BJA

British Journal of Anaesthesia 2015, i66–i76

doi: 10.1093/bja/aev114
ARTICLE

ARTICLE

Age-dependency of sevoflurane-induced electroencephalogram dynamics in children

O. Akeju[1,3,*], K. J. Pavone[1,†], J. A. Thum[3,5,†], P. G. Firth[1,2], M. B. Westover[2,3], M. Puglia[1,3], E. S. Shank[1,3], E. N. Brown[1,3,4,5,6], and P. L. Purdon[1,3,4,*]

[1]Department of Anesthesia, Critical Care and Pain Medicine, [2]Department of Neurology, Massachusetts General Hospital, Boston, MA, USA, [3]Harvard Medical School, Boston, MA, USA, [4]Department of Brain and Cognitive Science, [5]Harvard-Massachusetts Institute of Technology Division of Health Sciences and Technology, and [6]Institute for Medical Engineering and Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA

*Corresponding authors. E-mail: oluwaseun.akeju@mgh.harvard.edu; patrickp@nmr.mgh.harvard.edu

Abstract

Background: General anaesthesia induces highly structured oscillations in the electroencephalogram (EEG) in adults, but the anaesthesia-induced EEG in paediatric patients is less understood. Neural circuits undergo structural and functional transformations during development that might be reflected in anaesthesia-induced EEG oscillations. We therefore investigated age-related changes in the EEG during sevoflurane general anaesthesia in paediatric patients.

Methods: We analysed the EEG recorded during routine care of patients between 0 and 28 yr of age (n=54), using power spectral and coherence methods. The power spectrum quantifies the energy in the EEG at each frequency, while the coherence measures the frequency-dependent correlation or synchronization between EEG signals at different scalp locations. We characterized the EEG as a function of age and within 5 age groups: <1 yr old (n=4), 1–6 yr old (n=12), >6–14 yr old (n=14), >14–21 yr old (n=11), >21–28 yr old (n=13).

Results: EEG power significantly increased from infancy through ~6 yr, subsequently declining to a plateau at approximately 21 yr. Alpha (8–13 Hz) coherence, a prominent EEG feature associated with sevoflurane-induced unconsciousness in adults, is absent in patients <1 yr.

Conclusions: Sevoflurane-induced EEG dynamics in children vary significantly as a function of age. These age-related dynamics likely reflect ongoing development within brain circuits that are modulated by sevoflurane. These readily observed paediatric-specific EEG signatures could be used to improve brain state monitoring in children receiving general anaesthesia.

Key words: electroencephalography; pediatric; sevoflurane

Millions of children each year undergo general anaesthesia for surgical and medical procedures.[1] A growing body of evidence from animal models suggest that exposure to anaesthetic drugs can have neurotoxic effects in the developing brain, resulting in neurodegeneration and cognitive impairment.[1–3] It is unclear how this potential neurotoxicity translates to children receiving general anaesthesia or sedation. Moreover, we do not yet know how anaesthetic neurotoxicity influences circuit or systems level brain function. In addition, the relationship between anaesthetic actions and mechanisms of brain development remain unclear. Limited retrospective studies suggest that long-term cognitive effects are related to early anaesthetic exposure,[4] and

† Authors contributed equally.
Accepted: March 27, 2015

Editor's key points

- Age-dependent changes in the EEG effects of general anaesthetics in children are anticipated due to neurodevelopmental factors, but are poorly understood.
- The age-dependent effects of sevoflurane anaesthesia on EEG power spectrum and coherence were retrospectively analysed in 54 patients.
- EEG dynamics showed marked age-dependent effects, which has practical implications for EEG-based monitors of anaesthetic effects in children.

larger detailed prospective trials are in progress to further investigate these effects.[5]

A practical strategy for limiting potential neurotoxic effects of anaesthetic exposure in children would be to monitor paediatric patients' brain states during general anaesthesia and sedation, to ensure appropriate dosing. Currently, the prevailing approach to monitoring brain activity in anaesthetized patients is based on quantitative parameters or single-number indices developed from electroencephalogram (EEG) recordings during general anaesthesia in adults. However, the level of unconsciousness or 'depth of anaesthesia' implied by these indices in paediatric patients can vary substantially from clinical assessments.[6–12] For example, the bispectral index (BIS®), a calculated measure of anaesthetic depth, increases with decreasing age at one minimum alveolar concentration (MAC) of sevoflurane.[6] Similarly, we have observed that the SedLine PSI® is often far above the recommended range in paediatric patients, who by clinical indications are under general anaesthesia (unpublished observations). The apparent inaccuracy of these monitors in paediatric patients is consistent with findings in adults showing that these indices do not accurately reflect patients' state of awareness.[13] Fundamentally, these indices perform poorly because they do not relate directly to the underlying neurophysiology of the anaesthetic drugs. Fortunately, significant recent progress has been made to understand the systems neurophysiological mechanisms of anaesthesia and their manifestation in the EEG.

General anaesthetic and sedative agents induce highly structured oscillations in the EEG.[14–26] There is growing evidence that these oscillations relate directly to the systems-level mechanisms by which anaesthetics produce altered states of consciousness.[15–18 23 27 28] During normal brain function, oscillations regulate the timing and coordination of brain activity within and between functional systems and circuits.[29 30] Anaesthesia-induced oscillations are thought to disrupt this coordinated activity,[15–19 23 27 28] producing different states of altered arousal depending upon the receptors and circuits upon which the drugs act.[15–18 23 27] General anaesthesia with sevoflurane is characterized in the EEG by frontally coherent alpha (8–12 Hz), delta (1–4 Hz), and high amplitude slow (0.1–1Hz) oscillations.[18 31] This pattern, observed when adult patients are sufficiently anaesthetized to conduct surgery, is similar to that observed under propofol-induced general anaesthesia,[15–21 31 32] and suggests a common systems-level mechanism of action.[27 33]

Given that the brain rapidly develops and undergoes significant changes from childbirth into adulthood, anaesthesia-induced EEG oscillations in children might differ from those of adults, and could vary significantly with age. Characterizing the structure of the EEG in relation to age would help establish the foundations for age-appropriate monitoring of brain states during general anaesthesia and sedation in children. We aimed to examine the effects of age on the EEG during general anaesthesia, with sevoflurane as the sole hypnotic agent.

Methods

Subject selection and data collection

The Human Research Committee at Massachusetts General Hospital approved this retrospective observational study. We reviewed our database of 627 general anaesthesia cases with simultaneous EEG recordings collected between September 1, 2011 and April 1, 2014. We identified 201 patients to whom sevoflurane was administered. From these, we excluded 132 patients >28 yr of age. Of the remaining 69 patients, we identified 61 cases with sevoflurane as the sole anaesthetic agent. All data from the 61 selected cases were reviewed for artifacts and noise. Ultimately 54 patients were deemed suitable for analysis. We excluded patients who had poor quality data, most likely because of poor electrode contact, and patients who had neurological or psychiatric abnormalities.

Frontal EEG data were recorded using the Sedline brain function monitor (Masimo Corporation, Irvine, CA USA). The EEG data were recorded with a pre-amplifier bandwidth of 0.5–92 Hz, sampling rate of 250 Hz, with 16-bit, 29 nV resolution. The standard Sedline Sedtrace electrode array records from electrodes located approximately at positions Fp1, Fp2, F7, and F8, with ground electrode at Fpz and reference electrode approximately 1 cm above Fpz. Electrode impedance was <5 kΩ in each channel.

We selected EEG data segments using information from both the electronic anaesthesia record (Metavision, Dedham, MA USA) and EEG analysis in the spectral domain. EEG epochs were chosen after the onset of surgery and during an artifact free period in the EEG, as viewed in the spectrogram. We visually examined the EEG spectrogram to ensure that EEG dynamics were stable (i.e. not transitioning to burst suppression or emergence) for at least 10 min. The electronic medical record was used to confirm sevoflurane as the sole anaesthetic agent (isoflurane, desflurane or nitrous oxide were not co-administered), and that regional nerve block techniques were not used during or preceding the EEG epochs analysed. Sevoflurane concentrations were captured automatically, and care providers recorded other drugs administered manually in the electronic medical record. Table 1 summarizes the subject characteristics, end-tidal sevoflurane concentrations used during the selected maintenance phases of the EEG epochs, and additional information on co-administered medications. Two authors (O.A., K.J.P.) visually inspected all EEG data for each subject and manually selected data segments free of noise and artifacts for analysis.

Spectral analysis

For each subject, we computed the power spectrum and spectrogram, using multitaper spectral methods implemented in the Chronux toolbox.[34] The power spectrum quantifies the energy in the EEG at each frequency. The spectrogram is a time-varying version of the power spectrum estimated using consecutive windows of EEG data. To obtain estimates of power spectra, we used an EEG derivation that equally weighted signals obtained from FP1, FP2, F7 and F8. Parameters for the multitaper spectral analysis were: window length T=2 s with no overlap, time-bandwidth product TW=3, number of tapers K=5, and spectral resolution of 3 Hz. In addition to these spectral parameters, we computed an age-varying spectrogram using an overlapping

Table 1 Characteristics of patients studied. MAC, minimum alveolar concentration; SD, standard deviation

Characteristics	<1 yr (N=4)	1–6 yrs (N=12)	>6–14 yrs (N=14)	>14–21 yrs (N=11)	>21–28 yrs (N=13)
Age (yrs), mean (range)	0.7 (0.4–1)	3.2 (1.2–5.8)	10.8 (6.1–13.7)	18.5 (14.8–20.7)	25.5 (22.6–27.7)
Sex (male), N (%)	4 (100)	10 (83)	6 (43)	6 (55)	6 (46)
Weight (kg), mean (SD)	9.0 (0.8)	14.9 (1.0)	39.4 (11.6)	77.9 (20.0)	78.4 (21.5)
Length of surgery (mins) mean (SD)	36.5 (12.4)	67.4 (37.3)	54.4 (48.2)	93.3 (61.7)	84.3 (60.4)
Sevoflurane (vol % expired), mean (SD)	3.0 (0.6)	2.7 (0.5)	2.5 (0.4)	2.1 (0.3)	1.9 (0.5)
MAC	1.3 (0.3)	1.2 (0.2)	1.1 (0.2)	1.0 (0.1)	1.0 (0.2)
Propofol (mg), mean (SD)	26.7 (11.5), N=3	35.6 (23.0), N=9	122.0 (63.7), N=10	200.0 (66.6), N=11	212.5 (56.9), N=12
Fentanyl (mcg), mean (SD)	15.0 (8.6), N=3	20.8 (7.9), N=12	62.9 (24.4), N=12	155.0 (68.5), N=11	152.1 (69.5), N=13
Remifentanil (mcg)	30, N=1	N=0	N=0	N=0	0.75, N=1
Hydromorphone (mg), mean (SD)	N=0	N=0	N=0	0.9 (0.7), N=6	0.8 (0.6), N=6
Morphine (mg), mean (SD)	N=0	1.2 (0.8), N=3	2, N=1	3 (1), N=3	N=0
Ketorolac (mg), mean (SD)	N=0	9, N=1	18.8 (8.5), N=4	N=0	N=0
Neuromuscular blocking agents	N=0	N=3	N=4	N=9	N=10

(0.5 yr) moving window spanning a 2 yr range. To better illustrate the spectral dynamics of patients <1 yr old, we computed the age-varying spectrogram between 0–1.5 yr by computing the median spectrum across patients in 0.5 yr age bins. We also computed group-level spectra and spectrograms for sevoflurane epochs by taking the median across all patients within each age group: <1 yr old (n=4), 1–6 yr old (n=12), >6–14 yr old (n=14), >14–21 yr old (n=11), and >21–28 yr old (n=13). We calculated the spectrum for the selected EEG epochs in each group. We then averaged the resulting power spectra for all epochs, and computed 95% confidence intervals using multitaper-based jackknife techniques.[34]

Coherence analysis

The coherence $C_{xy}(f)$ between two signals x and y is defined as

$$Cxy(f) = \frac{|Sxy(f)|}{\sqrt{Sxx(f)Syy(f)}},$$

where $S_{xy}(f)$ is the cross-spectrum between signals $x(t)$ and $y(t)$, $S_{xx}(f)$ is the power spectrum of signal $x(t)$, and $S_{yy}(f)$ is the power spectrum of signal $y(t)$. Coherence can be interpreted as a frequency-dependent correlation coefficient, and also as a measure of synchrony between two signals at the same frequency. The coherogram is a time-varying version of the coherence, estimated using consecutive windows of EEG data. We estimated coherence between two frontal EEG electrodes F7 and F8, for each subject, using multitaper methods implemented in the Chronux toolbox as above.[34] In addition to these coherence parameters, we calculated an age-varying coherogram using overlapping (0.5-yr) moving windows spanning a 2 yr age range. In order to better illustrate the coherence dynamics of patients less than 1 yr old, we computed an age-varying coherogram for infants by taking the median coherogram across patients in 0.5 yr age bins. We also computed group-level coherograms for the sevoflurane epochs by taking the median across all patients within the age groups defined above. We calculated coherence for the selected EEG epochs in each group, averaged the coherence for all epochs, and calculated 95% confidence intervals using multitaper-based jackknife techniques.[34]

Statistical analysis

To compare spectral and coherence estimates between groups, we used jackknife-based methods, the two-group test for spectra, and the two-group test for coherence, as implemented in the Chronux toolbox routine.[35] This method accounts for the underlying spectral resolution of the spectral and coherence estimates, and considers differences to be significant only if they are present for contiguous frequencies over a frequency band wider than the spectral resolution 2 W. Specifically, for frequencies $f > 2$ W, the test statistic was significant if it exceeded the P value threshold over a contiguous frequency range ≥2 W. For frequencies $0 \leq f \leq 2$ W, to account for the properties of multitaper spectral estimates at frequencies close to zero, the test statistic was significant if it exceeded the P value threshold over a contiguous frequency range from 0 to max (f, W) ≤ 2W. We selected a significance threshold of $P < 0.001$ for comparisons groups and applied a Bonferroni correction for multiple comparisons. We used the polyfit function in MATLAB (MathWorks, Natick, MA USA) to obtain the best-fit regression model to describe the relationship between age and EEG power.

Results

Power spectra analysis

Total EEG power (1–50 Hz) exhibited an increase from infancy, peaked at 5–8 yr, and subsequently declined (Fig. 1). This decline in total power began to plateau at 18–21 yr (Fig. 1). When we examined the canonical EEG bands to determine the band(s) primarily responsible for this trend, we noticed that this trend was largely preserved for all the frequency bands studied (Supplementary material, Fig. 1).

Based on these power trends, visual inspection of the individual patients, and age varying spectral and coherence dynamics (Fig. 2), we categorized the data as: <1 yr old (Group 1, n=4), 1–6 yr old (Group 2, n=12), >6–14 yr old (Group 3, n=14), >14–21 yr old (Group 4, n=11), and >21–28 yr old (Group 5, n=13). Qualitatively, Groups 2 through 5 exhibited grossly similar EEG spectral dynamics (Fig. 3B, C, G, H) that are also readily observed on the spectrogram (Fig. 3E, F, I, J). Even though Group 1 (Fig. 3A, D) exhibited increased power in the slow, and delta frequency bands, prominent alpha oscillations were noticeably absent.

Groups 2 and 3 had significantly larger spectra over a wide frequency range spanning slow through gamma frequencies

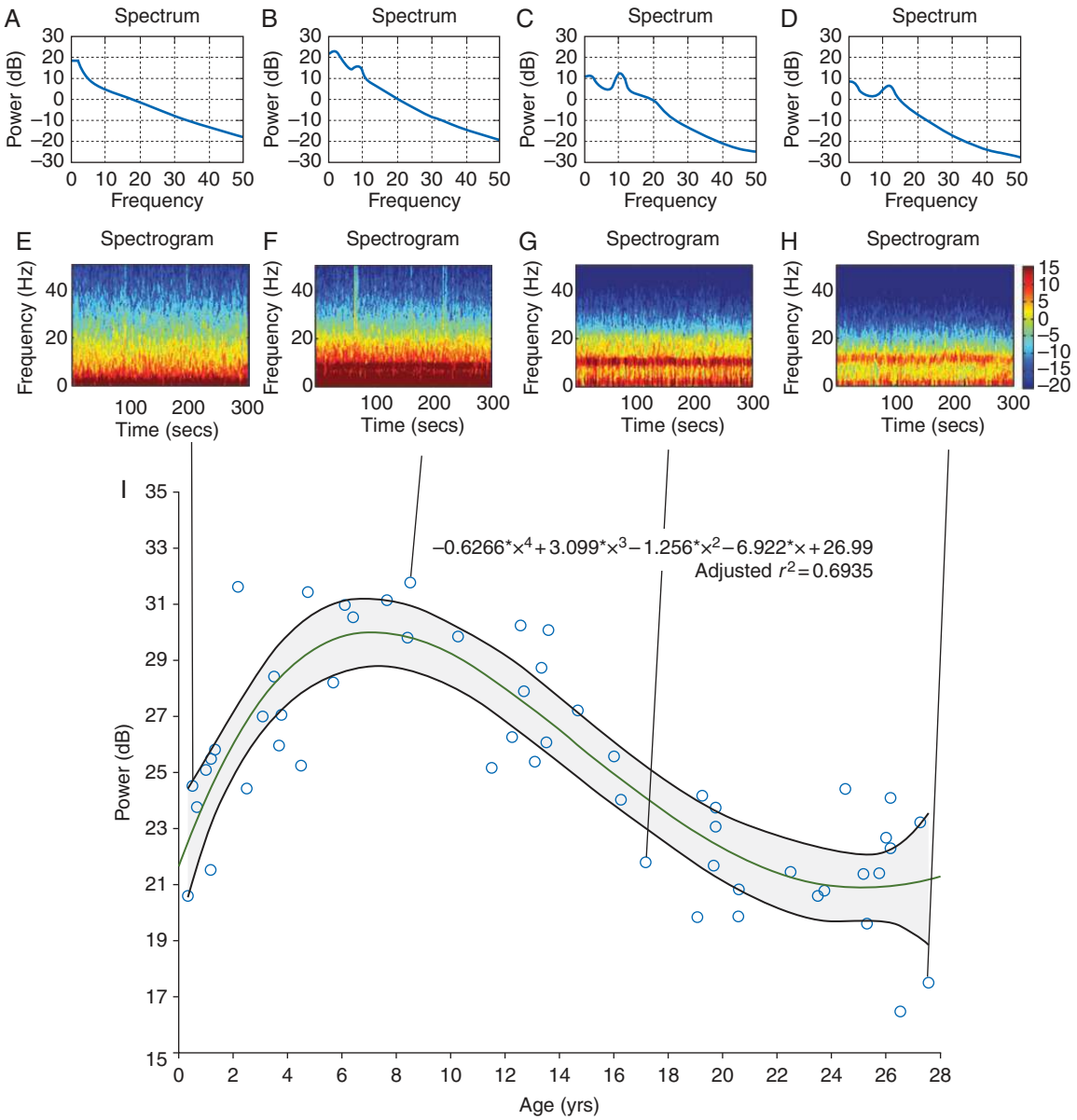

Fig 1 Trends in spectra, spectrograms, and total power with age from 0 to 28 yr old. (A–D) Representative frontal EEG spectra illustrating that slow (0.1–1 Hz), and delta (1–4 Hz) oscillations are present in all patients during general anaesthesia, maintained solely with sevoflurane. Alpha (8–12 Hz) oscillations appear to emerge after 1 yr old. (E–H) Representative frontal EEG spectrograms illustrating that slow (0.1–1 Hz), and delta (1–4 Hz) oscillations are present in all patients during general anaesthesia. Alpha (8–12 Hz) oscillations appear to emerge after 1 yr of age. (I) Total EEG power (1–50 Hz) for each subject, plotted as a function of age. The total EEG power exhibited an increase from infancy, peaked at approximately 5–8 yr old, and subsequently declined with increasing age. The green line represents a fourth degree polynomial regression model describing the relationship between age and EEG power. The shaded bounds represent the 95% confidence bounds of this regression model.

(Table 2). Compared with Group 1, alpha band power was significantly larger in Groups 2 through 5 (Table 2). Slow and delta oscillations were robust and larger in Group 1 compared with Groups 4 and 5, suggesting that this oscillatory dynamic is a feature of sevoflurane-induced general anaesthesia at this age (Table 2). Although spectral characteristics of Groups 4 and 5 were qualitatively similar, the spectra were significantly larger for Group 4 over a wide frequency range (Table 2).

Coherence analysis

We observed age-related similarities and differences in the coherence and coherograms during sevoflurane anaesthesia (Figs 2B, C, 4). Strikingly, alpha oscillation (8–13 Hz) coherence did not develop until approximately 1 yr of age. In addition, children <1 yr displayed a coherent oscillation in the slow and delta bands that was not observed in older children or adults. Otherwise, qualitatively, the coherence and coherograms appeared

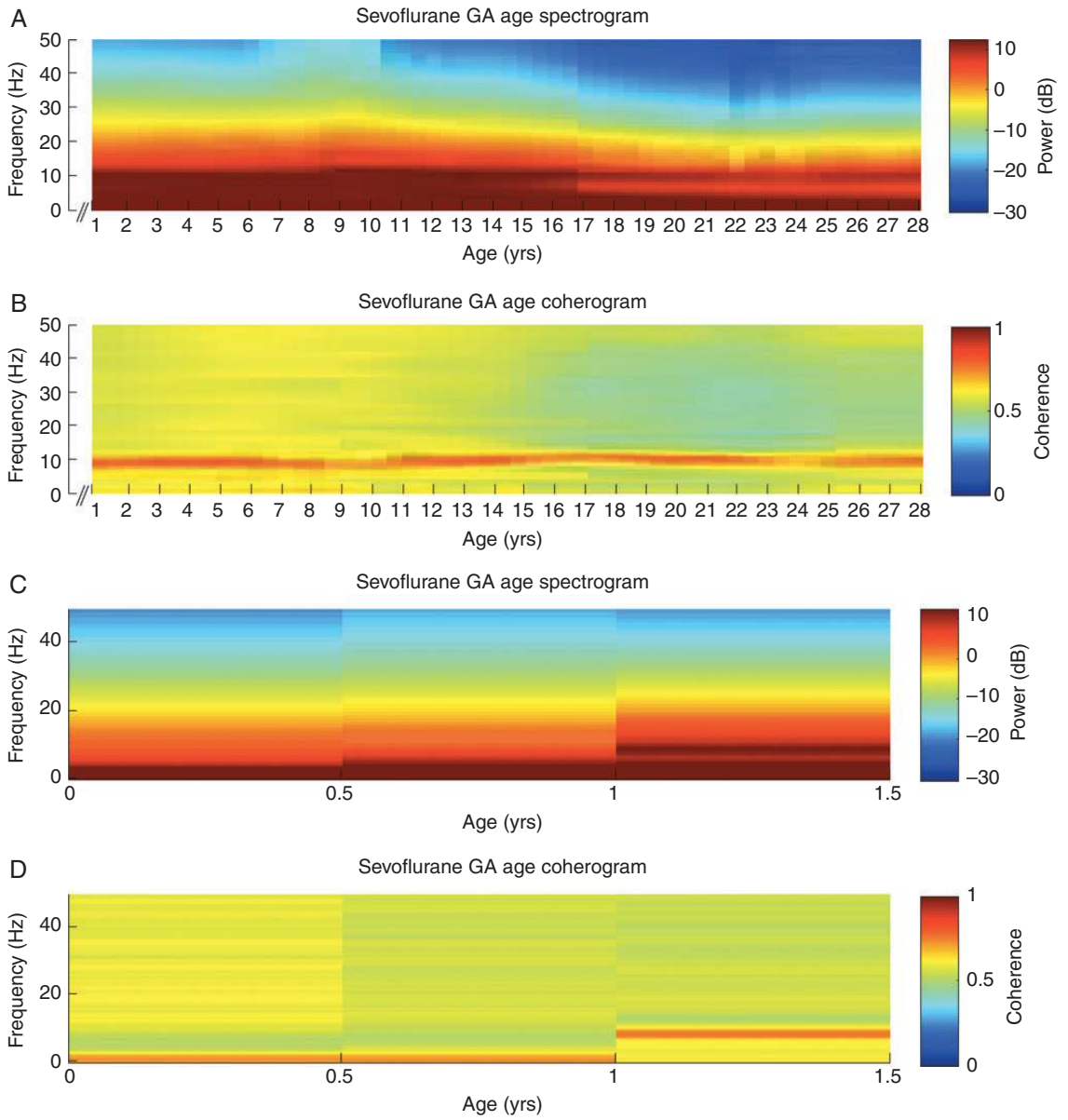

Fig 2 Age varying spectrograms and coherograms during sevoflurane general anaesthesia. (A) An age varying (1–28 yr) spectrogram representation of the EEG, showing that even though the EEG structure appears qualitatively preserved for all age ranges (presence of slow, delta, theta, and alpha oscillations), the power of these oscillations change as a function of age. (B) An age varying (1–28 yr) coherogram illustrating stably maintained, prominent alpha oscillation coherence. (C) An age varying spectrogram based representation of the EEG showing the relative absence of a well-defined alpha oscillation band at less than 1 yr of age. At approximately 1 yr of age the alpha oscillations become prominent. Slow, delta and theta oscillations are present from 0–1.5 yr. (D) An age varying coherogram illustrating the absence of alpha oscillation coherence, and slow delta band coherence, at less than 1 yr of age. This EEG dynamic appears at >1 yr of age, and is inversely correlated to slow oscillation coherence.

similar for all children >1 yr old, showing prominent coherence in the alpha band (Figs 2, 4). Compared with Group 1 (Fig. 4A, D), Groups 2 through 5 (Fig. 4B and C, E–J) exhibited significantly larger coherence in the alpha frequency range (Table 2). Also, Groups 2 through 5 exhibited similarities in coherence across a narrow coherence band overlapping the alpha band (Table 2). Compared with Groups 4 and 5, Groups 1, 2 and 3 exhibited increased coherence in a broad beta/gamma frequency range (Table 2). This could be explained by differences in brain coherence dynamics with age, or relative differences as a result of the administration of neuromuscular blocking agents (Table 1), which were used more frequently in Groups 4 and 5, and which would have a tendency to reduce frontal electromyogram signals that have high power in the beta/gamma bands.

Discussion

We found age-dependent changes in the EEG during sevoflurane anaesthesia in children. These age-dependent changes likely

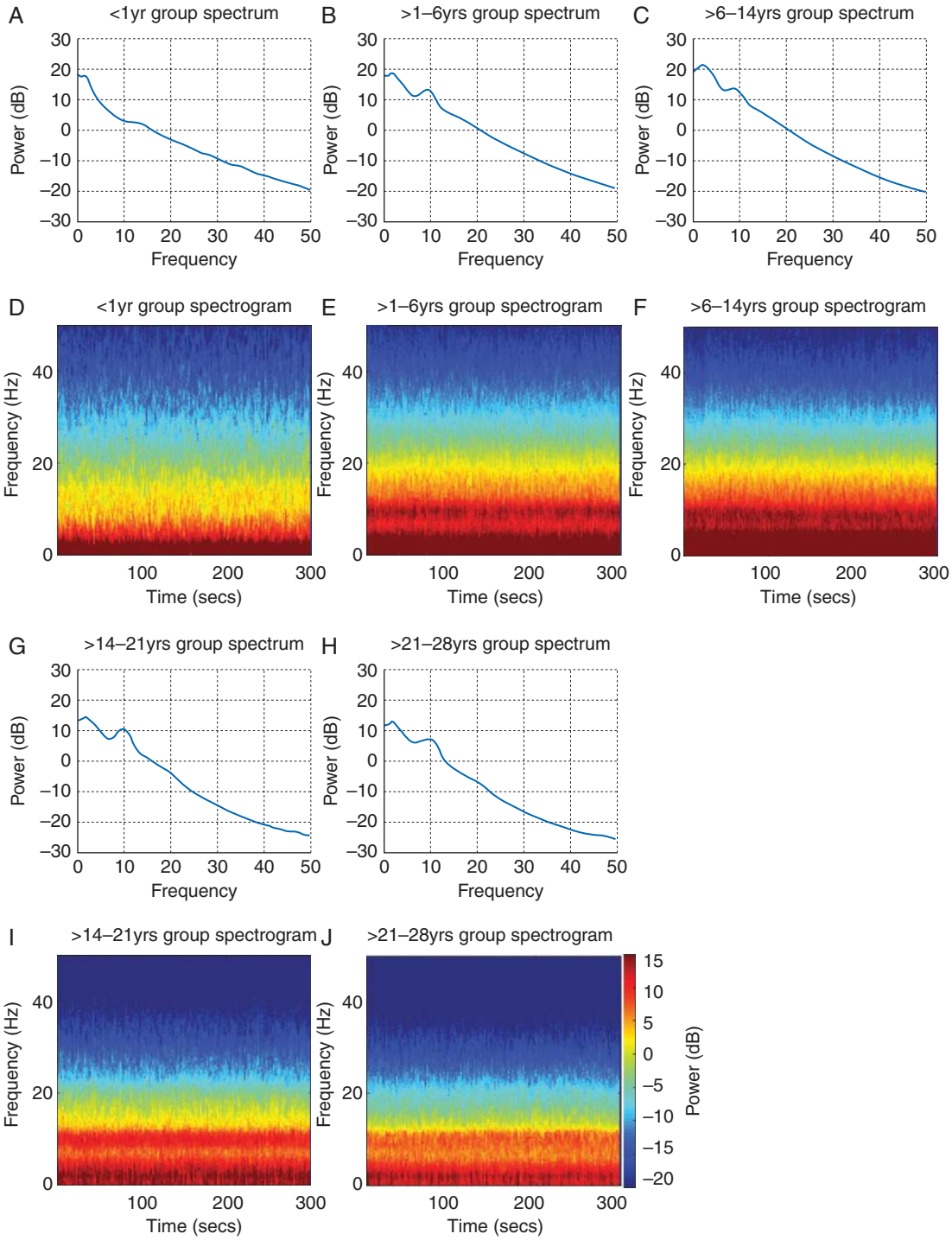

Fig 3 Median spectra and spectrograms of age groups. (A, D) Group 1 (<1 yr old). Both the power spectra and the group spectrogram show large power in the slow, delta and theta frequency bands. A prominent alpha oscillation structure is noticeably absent. (B, E) Group 2 (1–6 yr old). Both the power spectra and the group spectrogram show large power in the slow, delta, theta and alpha frequency bands. (C, F) Group 3 (>6–14 yr old). Both the power spectra and the group spectrogram show large power in the slow, delta, theta and alpha frequency bands. (G, I) Group 4 (>14–21 yr old). Both the power spectra and the group spectrogram show large power in the slow, delta, theta and alpha frequency bands. Compared with groups 2 and 3, the power in these bands is not as prominent. Power within the beta/gamma frequency band also shifts to lower levels. (H, J) Group 5 (>21–28 yr old). Both the power spectra and the group spectrogram show large power in the slow, delta, theta and alpha frequency bands. Compared with groups 2 and 3, the power in these bands is not as prominent. Power within the beta/gamma frequency band also shifts to lower levels.

Table 2 Results of statistical analysis

	Power spectra ($P<0.0001$, two group test spectra)	Coherence ($P<0.0001$, two group test coherence)
Group 1 (<1 yr) *vs* Group 2 (>1–6 yrs)	Group 2>0.1–43 Hz;	Group 1>0.1–2.9 Hz; Group 2>4.4–12.2 Hz;
Group 1 (<1yr) *vs* Group 3 (>6–14 yrs)	Group 3>0.1–33.7 Hz;	Group 1>0.1–2.9 Hz; 18.6–25.9 Hz; 27.8–38 Hz; Group 3>6.4–12.7 Hz; 44.9–48.8 Hz;
Group 1 (<1 yr) *vs* Group 4 (>14–21 yrs)	Group 1>0.1–2.9 Hz; 22.5–50 Hz; Group 4>3.9–19 Hz;	Group 1>0.1–3.9 Hz; 13.7–50 Hz; Group 4>8.3–12.7 Hz;
Group 1 (<1 yr) *vs* Group 5 (>21–28 yrs)	Group 1>0.1–6.8 Hz; 17.6–50 Hz; Group 5>7.8–13.7 Hz;	Group 1>0.1–3.9 Hz; 15.1–50 Hz; Group 5>6.8–13.2 Hz
Group 2 (>1–6 yrs) *vs* Group 3 (>6–14 yrs)	Group 2>27.9–34.2 Hz; Group 3>1.5–9.3 Hz; 12.7–18.1 Hz	Group 2>8.8–11.7 Hz; 18.6–37.6 Hz; 45.4–48.3 Hz
Group 2 (>1–6 yrs) *vs* Group 4 (>14–21 yrs)	Group 2>0.1–50 Hz	Group 2>0.1–10.7 Hz; 13.7–50 Hz;
Group 2 (>1–6 yrs) *vs* Group 5 (>21–28 yrs)	Group 2>0.1–50 Hz	Group 2>0.1–10.7 Hz; 15.1–45.9 Hz;
Group 3 (>6–14 yrs) *vs* Group 4 (>14–21 yrs)	Group 3>0.1–50 Hz	Group 3>0.1–4.4 Hz; 6.8–9.7 Hz; 13.1–38.6 Hz;
Group 3 (>6–14 yrs) *vs* Group 5 (>21–28 yrs)	Group 3>0.1–50 Hz	Group 3> 0.9–3.9 Hz; 15.6–34.2 Hz;
Group 4 (>14–21 yrs) *vs* Group 5 (>21–28yrs)	Group 4>0.1–45.4 Hz	Group 5>12.2–21.5 Hz; 41–48.8 Hz;

relate to changes in brain structure and function that occur during development, and could provide insights into why depth-of-anaesthesia monitoring devices do not accurately reflect the brain states of paediatric patients. We briefly summarize our findings as follows: (1) Compared with the adolescent (>14–21 yr) and young adult populations (>21–28 yr), EEG power in the paediatric population (>1 yr) was much larger between 0.1–50 Hz. (2) Alpha band coherence structure was similar between paediatric (>1 yr), young adult, and adult populations. (3) Infants (<1 yr) did not exhibit prominent power or coherence in the alpha band, suggesting that the neural circuitry necessary for this dynamic, develops at about 1 yr of age.

Age-related EEG power changes likely reflect the time course of typical human brain development. The brain is comprised of a complex network of neurones and supportive cells that follow a defined structural and functional spatiotemporal development pattern from embryogenesis, through infancy, childhood, adolescence, adulthood, and senescence.[36–38] These changes are governed by biological events such as neurogenesis, programmed cell death, myelination, axonal and dendritic growth, synaptogenesis, and refinement of synaptic connections.[37] In humans, synaptogenesis begins approximately post-birth and synaptic density increases to maximum levels by approximately 2 yr.[39–41] The brain subsequently undergoes a process of synaptic refinement and pruning to reduce the number of synapses to adult levels by mid-adolescence.[41–43] Data from human and non-human primate studies indicating a gradual increase (from birth) to a peak (approximately 5 yr), and then a gradual decline to a plateau (approximately 18 yr) of excitatory synaptic strength in the prefrontal cortex[38] parallels the sevoflurane-induced changes in EEG power that we observed. We conjecture that the age-related, sevoflurane-induced EEG power changes that we describe are a manifestation of typical developmental synaptic pruning and synaptic refinement. In addition, development in neuronal circuits is governed by 'critical periods' of enhanced plasticity during childhood, whose timing and trajectory are governed by GABAergic inhibitory circuits.[44] Recent findings suggest that sevoflurane-induced EEG oscillations are mediated by GABAergic circuits, similar to propofol.[18] We therefore conjecture that the observed age-dependent changes in EEG power could be related to the state of GABAergic circuits during childhood development, which in turn could reflect the state and trajectory of critical periods in the developing human brain.

A recent functional magnetic resonance imaging (fMRI) study, investigating the development of thalamocortical connectivity, found a log linear growth of functional connectivity between thalamus and cortex within the first two yrs of life.[45] Specifically, functional networks comprised of the thalamus and medial visual cortex, thalamus and the default mode network, developed at approximately 1 yr.[45] In the frontal EEG of infants (<1 yr), we found that the coherent frontal alpha oscillations that have been described for propofol[15 16 19–21 32] and sevoflurane[18] are markedly absent. We speculate that the establishment of thalamocortical connectivity necessary for spatially coherent anaesthesia-induced alpha oscillations develops at approximately 1 yr. Thus, the developmental time course of anaesthesia-induced oscillations may parallel the developing thalamocortical functional networks observed in these fMRI studies. Given that disruption of the early establishment of thalamocortical connectivity has been linked to developmental disorders such as schizophrenia,[22 46] bipolar disorder[47] and autism,[48] this anaesthesia-induced EEG signature in the context of these developmental disorders merits further study.

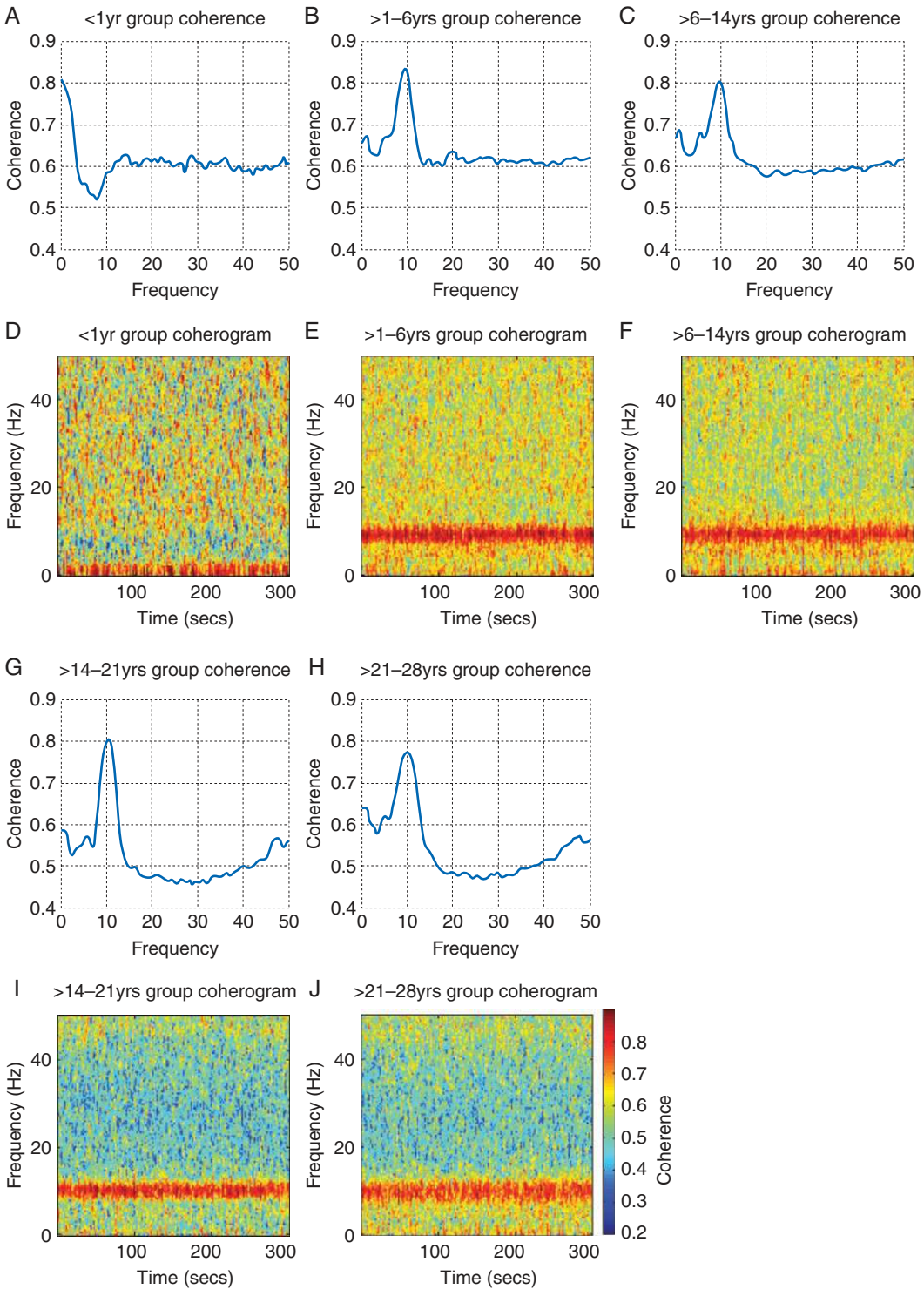

Fig 4 Median coherence and coherograms of age groups. (A, D) Group 1 (<1 yr old). The median coherence and coherogram shows a lack of coherence in the alpha frequency band and significant coherence in the slow, and delta bands. (B, E) Group 2 (1–6 yr old). The median coherence and coherogram shows a strong coherence in the alpha frequency band. (C, F) Group 3 (>6–14 yr old). The median coherence and coherogram shows a strong coherence in the alpha frequency band. (G, I) Group 4 (>14–21 yr old). The median coherence and coherogram shows a strong coherence in the alpha frequency band. (H, J) Group 5 (>21–28 yr old). The median coherence and coherogram shows a strong coherence in the alpha frequency band.

Our findings suggest a flaw in the current approach, of simplifying EEG data to a single index to represent depth of anaesthesia. Since EEG dynamics in the paediatric population varies as a function of age,[49–51] index-based depth of anaesthesia clinical brain monitors may not accurately summarize brain-states of paediatric patients. Elevated EEG power in high frequencies (e.g. beta and gamma bands) can signal lighter levels of anaesthesia in adults.[16 17 19] In contrast, our analysis shows that power in these higher-frequency bands is elevated in children greater than 1 yr of age at surgical concentrations of anaesthesia when compared with adults. This important difference could cause index-based depth of anaesthesia monitors to compute a falsely elevated index value in children. In such instances, these falsely elevated index values, could lead to increased anaesthetic drug dosing beyond what is required.

The spectral and coherence EEG signatures of sevoflurane reported here for children greater than 1 yr of age qualitatively resemble those previously identified in adults for propofol[15 16 19–21 32] and sevoflurane[18] at surgical anaesthetic concentrations. Other signatures may also be conserved between propofol[16 17] and sevoflurane[52 53] at non-surgical anaesthetic concentrations. This suggests that a similar, conceptually consistent approach could be used to monitor both children and adults during general anaesthesia, where drug- and age-specific EEG signatures are used to maintain the desired brain state dictated by the clinical indication. Under such a framework, anaesthetic brain monitoring may in fact be easier in children, as anaesthesia-induced EEG signals are much larger in children and thus easier to accurately estimate and track. Anaesthesia-induced EEG dynamics in children less than 1 yr of age are both quantitatively and qualitatively different from those of older children, suggesting that the anaesthesia-related neurophysiology of these infants must be studied in greater detail, and that an anaesthetic monitoring approach could be constructed specifically for children in this age range.

A limitation of this study is that anaesthetic agents and adjuncts were not equally administered (Table 1). It is therefore possible that the observed differences in EEG power and coherence reflect anaesthetic management rather than age. However, this is very unlikely given our prior knowledge of the clinical circumstances, our understanding of anaesthesia-induced EEG oscillations in adults, and the magnitude of age-dependent changes in EEG power and coherence observed. In this study, sevoflurane and adjuncts were administered to maintain a level of general anaesthesia necessary for the surgical stimulus in each individual patient, guided by clinical experience and assessment of physiological parameter, such that irrespective of age, patients would be unconscious and unresponsive to surgical stimuli. Under such conditions, the EEG showed age-dependent changes, where, for patients >1 yr of age, there were ~three-fold differences in signal amplitude (~9–10 dB; Fig. 1) across the age-range studied, and for patients <1 yr of age, there was a completely different dynamic in terms of spectrum and coherence (Figs 2, 3, and 4). Given that patients were on average unconscious and unresponsive, based on our understanding of the anaesthesia-induced EEG changes in adults,[14 16–18 54 55] it is highly unlikely that a ~three-fold difference in EEG amplitude could occur as a result of small differences in sevoflurane dose. Instead, changes in the effective dose of anaesthetic would tend to change the structure of the EEG signal, shifting alpha oscillation to a higher frequency at lower doses, and moving into burst suppression at higher doses.[14 16 54 55] Figs 1 through 4 clearly show that the alpha peak and overall structure of the signal are consistent for patients >1 yr of age, indicating that, on the whole, patients were in a similar brain state across the age range. Similarly, small changes in anaesthetic dose could not produce the dynamic patterns observed in the <1 yr-old patients.

Adult patients in our study were administered neuromuscular blocking agents more frequently than the paediatric population. Prior neurophysiological observations suggest that reduced neuromuscular blocking agent administration should cause increased high frequency power,[56–59] and possibly coherence, in the paediatric EEG. However, we noticed increased power in the lower frequency bands featuring highly structured oscillations that qualitatively resemble anaesthesia-induced EEG patterns in adults,[15–21 32] in the absence of muscle artifacts. It is therefore unlikely that the use of neuromuscular blocking agents could explain the large differences in EEG power (at frequencies <24 Hz) that we observed between children and adults.

Skull conductivity is known to change during normal human development and aging. In particular, fontanel closure and increases in skull thickness both decrease overall skull conductivity. This decrease in skull conductivity would have the effect of reducing EEG signal amplitude. Given the increase in EEG power we observed between 3 months and approximately 8 yr of age, age-dependent increases in skull conductivity likely mask a larger effect on the underlying cortical circuits that generate the EEG signal. At frequencies <100 Hz, changes in skull conductivity affect all frequencies equally, and would not alter the frequency structure of the EEG.[60] However, we found significant differences in alpha oscillation structure between <1 yr old and >1 yr old patients. We therefore conclude that the age-dependent changes in EEG power and coherence we observed during anaesthesia reflect neurobiological characteristics of the developing brain.

In contrast to the adult population, brain-state monitoring strategies for paediatric patients receiving general anaesthesia have not been developed. In adults, volunteer studies have been an important source of data relating the EEG to anaesthetic brain states. In children, however, such volunteer studies cannot be carried out because of safety and ethical concerns.[9 11 49–51 61] Therefore, retrospective and observational studies of paediatric patients receiving general anaesthesia or sedation as part of routine care are a crucial source of information, and may be one of the only viable sources of data for studying anaesthesia-related neurophysiology in children. By studying the age-related effects of sevoflurane anaesthesia on the EEG, we have found differences between paediatric and adult EEG dynamics that may reflect typical brain development processes. In the future, studies such as this will facilitate a more principled drug- and age-specific neurophysiological definition of anaesthetic brain states. A more precise neurophysiological definition of anaesthetic brain-states will lay the foundation for improved age-appropriate brain monitoring strategies, and may offer a practical approach to reducing potential anaesthetic risks in children.[61]

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

O.A., K.J.P., and J.A.T. contributed to data collection, data analysis, data interpretation, and writing of the manuscript. P.G.F., M.P. and E.S.S. contributed to data collection, and critically revising the manuscript. M.B.W. contributed to data analysis and critically revising the manuscript. E.N.B. and P.L.P. contributed to conceiving the project, data interpretation, data analysis, supervision of data analysis, and writing of the

manuscript. All of the authors read and approved the final manuscript.

Declaration of interest

O.A., E.N.B. and P.L.P. have submitted a provisional patent application describing the use of the EEG measures described in this manuscript, for monitoring sedation and general anaesthesia. All other authors do not have a conflict of interest to declare.

Funding

DP2-OD006454 (to P.L.P.); DP1-OD003646 and TR01-GM104948 (to E.N.B.) from the National Institutes of Health, Bethesda, MD USA; Foundation of Anesthesia Education and Research, Rochester, MN USA (to O.A.); Massachusetts General Hospital Faculty Development Award, Boston, MA USA (to O.A.); Funds from the Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA USA; Partners Innovation Award, Partners Healthcare, Boston, MA USA (to P.L.P.).

References

1. Jevtovic-Todorovic V, Absalom AR, Blomgren K, *et al*. Anaesthetic neurotoxicity and neuroplasticity: an expert group report and statement based on the BJA Salzburg Seminar. *Br J Anaesth* 2013; **111**: 143–51
2. Lin EP, Soriano SG, Loepke AW. Anesthetic neurotoxicity. *Anesthesiol Clin* 2014; **32**: 133–55
3. McCann ME, Soriano SG. General anesthetics in pediatric anesthesia: influences on the developing brain. *Curr Drug Targets* 2012; **13**: 944–51
4. Wilder RT, Flick RP, Sprung J, *et al*. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology* 2009; **110**: 796–804
5. Sanders RD, Hassell J, Davidson AJ, Robertson NJ, Ma D. Impact of anaesthetics and surgery on neurodevelopment: an update. *Br J Anaesth* 2013; **110**(Suppl 1): i53–72
6. Wodey E, Tirel O, Bansard JY, *et al*. Impact of age on both BIS values and EEG bispectrum during anaesthesia with sevoflurane in children. *Br J Anaesth* 2005; **94**: 810–20
7. Tirel O, Wodey E, Harris R, Bansard JY, Ecoffey C, Senhadji L. The impact of age on bispectral index values and EEG bispectrum during anaesthesia with desflurane and halothane in children. *Br J Anaesth* 2006; **96**: 480–5
8. Kim HS, Oh AY, Kim CS, Kim SD, Seo KS, Kim JH. Correlation of bispectral index with end-tidal sevoflurane concentration and age in infants and children. *Br J Anaesth* 2005; **95**: 362–6
9. Davidson AJ, Huang GH, Rebmann CS, Ellery C. Performance of entropy and Bispectral Index as measures of anaesthesia effect in children of different ages. *Br J Anaesth* 2005; **95**: 674–9
10. Edwards JJ, Soto RG, Bedford RF. Bispectral Index values are higher during halothane vs. sevoflurane anesthesia in children, but not in infants. *Acta Anaesthesiologica Scandinavica* 2005; **49**: 1084–7
11. Davidson AJ, Czarnecki C. The Bispectral Index in children: comparing isoflurane and halothane. *Br J Anaesth* 2004; **92**: 14–7
12. Klockars JG, Hiller A, Ranta S, Talja P, van Gils MJ, Taivainen T. Spectral entropy as a measure of hypnosis in children. *Anesthesiology* 2006; **104**: 708–17
13. Avidan MS, Jacobsohn E, Glick D, *et al*. Prevention of intraoperative awareness in a high-risk surgical population. *The New England Journal of Medicine* 2011; **365**: 591–600
14. Gibbs FA, Gibbs LE, Lennox WG. Effects on the electroencephalogram of certain drugs which influence nervous activity. *Arch Intern Med* 1937; **60**: 154–66
15. Lewis LD, Weiner VS, Mukamel EA, *et al*. Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness. *Proc Natl Acad Sci USA* 2012; **109**: E3377–86
16. Purdon PL, Pierce ET, Mukamel EA, *et al*. Electroencephalogram signatures of loss and recovery of consciousness from propofol. *Proc Natl Acad Sci USA* 2013; **110**: E1142–51
17. Akeju O, Pavone KJ, Westover MB, *et al*. A Comparison of Propofol- and Dexmedetomidine-induced Electroencephalogram Dynamics Using Spectral and Coherence Analysis. *Anesthesiology* 2014; **121**: 978–89
18. Akeju O, Westover MB, Pavone KJ, *et al*. Effects of Sevoflurane and Propofol on Frontal Electroencephalogram Power and Coherence. *Anesthesiology* 2014; **121**: 990–8
19. Cimenser A, Purdon PL, Pierce ET, *et al*. Tracking brain states under general anesthesia by using global coherence analysis. *Proc Natl Acad Sci USA* 2011; **108**: 8832–7
20. Feshchenko VA, Veselis RA, Reinsel RA. Propofol-induced alpha rhythm. *Neuropsychobiology* 2004; **50**: 257–66
21. Gugino LD, Chabot RJ, Prichep LS, John ER, Formanek V, Aglio LS. Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane. *Br J Anaesth* 2001; **87**: 421–8
22. Klingner CM, Langbein K, Dietzek M, *et al*. Thalamocortical connectivity during resting state in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience* 2014; **264**: 111–9
23. Ching S, Cimenser A, Purdon PL, Brown EN, Kopell NJ. Thalamocortical model for a propofol-induced alpha-rhythm associated with loss of consciousness. *Proc Natl Acad Sci USA* 2010; **107**: 22665–70
24. Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA. Disruption of frontal-parietal communication by ketamine, propofol, and sevoflurane. *Anesthesiology* 2013; **118**: 1264–75
25. Mhuircheartaigh NR, Warnaby C, Rogers R, Jbabdi S, Tracey I. Slow-wave activity saturation and thalamocortical isolation during propofol anesthesia in humans. *Sci Transl Med* 2013; **5**: 208ra148
26. Murphy M, Bruno MA, Riedner BA, *et al*. Propofol anesthesia and sleep: a high-density EEG study. *Sleep* 2011; **34**: 283–91
27. Brown EN, Purdon PL, Van Dort CJ. General anesthesia and altered states of arousal: a systems neuroscience analysis. *Annu Rev Neurosci* 2011; **34**: 601–28
28. Vizuete JA, Pillay S, Ropella KM, Hudetz AG. Graded defragmentation of cortical neuronal firing during recovery of consciousness in rats. *Neuroscience* 2014; **275**: 340–51
29. Buzsaki G, Anastassiou CA, Koch C. The origin of extracellular fields and currents–EEG, ECoG, LFP and spikes. *Nature Reviews Neuroscience* 2012; **13**: 407–20
30. Buzsáki G. *Rhythms of the Brain*. Oxford, New York: Oxford University Press, 2006
31. Brown EN, Solt K, Purdon PL, Akeju O. Monitoring Brain State During General Anesthesia and Sedation. *Miller's Anesthesia*: Philadelphia: Elsevier, 2014 (Chapter 50)
32. Supp GG, Siegel M, Hipp JF, Engel AK. Cortical hypersynchrony predicts breakdown of sensory processing during loss of consciousness. *Curr Biol* 2011; **21**: 1988–93
33. Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. *The New England Journal of Medicine* 2010; **363**: 2638–50

34. Percival DB, Walden AT. *Spectral Analysis for Physical Applications*. Cambridge: Cambridge University Press, 1993 (Chapter 7)
35. Bokil H, Purpura K, Schoffelen JM, Thomson D, Mitra P. Comparing spectra and coherences for groups of unequal size. *Journal of Neuroscience Methods* 2007; **159**: 337–45
36. Power JD, Fair DA, Schlaggar BL, Petersen SE. The development of human functional brain networks. *Neuron* 2010; **67**: 735–48
37. Borre YE, O'Keeffe GW, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota and neurodevelopmental windows: implications for brain disorders. *Trends in Molecular Medicine* 2014; **20**: 509–18
38. Insel TR. Rethinking schizophrenia. *Nature* 2010; **468**: 187–93
39. Herschkowitz N, Kagan J, Zilles K. Neurobiological bases of behavioral development in the first year. *Neuropediatrics* 1997; **28**: 296–306
40. Petanjek Z, Judas M, Simic G, *et al*. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proc Natl Acad Sci USA* 2011; **108**: 13281–6
41. Glantz LA, Gilmore JH, Hamer RM, Lieberman JA, Jarskog LF. Synaptophysin and postsynaptic density protein 95 in the human prefrontal cortex from mid-gestation into early adulthood. *Neuroscience* 2007; **149**: 582–91
42. Huttenlocher PR. Synaptic density in human frontal cortex - developmental changes and effects of aging. *Brain Research* 1979; **163**: 195–205
43. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *The Journal of Comparative Neurology* 1997; **387**: 167–78
44. Hensch TK. Critical period plasticity in local cortical circuits. *Nature Reviews Neuroscience* 2005; **6**: 877–88
45. Alcauter S, Lin W, Smith JK, *et al*. Development of thalamocortical connectivity during infancy and its cognitive correlations. *The Journal of Neuroscience* 2014; **34**: 9067–75
46. Marenco S, Stein JL, Savostyanova AA, *et al*. Investigation of anatomical thalamo-cortical connectivity and FMRI activation in schizophrenia. *Neuropsychopharmacology* 2012; **37**: 499–507
47. Anticevic A, Cole MW, Repovs G, *et al*. Characterizing Thalamo-Cortical Disturbances in Schizophrenia and Bipolar Illness. *Cerebral Cortex* 2014; **24**: 3116–30
48. Nair A, Treiber JM, Shukla DK, Shih P, Muller RA. Impaired thalamocortical connectivity in autism spectrum disorder: a study of functional and anatomical connectivity. *Brain : A Journal of Neurology* 2013; **136**: 1942–55
49. Davidson AJ, Sale SM, Wong C, *et al*. The electroencephalograph during anesthesia and emergence in infants and children. *Paediatric Anaesthesia* 2008; **18**: 60–70
50. McKeever S, Johnston L, Davidson AJ. An observational study exploring amplitude-integrated electroencephalogram and spectral edge frequency during paediatric anaesthesia. *Anaesthesia and Intensive Care* 2012; **40**: 275–84
51. Hayashi K, Shigemi K, Sawa T. Neonatal electroencephalography shows low sensitivity to anesthesia. *Neuroscience Letters* 2012; **517**: 87–91
52. Kaskinoro K, Maksimow A, Georgiadis S, *et al*. Electroencephalogram reactivity to verbal command after dexmedetomidine, propofol and sevoflurane-induced unresponsiveness. *Anaesthesia* 2015; **70**: 190–204
53. Blain-Moraes S, Tarnal V, Vanini G, *et al*. Neurophysiological Correlates of Sevoflurane-induced Unconsciousness. *Anesthesiology* 2015; **122**: 307–16
54. Bennett C, Voss LJ, Barnard JP, Sleigh JW. Practical use of the raw electroencephalogram waveform during general anesthesia: the art and science. *Anesthesia and Analgesia* 2009; **109**: 539–50
55. Martin JT, Faulconer A Jr, Bickford RG. Electroencephalography in anesthesiology. *Anesthesiology* 1959; **20**: 359–76
56. Messner M, Beese U, Romstock J, Dinkel M, Tschaikowsky K. The bispectral index declines during neuromuscular block in fully awake persons. *Anesthesia and Analgesia* 2003; **97**: 488–91, table of contents
57. Vivien B, Di Maria S, Ouattara A, Langeron O, Coriat P, Riou B. Overestimation of Bispectral Index in sedated intensive care unit patients revealed by administration of muscle relaxant. *Anesthesiology* 2003; **99**: 9–17
58. Dahaba AA, Mattweber M, Fuchs A, *et al*. The effect of different stages of neuromuscular block on the bispectral index and the bispectral index-XP under remifentanil/propofol anesthesia. *Anesthesia and Analgesia* 2004; **99**: 781–7, table of contents
59. Hans P, Giwer J, Brichant JF, Dewandre PY, Bonhomme V. Effect of an intubation dose of rocuronium on Spectral Entropy and Bispectral Index responses to laryngoscopy during propofol anaesthesia. *Br J Anaesth* 2006; **97**: 842–7
60. Hamalainen M, Hari R, Ilmoniemi RJ, Knuutila J, Lounasmaa OV. Magnetoencephalography– theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics* 1993; **65**: 413–97
61. Davidson AJ. Monitoring the anaesthetic depth in children - an update. *Current Opinion in Anaesthesiology* 2007; **20**: 236–43

Handling editor: H. C. Hemmings