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The Ageing Brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia

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Abstract

Background: Anaesthetic drugs act at sites within the brain that undergo profound changes during typical ageing. We postulated that anaesthesia-induced brain dynamics observed in the EEG change with age.
Methods: We analysed the EEG in 155 patients aged 18–90 yr who received propofol (n=60) or sevoflurane (n=95) as the primary anaesthetic. The EEG spectrum and coherence were estimated throughout a 2 min period of stable anaesthetic maintenance. Age-related effects were characterized by analysing power and coherence as a function of age using linear regression and by comparing the power spectrum and coherence in young (18- to 38-yr-old) and elderly (70- to 90-yr-old) patients.
Results: Power across all frequency bands decreased significantly with age for both propofol and sevoflurane; elderly patients showed EEG oscillations ~2- to 3-fold smaller in amplitude than younger adults. The qualitative form of the EEG appeared similar regardless of age, showing prominent alpha (8–12 Hz) and slow (0.1–1 Hz) oscillations. However, alpha band dynamics showed specific age-related changes. In elderly compared with young patients, alpha power decreased more than slow power, and alpha coherence and peak frequency were significantly lower. Older patients were more likely to experience burst suppression.
Conclusions: These profound age-related changes in the EEG are consistent with known neurobiological and neuroanatomical changes that occur during typical ageing. Commercial EEG-based depth-of-anaesthesia indices do not account for age and are therefore likely to be inaccurate in elderly patients. In contrast, monitoring the unprocessed EEG and its spectrogram can account for age and individual patient characteristics.

Key words: ageing; brain monitoring; EEG; elderly; electroencephalography; propofol; sevoflurane

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Editor's key points

- The brain undergoes normal age-related changes in structure and function that might influence anaesthetic-induced changes in the EEG.
- Age-dependent changes in EEG spectrum and coherence were analysed in 60 patients receiving propofol and 95 patients receiving sevoflurane anaesthesia.
- Elderly patients showed reduced alpha-band EEG power and coherence, consistent with age-dependent changes in thalamocortical function.
- Elderly patients were also more likely to experience episodes of burst suppression.
- These age-dependent changes in the effects of anaesthesia on the EEG have important implications for the utility of EEG-based depth-of-anaesthesia monitors.

In the USA, nearly 100 000 patients receive general anaesthesia and sedation daily to facilitate surgical procedures and non-surgical diagnostic procedures.[1] A high proportion of the patients receiving anaesthesia care are elderly, defined as 60 yr of age or older. As the population ages, the proportion of the elderly that will require anaesthesia care will continue to increase.[2] In fact, it is almost certain that a 70-yr-old will have a minimum of one anaesthetic exposure.

Anaesthetic management of older patients requires different approaches compared with that of younger patients. Anaesthetic doses required to achieve the same anaesthetic state in elderly patients can be up to half those needed for younger patients.[3] The lower anaesthetic requirements for the elderly have been ascribed to declines in cardiovascular, respiratory, hepatic and renal function that occur with ageing.[4] Although these factors certainly contribute, the primary sites of anaesthetic effects are in the central nervous system. The adverse consequences of these effects are now readily apparent, as delirium and postoperative cognitive dysfunction after general anaesthesia and sedation are growing concerns in elderly patients showing typical ageing,[5] defined as anatomical and physiological changes that occur in the brain with age in the absence of a neuropsychiatric or neurodegenerative disorder.[6] Hence, more attention must to be paid to the brain and how typical brain ageing affects anaesthetic requirements and increased susceptibility to cognitive disorders.[7]

The changes in brain anatomy and physiology associated with typical ageing are numerous. They include reduced brain volume and cortical thinning, particularly in the prefrontal cortex;[6 8] decreases in the number of dendritic spines on pyramidal neurons;[9] myelin damage;[10] loss of white matter;[11] and increases in ventricular size.[11] There is also a decrease in neurotransmitter synthesis,[10] reduced neuroprotection and neurogenesis mechanisms,[12] and increased susceptibility to oxidative stress and inflammation.[13 14] Given that typical ageing affects every part of the brain, it is not surprising that anaesthetic requirements of elderly patients decline and postoperative cognitive disorders are more likely to occur.

Anaesthetic effects can be monitored with the electroencephalogram (EEG), which can be used to guide anaesthetic administration.[7 15–19] EEG-derived depth-of-anaesthesia indices available in commercially marketed brain monitors are widely available;[20–28] however, these indices are not age adjusted because they have been constructed under the assumption that the same index value defines an equivalent anaesthetic state independent of anaesthetic agent and patient age. It is now appreciated that the patterns observed in the unprocessed EEG and the spectrogram during general anaesthesia maintained by either propofol or an ether-based anaesthetic have two readily visible characteristics: simultaneous slow (<1 Hz) and alpha oscillations (8–12 Hz) present predominantly in the frontal EEG leads.[29–34] For propofol and sevoflurane, the alpha oscillations are coherent across the front of the head.[31–33] In contrast, propofol-induced slow oscillations are present across the entire head, yet do not appear to be coherent.[29 31 32] Furthermore, for propofol, these patterns can be linked to the molecular targets and neural circuits on which it is believed to act.[1 31 35–37] Given the profound changes that occur in brain anatomy and physiology with typical ageing, it is reasonable to postulate that the EEG patterns of elderly patients and young patients under general anaesthesia differ.

As a first step towards devising an age-adjusted approach to monitoring the anaesthetic states in elderly patients, we characterized the differences in the spectral features of the EEG at surgical planes of general anaesthesia across a cohort of patients from 18 to 90 yr of age for whom the primary anaesthetic was either propofol or sevoflurane.

Methods

Patient selection and data collection

The Human Research Committee at Massachusetts General Hospital approved this retrospective observational study. We reviewed our database of 627 patients who underwent general anaesthesia and simultaneous EEG recordings collected between September 1, 2011 and May 1, 2014. We identified 328 patients for whom either sevoflurane (n=210) or propofol (n=118) was administered as the primary anaesthetic. From these, we excluded 46 patients younger than 18 yr of age, 36 instances where patients received an epidural or nerve block, and 19 instances where patients were breathing spontaneously. Of the remaining 227 patients, we identified 81 patients with propofol as the sole hypnotic agent and 146 patients with sevoflurane as the sole hypnotic. All 227 EEGs were reviewed for spectral artefacts and noise. We excluded patients who were improperly fitted with EEG electrodes resulting in poor data quality, spectral artefacts caused by train-of-four monitors or electrocautery, and patients who were undergoing a procedure that interfered with electrode placement or connections. Ultimately, 155 patients, 60 for propofol and 95 for sevoflurane, were deemed suitable for analysis. For each drug, we identified a cohort of young patients (age 18–38 yr) and a cohort of elderly patients (age 70–90 yr) to be analysed as separate groups to assess differences in EEG structure [propofol young, n=18, age 27.7 (SD 6.8) yr; propofol old, n=8, age 80 (6.0) yr; sevoflurane young, n=34, age 26.9 (6.0) yr; and sevoflurane old, n=12, age 77.2 (5.4) yr].

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, and 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 earth electrode at Fpz and reference electrode ~1 cm above Fpz. Electrode impedance was less than 5 kΩ for each electrode.

We selected EEG data segments using information from both the electronic anaesthesia record (Metavision, Dedham, MA, USA) and EEG spectral analysis. For each subject, we selected a contiguous 2 min window of EEG for analysis, beginning ~10 min after the start of surgery. We visually inspected the EEG spectrogram to ensure that the analysis windows were free of artefacts, did not contain burst suppression, and that EEG dynamics were stable (i.e. not transitioning to burst suppression

or emergence). Sevoflurane concentrations were captured automatically, and care providers recorded other drugs administered manually in the electronic medical record. Table 1 summarizes the subject characteristics, the end-tidal sevoflurane vapour concentrations, and the propofol infusion rates used during the selected maintenance phases of the EEG epochs, and provides additional information on co-administered drugs. We characterized the relationship between end-tidal sevoflurane concentration and age using linear regression analysis after converting end-tidal concentrations to age-adjusted minimal alveolar concentration (MAC) equivalent values.[38] Two of the authors (P.L.P. and K.J.P.) visually inspected all EEG data for each subject and manually selected data segments free of noise and artefacts for analysis.

Spectral analysis

We computed the power spectrum and spectrogram for each subject using multitaper spectral estimation methods implemented in the Chronux toolbox.[39] The power spectrum or 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 derived an approximate Laplacian EEG electrode that equally weighted the signals obtained from Fp1, Fp2, F7, and F8. We estimated the spectra and spectrograms using the following parameters: window length T=2 s with no overlap, time–bandwidth product TW=3, number of tapers K=5, and spectral resolution of 2W=3 Hz. We also computed an age-varying spectrogram using a sliding window spanning ±5 yr at each age value from 18 to 90 yr old, sliding the window in 0.5 yr increments.

We analysed the relationship between EEG power and age. For each subject, we calculated the average power within seven different frequency bands: slow (0.1–1 Hz), delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–25 Hz), gamma (25–40 Hz), and total power (0.1–40 Hz). We then performed linear regression analysis of power in each band as a function of age, using the Bonferonni correction to adjust for multiple comparisons.

In order to analyse the age-dependent structure of the EEG in greater detail, we compared the spectrum in young (18- to 38-yr-old) and elderly (70- to 90-yr-old) patients for both propofol and sevoflurane. We computed group level spectrograms for each group by taking the median across patients. We computed the group level spectrum by averaging across all time epochs and patients within each group. We calculated 95% confidence intervals (CIs) for each spectral estimate and differences between power spectra using a bootstrap procedure. Briefly, bootstrap samples (n=1000) for the mean spectrum and difference in spectra were drawn from the full sample of data, consisting of 60 non-overlapping 2 s EEG windows for each subject. Bootstrap confidence intervals were calculated using the percentile method.[40] To account for the spectral resolution of the power spectral estimates, for frequencies f>2W, we deemed differences in spectra to be significant only if the significance threshold was exceeded for contiguous frequencies throughout a band greater than or equal to the spectral resolution 2W. For frequencies $0 \le f \le 2W$, to account for the properties of spectral estimates close to zero frequency, we deemed differences in spectra to be significant only if the significance threshold was exceeded throughout a contiguous frequency range from zero to max (f, W)≤2W.

In order to assess relative changes in power between different frequency bands, we compared the ratio of alpha band power to slow band power by computing the alpha-to-slow ratio. We did this by first computing the average power in the alpha and slow bands, taking the ratio, and transforming to a decibel scale [in decibels; $10\log_{10}(P_{alpha}/P_{slow}) = 10\log_{10}(P_{alpha}) - 10\log_{10}(P_{slow})$]. In decibel units, the value of the alpha-to-slow ratio, computed in this fashion, relates to the difference in height between the slow and alpha band peaks in the power spectrum. We computed confidence intervals for the difference in alpha-to-slow ratio between young and elderly patients using the bootstrap procedure described above.

Table 1 Patient characteristics and anaesthetic adjuncts. Age range is indicated in parentheses; other values are means (SD). MAC, minimal alveolar concentration

Parameter	Sevoflurane (n=95)	Propofol (n=60)
Mean age (yr)	48 (18–89)	50 (18–89)
Male sex (%)	43	35
Weight (kg)	81.6 (18.5)	77.8 (17.8)
BMI (kg m^{-2})	29.1 (6.5)	27.28 (5.8)
Length of surgery (min)	93.4 (72.4)	115.05 (85.8)
Sevoflurane (% expired) during epoch	1.74 (0.43)	–
MAC during epoch	1.01 (0.23)	–
Propofol infusion rate (μg kg^{-1} min^{-1}) during epoch	–	119.3 (25.7)
Induction		
Midazolam (mg)	1.87 (0.49), n=67	1.93 (0.67), n=32
Fentanyl (mg)	157 (74), n=82	165 (82), n=46
Propofol (mg)	199 (61), n=92	185 (60), n=58
Etomidate (mg)	14, n=1	14, n=1
Methohexitol (mg)	110 (36.1), n=3	110 (36.1), n=3
Neuromuscular blocking agents		
Rocuronium (mg)	44 (20), n=17	48 (11), n=17
Atracurium (mg)	50, n=1	30, n=1
Cisatracurium (mg)	10 (4), n=32	13 (5), n=8
Vecuronium (mg)	6.5 (3.3), n=16	7.1 (1.8), n=10
Succinylcholine (mg)	98 (26), n=35	85 (14), n=24
Additional drugs administered during maintenance of general anaesthesia		
Fentanyl (μg)	118 (64), n=36	93 (59), n=11
Propofol (mg)	61 (37), n=14	70 (35), n=21
Remifentanil bolus (μg)	0.75, n=1	9 (12.4), n=5
Remifentanil infusion (μg kg^{-1} min^{-1})	n=0	0.13 (0.10), n=48
Hydromorphone (mg)	0.76 (0.55), n=31	0.88 (0.60), n=16
Morphine (mg)	7.0 (4.2), n=2	n=0
Ketorolac (mg)	15, n=1	30, n=1

Coherence analysis

We computed the coherence and cohereogram for each subject using multitaper methods implemented in the Chronux toolbox.[39] 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 cohereogram is a time-varying version of coherence, estimated using consecutive windows of EEG data. The coherence $C_{xy}(f)$ between two signals x and y is defined as follows:

$$C_{xy}(f) = \frac{|S_{xy}(f)|}{\sqrt{S_{xx}(f)S_{yy}(f)}},$$

where $S_{xy}(f)$ is the cross-spectrum between the signals $x(t)$ and $y(t)$, $S_{xx}(f)$ is the power spectrum of the signal $x(t)$, and $S_{yy}(f)$ is the power spectrum of the signal $y(t)$. We estimated the coherence between two frontal EEG electrodes F7 and F8 for each subject using the following parameters: window length T=2 s with no overlap, time–bandwidth product TW=3, number of tapers K=5, and spectral resolution of 2W=3 Hz. We also computed an age-varying cohereogram using a sliding window spanning 5 yr at each age from 18 to 90 yr old, sliding the window in 0.5 yr increments.

To characterize how coherent EEG oscillations vary with age, we analysed the relationship between alpha band coherence and age. For each subject, we calculated the average coherence within the alpha band (8–12 Hz) and then performed linear regression analysis of alpha band coherence with respect to age. We also compared coherence in young (18- to 38-yr-old) and elderly (70- to 90-yr-old) patients for both propofol and sevoflurane in a manner identical to the power spectral analyses described in the previous subsection.

We analysed and compared peak alpha band coherent frequency for the young and elderly groups. To find the peak frequency, we performed a grid search for the maximal value of coherence in the alpha band. To reduce discretization error in the frequency domain, we zero-padded the time-domain EEG epochs by 8-fold before spectral analysis, equivalent to upsampling and interpolating coherence by 8-fold.[41] We computed confidence intervals for the difference in peak frequency between the young and elderly groups using the bootstrap procedure described in the previous subsection.

Burst suppression analysis

During visual inspection of the EEG spectrograms to select EEG analysis windows, we noticed that some patients exhibited brief periods of burst suppression lasting at most a few minutes. To characterize the likelihood of an episode of burst suppression as a function of age, we visually scored each record for episodes of burst suppression. For each subject, we identified a post-induction period beginning ~10 min after induction and concluding at the end of the procedure. We then visually analysed the spectrogram for periods of burst suppression,[35 42] defined operationally by the presence of at least three consecutive suppression events within a 1 min period. Patients showing burst suppression during the postinduction period were graded with a '1', while patients who did not show burst suppression were graded with a '0'.

We estimated an age-dependent probability of an episode of burst suppression for each drug using a state-space approach.[43] We used a random walk state-space model to model the probability of burst suppression as a function of age, as described previously for the analysis of behavioural response data using both empirical Bayes and Bayesian approaches.[43 44] We treated age intervals with no observations (i.e. no patients) as missing data. To account for age intervals with multiple observations, we used a binomial observation equation. We estimated the model using a fully Bayesian approach and Markov Chain Monte Carlo methods implemented in the software package WinBUGS.[45] Posterior densities for the probability of burst suppression were estimated from 5000 samples stored after an initial 1000 iteration burn-in period. Under this Bayesian state-space approach, priors are required for the initial state and for the variance of the random walk process. We used a broad uniform prior distribution to represent the initial state, centred at −4.59 with a range of 10. This corresponds to an initial assumption that the probabilty of burst suppression is centred at 0.01 with range [7×10^{-5}, 0.6]. We used an inverse gamma distribution with parameters (5, 1) to represent the initial state variance, corresponding to a distribution with mean and variance of 5. Other choices for prior distributions on the initial condition and state-space variance resulted in very similar estimates of probability of burst suppression.

We compared the proportion of young (18- to 38-yr-old) and elderly (70- to 90-yr-old) patients displaying an episode of burst suppression using a Bayesian approach. We modelled this proportion as a beta distribution. We estimated the posterior density for the difference in the proportion of young and elderly patients displaying an episode of burst suppression using a Markov Chain Monte Carlo approach as described.[46] We chose a uniform prior distribution and used 1000 Monte Carlo samples to compute the posterior density.

Results

The spectral analysis showed decreasing power across all frequencies with increasing age from 18 to 90 yr for both propofol and sevoflurane anaesthesia (Figs 1 and 2). This was evident in the age-dependent spectrogram (Figs 1A and 2A) and in linear regression analyses of power, as shown for the alpha band (Figs 1B and 2B; P<0.01 for a linear regression model of power as a function of age for both propofol and sevoflurane). Similar linear regression relationships are shown in the Supplementary Information for total power and other canonical frequency bands (Supplementary Fig. S1). Alpha band coherence also decreased as a function of age, evident in the age-dependent cohereogram (Figs 1C and 2C) and the linear regression analysis of alpha band coherence (Figs 1D and 2D; P<0.01 for a linear regression model of coherence as a function of age for both propofol and sevoflurane). Despite these quantitative changes in the EEG spectrum and coherence, the form of the EEG appeared qualitatively similar regardless of age, showing prominent slow and alpha oscillations, coherent alpha waves, and theta power in the case of sevoflurane. These qualitative features, though smaller in older patients, are consistent with previous EEG studies of these drugs.[32 33]

Detailed analyses of EEG power spectra and coherence showed significant differences between young (18–38 yr) and elderly patients (70–90 yr), not only in terms of power and coherence values, but also in the frequency-domain morphology of the signal. For both sevoflurane and propofol, EEG power was significantly lower in elderly patients across all frequency bands (P<0.05, parametric bootstrap, all frequencies). For propofol, slow oscillation power was 4.91 dB lower in elderly than in young patients, corresponding to slow oscillations that are ~1.76-fold smaller in amplitude in the elderly compared with the young. Alpha band power was 8.68 dB lower in elderly than in young patients, corresponding to alpha oscillations that are ~2.7-fold smaller in amplitude in the elderly compared with the young. For sevoflurane, slow oscillation power was 5.45 dB lower in elderly than in young patients, corresponding to slow oscillations that are ~1.87-fold smaller in amplitude in the elderly compared with the young. Alpha band power was 8.56 dB lower in elderly than young patients, corresponding to alpha oscillations that are ~2.68-fold smaller in amplitude in the elderly compared with the young. Thus, propofol- and sevoflurane-induced oscillations are 2- to 3-fold smaller in elderly compared with young patients.

Analysis of the alpha-to-slow ratio showed significant differences between young and elderly patients. As suggested above, in relative terms, alpha band power decreased more in elderly patients than did slow oscillation power. In particular, the

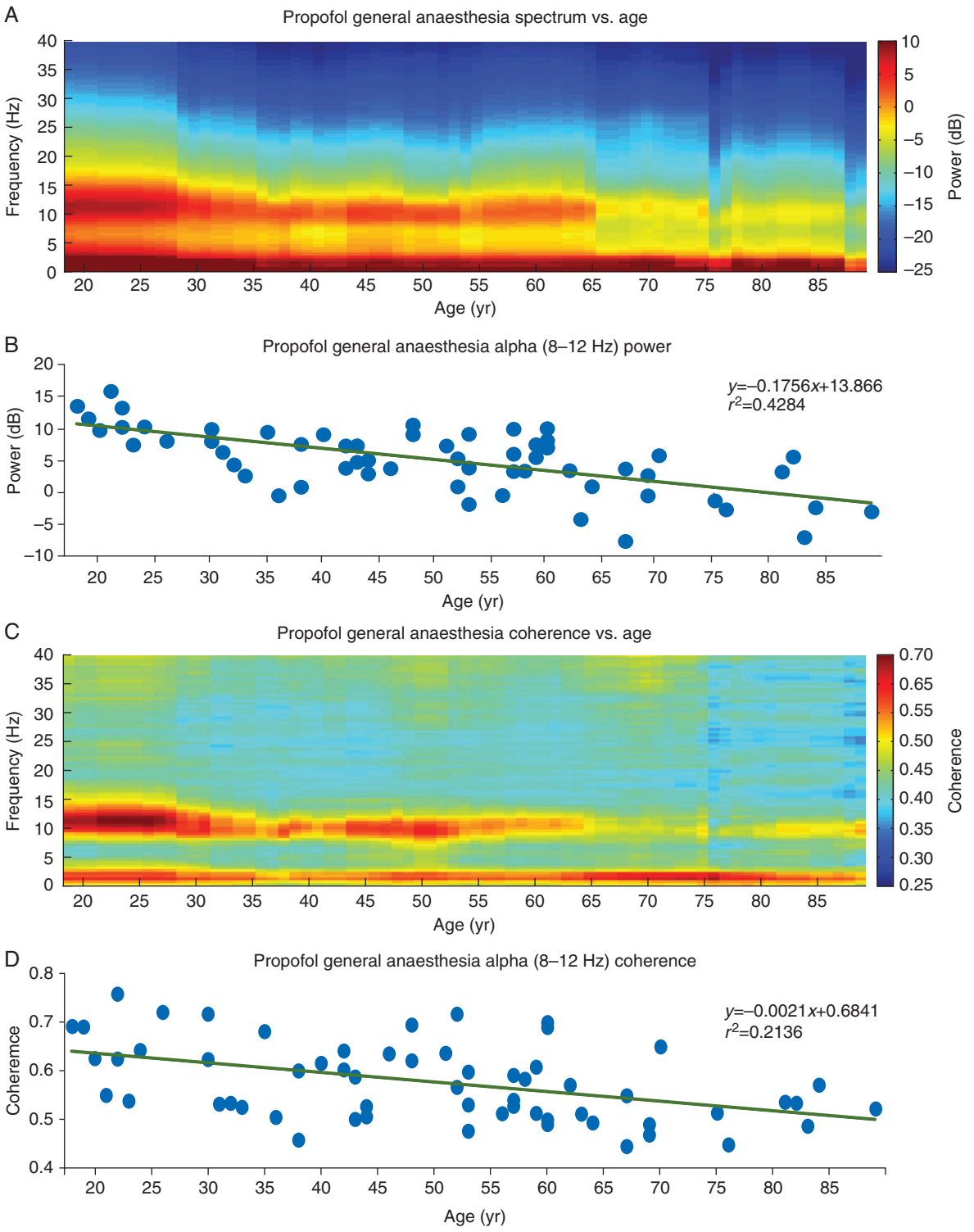

Fig 1 Trends in the spectrum and coherence from 18 to 90 yr old during propofol anaesthesia. (A) The frontal EEG spectrum as a function of age. Slow (0.1–1 Hz) oscillations are present in all patients during general anaesthesia maintained solely with propofol. Alpha (8–12 Hz) oscillations appear to diminish with age. (B) The trend in alpha power appears to decrease with age. The green line represents a linear regression model describing the relationship between age and alpha power. (C) The frontal EEG coherence as a function of age. The alpha band coherence is robust in young patients and decreases with age, starting at about 65 yr. (D) The trend in alpha coherence decreases with age. The green line represents a linear regression model describing the relationship between age and alpha coherence.

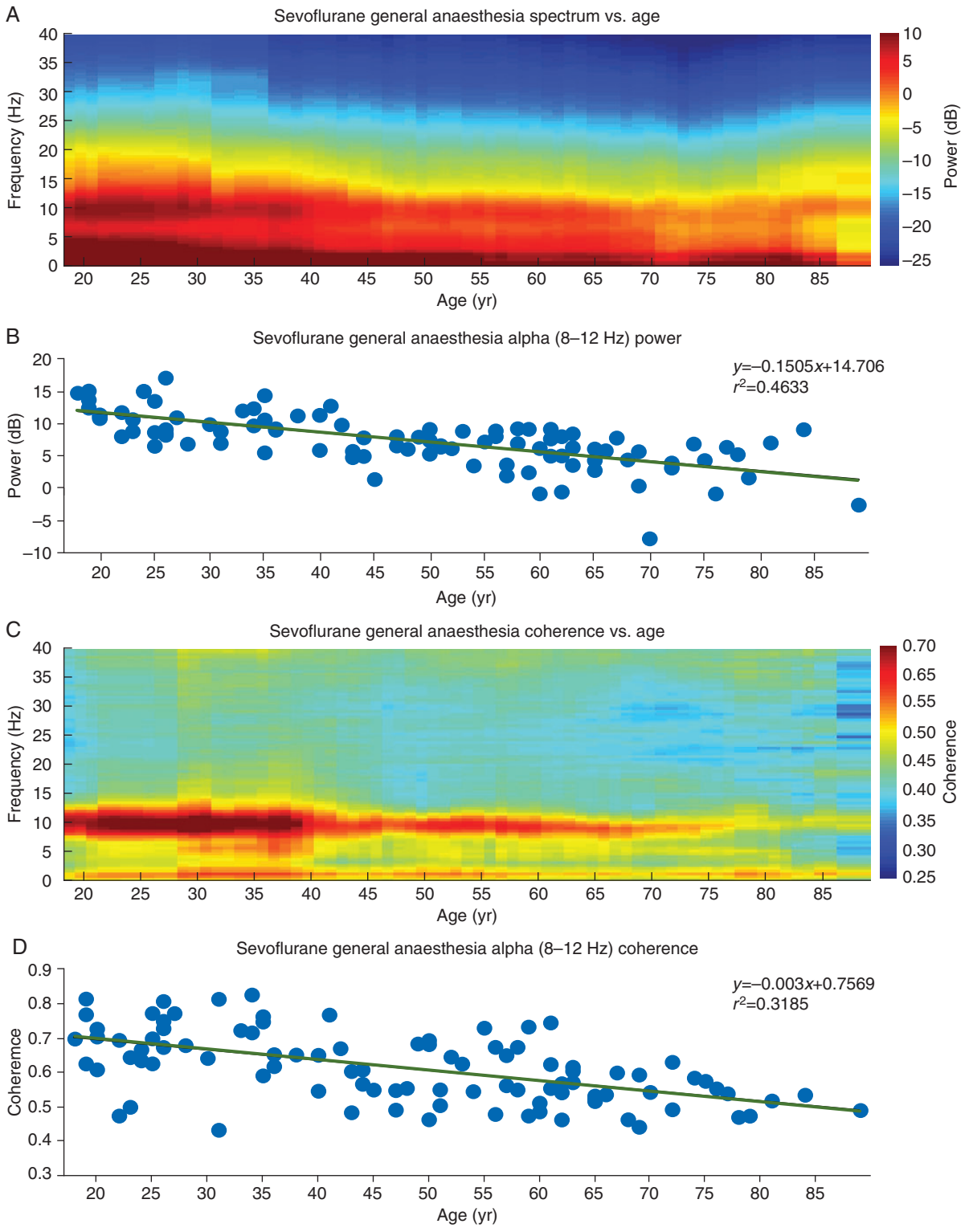

Fig 2 Trends in the spectrum and coherence from 18 to 90 yr old during sevoflurane anaesthesia. (A) The frontal EEG spectrum as a function of age. Slow (0.1–1 Hz) oscillations are present in all patients during general anaesthesia maintained solely with sevoflurane. Alpha (8–12 Hz) oscillations are evident during young adulthood and appear to diminish with age. (B) The trend in alpha power appears to decrease with age. The green line represents a linear regression model describing the relationship between age and alpha power. (C) The frontal EEG coherence as a function of age. The alpha band coherence is robust in young patients and decreases with age, starting at about 65 yr. (D) The trend in alpha coherence decreases with age. The green line represents a linear regression model describing the relationship between age and alpha coherence.

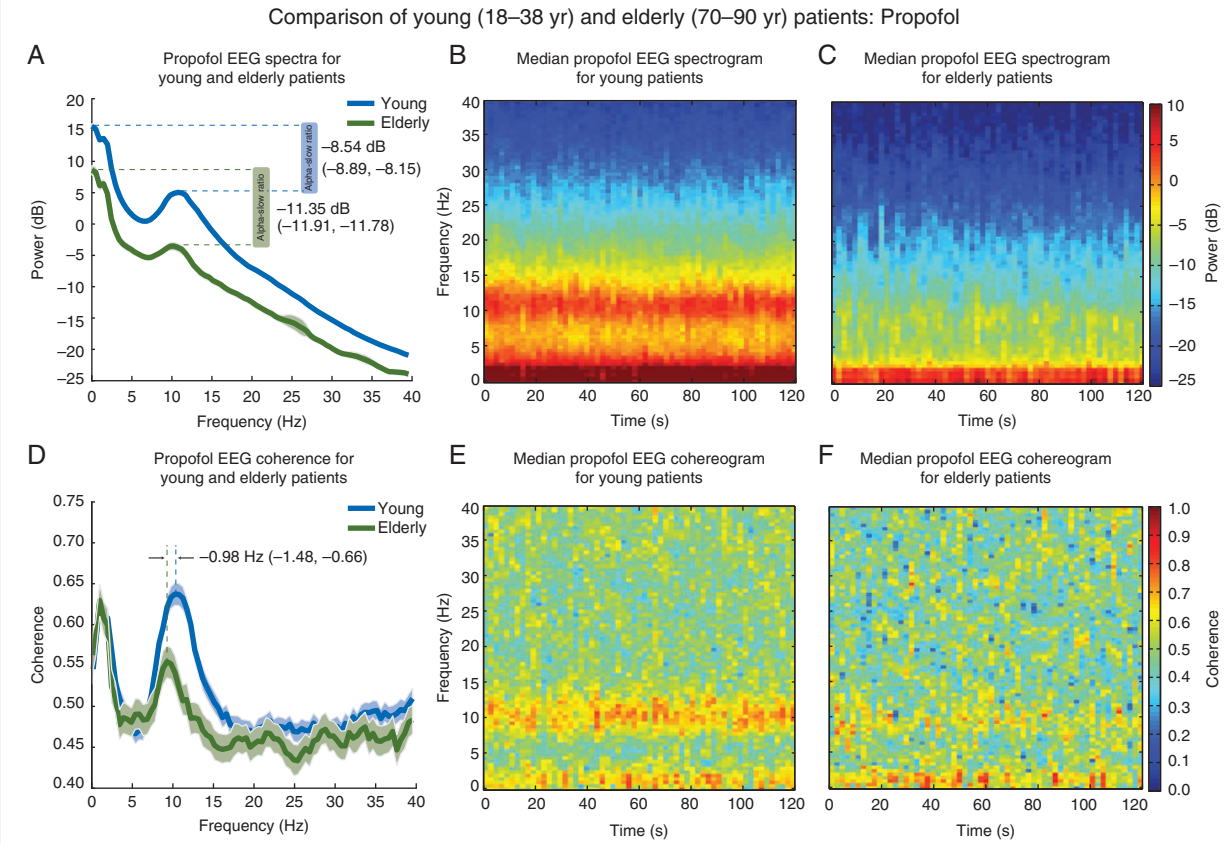

Fig 3 Median spectra, coherence, spectrograms, and cohereogram of young and elderly age groups for propofol. (A) Power spectrum for both young patients (18–38 yr old), represented by blue line, and elderly patients (70–90 yr old), represented by green line. The power spectra show peaks in the slow (0.1–1 Hz) and alpha (8–12 Hz) frequency bands. The elderly patients show a marked decrease in power across all frequency bands. The power in the alpha band appears to decrease more than other bands, quantified in terms of alpha-to-slow ratio. (B) The group spectrogram for young patients shows prominent power in the slow and alpha frequency bands. (C) The group spectrogram for elderly patients shows a visible absence of power in the alpha frequency band. (D) Coherence for both young patients (18–38 yr old), represented by blue line, and elderly patients (70–90 yr old), represented by green line. The coherence is significantly lower in elderly patients, particularly in the alpha band. The peak coherent frequency is also lower in elderly patients. (E) The group cohereogram for young patients shows prominent coherence in the slow and alpha frequency bands. (F) The group cohereogram for elderly patients shows a visible absence of coherence in the alpha frequency band.

alpha-to-slow ratio was significantly lower in elderly compared with young patients (Figs 3A and 4A): 2.81 dB lower for propofol (95% CI: −3.0120, −2.6154), and 2.07 dB lower for sevoflurane (95% CI: −2.18, −1.95). These differences on a decibel scale correspond to a reduction in relative alpha power of ~90 and 61% for propofol and sevoflurane, respectively, for elderly compared with young patients. Coherence was also lower in elderly patients across broad frequency ranges for both propofol ($P<0.05$, bootstrap, for frequencies 6.84–27.79 and 29.79–39.55 Hz) and sevoflurane ($P<0.05$, bootstrap, for frequencies 0–35.16 and 36.13–39.55 Hz). We observed that the peak coherent frequency in the alpha band decreased in elderly compared with young patients for both propofol and sevoflurane (Figs 3D and 4D). The peak coherent frequency decreased by 0.97 Hz for propofol (95% CI: −1.48, −0.66) and by 0.49 Hz for sevoflurane (95% CI: −0.58, −0.44). Thus, there appears to be an effect of age that is unique to alpha band oscillations in terms of relative power, coherence, and peak coherent frequency.

These changes in the power spectrum and coherence were also readily visible in the time–frequency representation, i.e. the spectrogram and cohereogram (Figs 3B,C,E and F and 4B,C,E and F). The age-dependent spectrogram, cohereogram, and linear regression analyses of EEG power and coherence shown in Figs 1, 2, and Supplementary Fig. S1 suggest that middle-aged patients have power and coherence values that lie somewhere in between those shown in Figs 3 and 4 for the young and elderly.

The probability that patients showed an episode of burst suppression increased with age for both propofol and sevoflurane (Fig. 5A and B). This effect appeared to be more pronounced for propofol, where burst suppression probability approached 1 for the oldest patients, compared with 0.6 for sevoflurane. For both propofol and sevoflurane, the probability of burst suppression was significantly greater in elderly patients compared with young patients (Fig. 5C and D).

End-tidal sevoflurane concentrations associated with the EEG analysis windows in each subject, after conversion to age-adjusted MAC values,[38] showed no significant linear relationship with age ($P=0.986$ for inclusion of age covariate) and were well-approximated by a constant value of ~1 MAC (age adjusted) across the full cohort ($P<0.01$ for constant value). Propofol infusion rates showed a slight linear decrease with age of ~0.39 mg kg^{-1} min^{-1} ($P<0.01$ for inclusion of age covariate). Age-adjusted

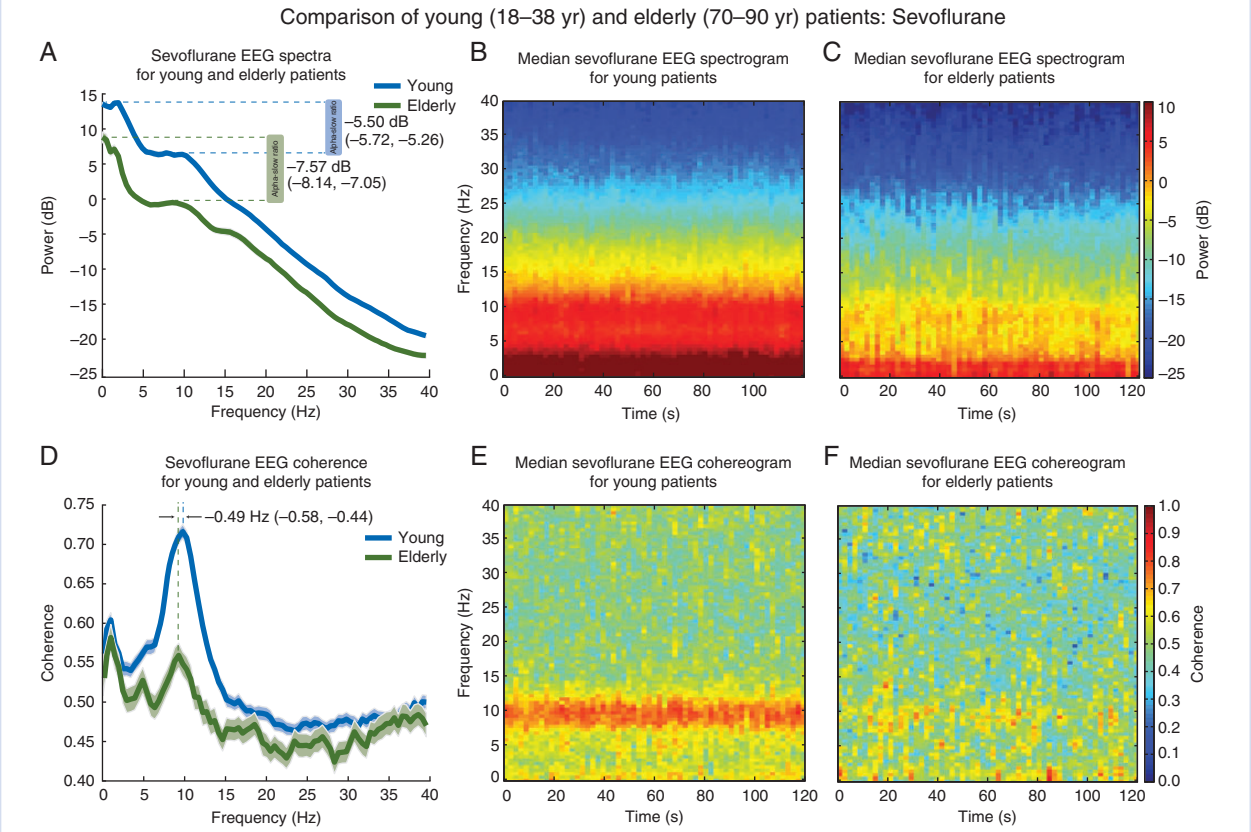

Fig 4 Median spectra, coherence, spectrograms, and cohereogram of young and elderly age groups for sevoflurane. (A) Power spectrum for both young patients (18–38 yr old), represented by blue line, and elderly patients (70–90 yr old), represented by green line. The power spectra show peaks in the slow (0.1–1 Hz) and alpha (8–12 Hz) frequency bands. The elderly patients show a marked decrease in power across all frequency bands. The power in the alpha band appears to decrease more than other bands, quantified in terms of alpha-to-slow ratio. (B) The group spectrogram for young patients shows prominent power in the slow and alpha frequency bands. (C) The group spectrogram for elderly patients shows a visible absence of power in the alpha frequency band. (D) Coherence for both young patients (18–38 yr old), represented by blue line, and elderly patients (70–90 yr old), represented by green line. The coherence is significantly lower in elderly patients, particularly in the alpha band. The peak coherent frequency is also lower in elderly patients. (E) The group cohereogram for young patients shows prominent coherence in the alpha frequency band. (F) The group cohereogram for elderly patients shows a visible absence of coherence in the alpha frequency band.

sevoflurane MAC and propofol infusion rate data are shown in the Supplementary Information (Supplementary Fig. S2).

Discussion

We describe significant age-dependent changes in the characteristics of the effects of anaesthesia on the EEG with increasing age. Both propofol- and sevoflurane-induced EEG oscillations showed marked reductions in signal power across all frequencies with increasing age. For both anaesthetics, we observed a specific effect of age on alpha band oscillations (8–12 Hz), namely a greater reduction in alpha band power compared with other frequencies, a loss of alpha band coherence, and a lower peak coherent frequency. In addition, elderly patients were significantly more likely to experience episodes of burst suppression compared with young patients.

These changes in the EEG signal could be explained by a number of structural and functional neurobiological factors associated with typical ageing. Cortical thinning and reductions in brain volume are associated with ageing and dementia, and most likely reflect a reduced functional capacity in affected brain structures.[6 8] In addition, cortical thinning and grey matter atrophy have the net effect of increasing the distance between the cortical surface and the scalp, which would reduce the size of the EEG signal based on the inverse square law relationship between electromagnetic field strength and distance.[47] These structural changes can also increase the volume of cerebrospinal fluid between the cortex and inner skull surface, which would also attenuate the EEG signal.[48] Age-related reductions in skull conductivity might also contribute to this effect.[49] For EEG frequencies studied in this paper (<40 Hz), these biophysical effects would influence all frequencies equally[47] and would not change the frequency distribution of EEG power. Thus, the changes in relative alpha band power that we observed most likely reflect underlying changes in the functional properties of the neural circuits that generate alpha oscillations. Recent studies also suggest a link between frontal grey matter volume and slow oscillation amplitude.[50]

The EEG is thought to be generated primarily by postsynaptic currents within the cerebral cortex.[47] The age-related reduction in EEG power might therefore be a consequence of an age-related decline in synaptic density, changes in dentritic dynamics, or decline in neurotransmitter synthesis within the cortex, any of which in turn could reduce postsynaptic current densities. The coherent

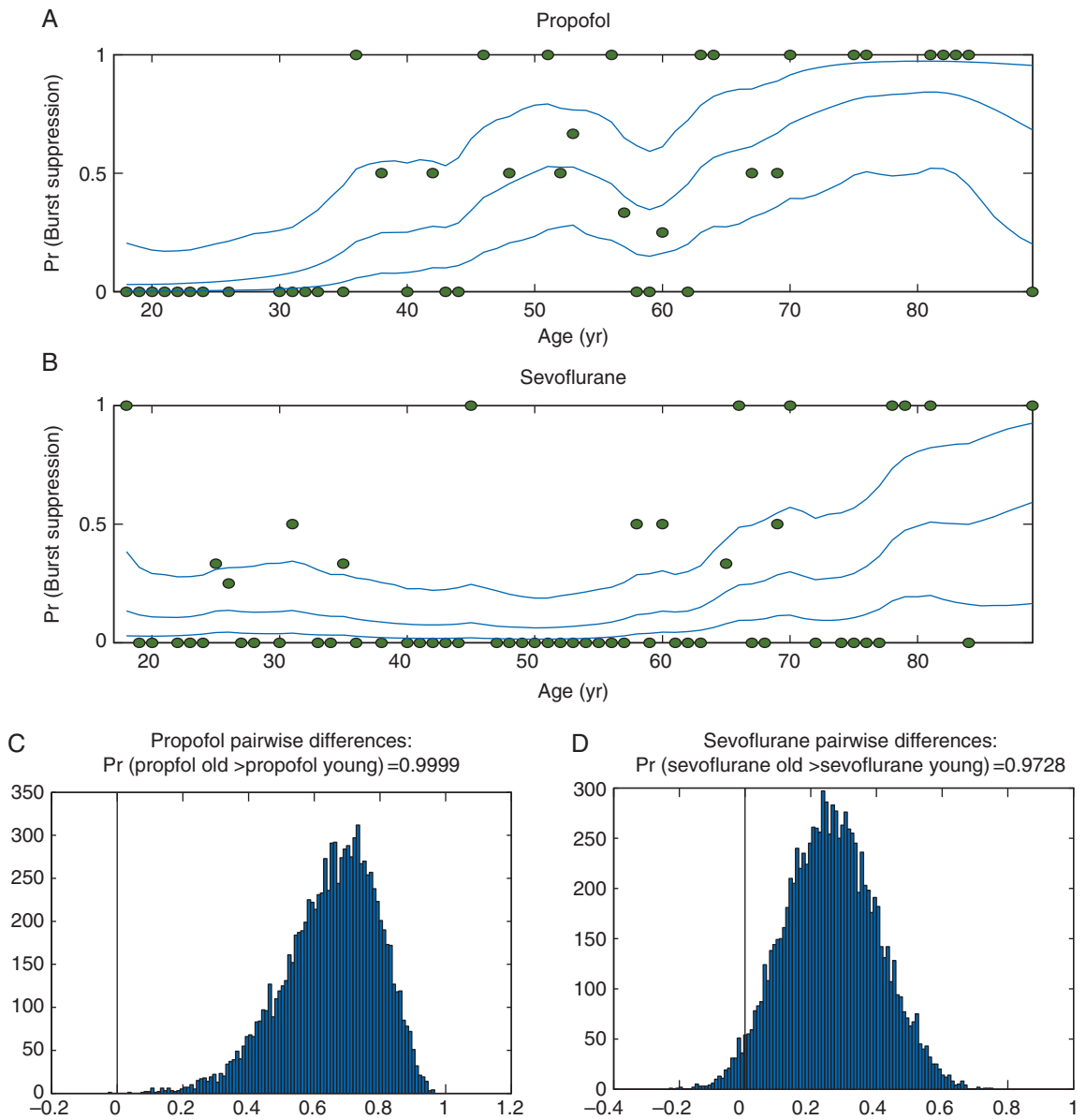

Fig 5 Analysis of episodes of burst suppression under propofol or sevoflurane. (A) Representation of the probability (Pr) that patients experience an episode of burst suppression during anaesthetic maintenance with propofol. (B) Representation of the probability that patients experience an episode of burst suppression during anaesthetic maintenance with sevoflurane. (C) The proportion of elderly patients who experience burst suppression is greater than that for young patients under propofol. (D) The proportion of elderly patients who experience burst suppression is greater than that for young patients under sevoflurane.

frontal alpha wave observed during propofol-induced unconsciousness is thought to be a γ-aminobutyric acid (GABA)-mediated thalamocortical oscillation.[36] Sevoflurane has been shown to produce a coherent frontal alpha rhythm similar to propofol.[33] Thus, the unique age-related alpha band effects that we observed might reflect functional changes in GABA-dependent frontal thalamocortical circuits. The age-related alpha band effects, namely reduced relative alpha power, reduced coherence, and lower peak frequency, were more pronounced under propofol than sevoflurane anaesthesia. This could reflect differences in the underlying molecular mechanisms of these drugs. For instance, propofol appears to act selectively at β3 $GABA_A$-subunit-containing receptors, whereas inhaled anaesthetics are postulated to act at more diverse sites.[51]

More broadly, the age-related EEG changes we observed under general anaesthesia have parallels in typical awake and sleep EEG rhythms. Slow wave power, occipital alpha power, and occipital alpha frequency all decline with age.[52–54] Thus, the age-related changes we see in the EEG are consistent with the neurobiology and neurophysiology of ageing. Cortical thinning during typical ageing follows a 'last to develop, first to degenerate' pattern, where brain regions showing the greatest postnatal developmental expansion also show the greatest declines in cortical thickness in old age.[8] Anaesthesia-induced frontal alpha coherence follows this same pattern, developing relatively late at ~1 yr of age,[55] and then receding with increasing age. In addition, the cortical generators of propofol-induced frontal alpha oscillations[56]

appear to overlap with regions that show significant age-dependent cortical thinning.[8]

The increased probability of episodes of burst suppression observed with age is consistent with previous reports of burst suppression in older patients.[57 58] The mechanisms underlying burst suppression are at present poorly understood. Recent modelling studies suggest that burst suppression could have an underlying metabolic mechanism, in which ATP-dependent potassium channels govern the alternation of burst and suppression periods.[35] Age-related changes in brain metabolism[59] might therefore play a role in explaining the increased likelihood of burst suppression with age.

A limitation of this study is that the anaesthetics were not administered prospectively in a controlled fashion. Instead, anaesthetics were administered based solely on clinical requirements. It is possible that the observed EEG features could have been confounded by hidden systematic age-related differences in drug administration. A *posteriori* analysis of end-tidal sevoflurane concentrations in our study cohort, normalized to age-adjusted MAC,[38] showed no trend with age. Propofol infusion rates tended to decrease with age in our cohort, but this trend might have been offset by the tendency for propofol EC_{50} to decrease with age.[60] Although the proportion of patients exhibiting an episode of burst suppression during maintenance of general anaesthesia increased with age, these episodes of burst suppression for any given subject tended to be brief, lasting at most a few minutes. The 2 min EEG windows used for spectral and coherence analysis did not contain burst suppression. The spectral and coherence analyses therefore reflect a brain state consistent with anaesthesia-induced unconsciousness, but not burst suppression. As a result, the observed spectral and coherence effects are unlikely to be the result of grossly higher effective drug doses in elderly patients and are more likely to reflect age-related differences in underlying neurophysiology. More detailed EEG studies featuring controlled drug administration and structured behavioural measurements are clearly warranted.[32 61] Overall, the EEG phenomena we have observed are broadly representative of what happens clinically and reflect patient brain states at surgical levels of general anaesthesia. It is remarkable that these age-dependent features are readily visible in the EEG spectrum and spectrogram despite the inherent variability introduced by clinical circumstances, indicating that these age-related neurophysiological effects are very robust.

Previous studies have shown decreasing anaesthetic requirements with ageing.[38 60] Our results suggest that there might be an underlying neurophysiological and neurobiological basis for these reduced requirements.[7] Previous studies by Schultz and colleagues[57 62] have reported reductions in EEG signal power and amplitude and increased likelihood of burst suppression. Our studies significantly advance this understanding by showing how the detailed structure in the anaesthesia-induced EEG changes with age.

These findings have important implications for clinical monitoring and management of general anaesthesia in elderly patients. The increased likelihood of burst suppression in elderly patients, combined with the age-dependent changes in the EEG power spectrum, suggest that anaesthetic management using EEG-based depth-of-anaesthesia indices could predispose elderly patients to higher doses of anaesthetic than that required for unconsciousness and general anaesthesia. These depth-of-anaesthesia indices rely on power and relative power in the slow, delta, and alpha bands,[16 63] in addition to measures of burst suppression,[64] to indicate unconsciousness and anaesthetic depth. In elderly patients, depth-of-anaesthesia indices might provide elevated index readings at anaesthetic concentrations that produce unconsciousness, because EEG power in the highly informative slow, delta, and alpha bands, and relative power (e.g. alpha-to-slow ratio), would be significantly lower than in younger adults. To achieve a desired target index value, the anaesthetic dose would then have to be increased, which would be likely to lead to burst suppression, the only remaining quantitative indicator that could drive the index value lower.[64] This prediction is supported by recent clinical studies, in which elderly patients showed a significantly higher incidence of burst suppression while being maintained within a manufacturer-recommended index range.[58]

An alternative approach to a single numerical index is to interpret the unprocessed EEG,[17 18] or spectrum and spectrogram.[7 15 16] Our results suggest that, although the size and quantitative features of the EEG signal change with age, the qualitative form, consisting of slow and alpha oscillations, remains the same. Clinicians could learn to recognize EEG signatures associated with sedation and general anaesthesia induced by the drugs they are administering.[7 15 16 19] Age adjustments could be made by tuning, either automatically or manually, the scale at which the EEG is viewed. Recent studies show that delta and alpha oscillations decline with increasing severity of dementia,[65] suggesting that patients with cognitive impairment or Alzheimer's disease might show more pronounced age-related alterations in anaesthesia-induced EEG features. If pre-existing cognitive disease is associated with postoperative delirium or cognitive dysfunction, then so too might anaesthesia-induced EEG oscillations and their non-anaesthesia counterparts. The between-subject variability in EEG power that we observed suggests that appropriate visualization of the EEG could facilitate individualized patient care by revealing not only each patient's instantaneous brain state, but also their underlying brain age. This might be particularly important in middle-aged patients, whose EEG power and coherence lie somewhere between the young and the elderly. Although further study will be required, we propose that the unprocessed EEG and its spectrogram could be used to monitor brain states of elderly patients receiving general anaesthesia and sedation, and that doing so could reduce anaesthetic requirements for elderly patients below current age-adjusted levels in a manner that accounts for individual differences in drug response.

Supplementary material

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

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Authors' contributions

Conceived the project: P.L.P., E.N.B.
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Supervised data analysis: E.N.B.
Analysed data: P.L.P., K.J.P., O.A., A.C.S., A.L.S., J.L., D.W.Z.
Interpreted data: P.L.P., O.A., K.S., E.N.B.
Wrote the manuscript: P.L.P., A.C.S., E.N.B.
Critically revised the manuscript: K.J.P., K.S.

Declaration of interests

P.L.P., O.A., and E.N.B have submitted a provisional patent application describing the use of the EEG measures described in this manuscript for monitoring sedation and general anaesthesia. Some of these patents have been licensed to Masimo Corporation by Massachusetts General Hospital. P.L.P., O.A., and E.N.B. are due to receive institutionally distributed royalties under this licensing agreement. P.L.P. and E.N.B. have consulting agreements with Masimo Corporation.

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