (2–87 yrs) spectrogram representation of the EEG during propofol general anaesthesia showing that, even though the EEG structure appears qualitatively preserved for all age ranges (slow-δ and α oscillations), the power of these oscillations changes systematically as a function of age. These changes may reflect neurobiological changes associated with the normal ageing process. The clinical relevance of EEG oscillations that deviate from age norms is not yet clear.

possible to track these oscillations in real time for every anaesthetised patient. An EEG education resource has been developed at Washington University (www.icetap.org) and Massachusetts General Hospital (www.eegforanaesthesia@iars.org) to train anaesthesia caregivers on how to read the unprocessed EEG time series and its associated spectrogram.

The benefits of monitoring the unprocessed EEG and the spectrogram together are likely to extend beyond the prevention of AAGA. For example, intraoperative burst suppression during general anaesthesia may reflect a neurobiological predisposition to delirium.[14] Thus, patients with a high burden of intraoperative burst suppression at clinically relevant anaesthetic concentrations may be identified for focused postoperative care. Further, clinical experience with intraoperative anaesthetic state monitoring will help make clear the clinical implications of patients with characteristic EEG changes that deviate from age norms.

We conclude that monitoring the unprocessed EEG time series and its spectrogram will enable the ability to track the depth of general anaesthesia based on mechanistic principles. Further, this approach may elicit previously unrecognised associations between a patient's comorbidities and intraoperative EEG oscillations. We do not discount the utility of the index-based approach to anaesthetic state monitoring. However, instead of a 'one-index-fits-all' approach, we suggest that indices should be constructed to account for patients' age, anaesthetic drug or drug-class combinations and, perhaps, critical illness. We also suggest that monitoring the EEG time series and its spectrogram is a principled approach to anaesthetic state monitoring that may lead to fundamental new insights into brain function.

Declaration of interests

The authors declare that they have no conflicts of interest.

MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to *BJA Education*.

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Update

BJA Education

Volume 20, Issue 7, July 2020, Page 249

DOI: https://doi.org/10.1016/j.bjae.2020.04.001

BJA Education, 20(7): 249 (2020)

doi: 10.1016/j.bjae.2020.04.001
Advance Access Publication Date: 4 May 2020

Corrigendum to 'Role of electroencephalogram oscillations and the spectrogram in monitoring anaesthesia' [BJA Education 20 (2020) 166–172]

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DOI of original article: https://doi.org/10.1016/j.bjae.2020.01.004.

The authors regret that errors were present in the above article; references in the text to some of the Figures were incorrect.

Reference in the text to Figure 2 should refer to Figure 4.
Reference in the text to Figure 3 should refer to Figure 2.
Reference in the text to Figure 4 should refer to Figure 3.

The Figures and their legends are correct.

The authors would like to apologise for any inconvenience caused.

DOI of original article: 10.1016/j.bjae.2020.01.004.