

## ORIGINAL ARTICLE

# Clinical signs and electroencephalographic patterns of emergence from sevoflurane anaesthesia in children

## *An observational study*

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**BACKGROUND** Few studies have systematically described relationships between clinical–behavioural signs, electroencephalographic (EEG) patterns and age during emergence from anaesthesia in young children.

**OBJECTIVE** To identify the relationships between end-tidal sevoflurane (ETsevoflurane) concentration, age and frontal EEG spectral properties in predicting recovery of clinical–behavioural signs during emergence from sevoflurane in children 0 to 3 years of age, with and without exposure to nitrous oxide. The hypothesis was that clinical signs occur sequentially during emergence, and that for infants aged more than 3 months, changes in alpha EEG power are correlated with clinical–behavioural signs.

**DESIGN** An observational study.

**SETTING** A tertiary paediatric teaching hospital from December 2012 to August 2016.

**PATIENTS** Ninety-five children aged 0 to 3 years who required surgery below the neck.

**OUTCOME MEASURES** Time–course of, and ETsevoflurane concentrations at first gross body movement, first cough, first grimace, dysconjugate eye gaze, frontal (F7/F8) alpha

EEG power (8 to 12 Hz), frontal beta EEG power (13 to 30 Hz), surgery-end.

**RESULTS** Clinical signs of emergence followed an orderly sequence of events across all ages. Clinical signs occurred over a narrow ETsevoflurane, independent of age [movement: 0.4% (95% confidence interval (CI), 0.3 to 0.4), cough 0.3% (95% CI, 0.3 to 0.4), grimace 0.2% (95% CI, 0 to 0.3);  $P > 0.5$  for age vs. ETsevoflurane]. Dysconjugate eye gaze was observed between ETsevoflurane 1 to 0%. In children more than 3 months old, frontal alpha EEG oscillations were present at ETsevoflurane 2.0% and disappeared at 0.5%. Movement occurred within 5 min of alpha oscillation disappearance in 99% of patients. Nitrous oxide had no effect on the time course or ETsevoflurane at which children showed body movement, grimace or cough.

**CONCLUSION** Several clinical signs occur sequentially during emergence, and are independent of exposure to nitrous oxide. Eye position is poorly correlated with other clinical signs or ETsevoflurane. EEG spectral characteristics may aid prediction of clinical–behavioural signs in children more than 3 months.

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## Introduction

Sevoflurane is now the most widely used volatile anaesthetic in paediatric anaesthesia in developed countries because of its tolerability during inhalational induction, relative haemodynamic stability and rapid emergence. Few studies have described relationships between

clinical–behavioural signs of emergence, end-tidal sevoflurane (ETsevoflurane) concentration, age or electroencephalographic (EEG) properties, particularly in neonates and infants.<sup>1–15</sup> Previous paediatric investigations have applied different analysis methods, and

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clinical-behavioural parameters have not been analysed through postnatal development or as a sequence of events. Characterisation of recovery of consciousness relies on indirect measures because neonates and infants are nonverbal, and dose-titration experiments commonly conducted in adults cannot be performed for ethical reasons in children. Age dependence of EEG during sevoflurane anaesthesia has been examined previously.<sup>1–6</sup> Recent work has shown that around 4 months of age, alpha power (8 to 12 Hz) emerges as a feature of the anaesthetic state.<sup>1,2</sup>

The study aim was to examine the relationships among ETsevoflurane, age and frontal EEG spectral properties in predicting recovery of clinical-behavioural signs during emergence from sevoflurane in children 0 to 3 years of age, with and without exposure to nitrous oxide (N<sub>2</sub>O). We hypothesised that clinical signs occur sequentially during emergence, and that for infants (>3 months), changes in alpha EEG power are correlated with the onset of clinical-behavioural signs. Outcome measures were time course of, and ETsevoflurane concentrations at first gross body movement, first cough, first grimace, dysconjugate eye gaze, frontal alpha EEG power (8 to 12 Hz), frontal beta EEG power (13 to 30 Hz) and surgery-end.

## Materials and methods

The current observational study prospectively enrolled 112 children aged 0 to 3 years at Boston Children's Hospital (Boston, Massachusetts, USA), from December 2012 to August 2016. A total of 95 children were included in the final analysis of data extending from the start of sevoflurane anaesthesia until recovery. End-tidal anaesthetic gas concentration and video recordings of behavioural activity were time-locked to EEG recordings. Data were recorded from the beginning of sevoflurane general anaesthesia administration until recovery in the Post-Anaesthesia Care Unit (PACU).

Eligibility criteria were children aged from 0 to 3 years who required elective surgery below the neck. All children were clinically stable on the day of study and American Society of Anaesthesiologists' physical status 1 or 2. Exclusion criteria were congenital malformations or other genetic conditions thought to influence brain development, neurological or cardiovascular disorder, or children born at postmenstrual age less than 32 weeks.

Ethical approval for this study was provided by Boston Children's Hospital Institutional Review Board, Boston, Massachusetts, USA (Protocol No. P000003544; Chairperson: Dr Young Poussaint) on 6 July 2012. Informed written consent was obtained from legal guardians. The study conformed to the Declaration of Helsinki and Good Clinical Practice guidelines.

Each patient received anaesthetic induction with sevoflurane ± N<sub>2</sub>O. Sevoflurane administration with air and

oxygen (air/O<sub>2</sub>) or N<sub>2</sub>O and O<sub>2</sub> was titrated to clinical signs. ETsevoflurane was adjusted according to the anaesthetist's impression of clinical need, not a preset ETsevoflurane concentration; there was no study investigator influence on the choice of medications.

Patient characteristics, clinical information and perioperative event data (e.g. procedure end) were collected from electronic medical health records and the in-house Anaesthesia Information Management System. ETsevoflurane and N<sub>2</sub>O concentrations were downloaded from the anaesthetic monitoring system (Dräger Apollo; Dräger Medical Inc., Telford, Pennsylvania, USA) in real time at a 1-Hz sampling rate using ixTrend software (Ixcelligence, Wildau, Germany).

Body movement was recorded with a camcorder directed at the whole body, and time-locked to the EEG recording (Xltek EMU40; Natus Medical Inc., Oakville, Ontario, Canada). Facial expression was recorded with a ceiling-mounted camera directed at the head (VuCapture; STERIS plc., Mentor, Ohio, USA).

Eye position, where clinically permitted, was assessed by lifting the eye lids at an ETsevoflurane concentration starting from 2.2 to 0%; checks were made in a step-wise fashion at 0.2% decrements or 30-s intervals (whichever was shorter). Eye position was recorded with a handheld camcorder (Canon Vixia HFR52; Canon, Tokyo, Japan; or iPhone6S; Apple, San Francisco, California, USA) and was positioned in the field of video of the Xltek camcorder for time-locking purposes. Video recordings were captured at 60 frames per second to allow a 16.7 ms resolution.

EEG data were collected using an EEG cap (Waveguard; Advanced Neurotechnology, Enschede, The Netherlands) as described previously.<sup>1</sup> Reference and ground electrodes were located at Fz and AFz, respectively. EEG prepping gel was used to reduce skin impedance (Nu-Prep gel; DO Weaver & Co., Aurora, Colorado, USA), and conductive EEG gel was used to optimise contact with the electrodes (Onestep-Clear gel; H+H Medical Devices, Dulmen, Germany). EEG activity from 0 to 500 Hz was recorded with an Xltek EEG recording system (EMU40EX; Natus Medical Inc.). Signals were digitised at a sampling rate of 1024 Hz (or 256 Hz in six cases).

The primary outcome measure was ETsevoflurane during the first gross body movement. Secondary measures were the time to appearance of, and ETsevoflurane at first gross body movement, first cough, first grimace, dysconjugate eye gaze, frontal alpha power (8 to 12 Hz) and frontal beta power (13 to 30 Hz).

Gross body movement was defined as spontaneous movements of the extremities. Coughing was defined as spontaneous mouth opening accompanied by deep chest or shoulder movement (per video), or per audio. Grimace was defined as eye squeeze and/or brow furrow.

Dysconjugate eye gaze was defined as failure of both eyes to align in the same horizontal and vertical planes.

Video recordings were reviewed *posthoc* by observers blinded to ETsevoflurane. Videos were reviewed frame-by-frame to identify the time point (seconds) when each clinical-behavioural sign first occurred. Video data were excluded if the extremities, head and/or an eye were hidden from the plane of view (as appropriate for each outcome measure). We recorded time from end of surgery and ET sevoflurane when each clinical-behavioural sign first occurred.

EEG pre-processing was performed using MATLAB (MathWorks, Natick, Massachusetts, USA), and the Brainstorm toolbox (<http://neuroimage.usc.edu/brainstorm>).<sup>16</sup> EEG properties were evaluated at the frontal leads (F7 and F8). We applied an antialiasing filter of 80 Hz and down-sampled the EEG data to 256 Hz. For each patient, a continuous EEG segment starting from maintenance of general anaesthesia adequate for surgery, and finishing when the patient was awake, was selected manually. Channels with noise or artefact were excluded from analysis.

For each patient, the power spectrum was computed using Brainstorm; the spectrogram was computed using the Chronux toolbox (<http://chronux.org>) as described previously.<sup>1,17</sup> The power spectrum quantifies the energy in the EEG at each frequency. The spectrogram is a time-varying version of the power spectrum using consecutive windows of EEG data. Multitaper parameters used window lengths of 2 s with overlap of 1.9 s. The spectrum of frequencies over time within the 0 to 40 Hz range was plotted for F7 and F8 electrodes.

### Statistical analysis

Data were tested for normality using a D'Agostino and Pearson omnibus test. *P* less than 0.05 was considered statistically significant. Data are reported as median with 95% confidence interval limits (95% CI) in parenthesis unless otherwise stated. Statistical analyses were performed using GraphPad Prism 7.0 (GraphPad Software Inc., La Jolla, California, USA) and Statistical Analysis Software (SAS Institute Inc., Cary, North Carolina, USA).

Patients were allocated to one of two groups according to the choice of anaesthetic management during emergence: sevoflurane in air/O<sub>2</sub>, and sevoflurane in N<sub>2</sub>O/O<sub>2</sub>. To test the relationship with demographic and clinical variables, group comparisons were made using a  $\chi^2$  or Mann-Whitney *U* test. To test the relationship between ETsevoflurane and the first appearance of each clinical-behavioural sign, within-patient comparisons were made using the Friedman repeated measures test followed by Dunn's post-hoc multiple comparisons (with a corrected *P* < 0.05). The relationship between ETsevoflurane and age for each clinical-behavioural sign was evaluated

using linear regression analysis. The presence or absence of body movement was evaluated using binomial logistic modelling; ETsevoflurane, frontal alpha power and frontal beta power were the dependent variables. Exploratory analysis of ETsevoflurane and EEG characteristics in predicting body movement were performed using a receiver operating characteristic (ROC) curve.

The data described in this article form part of a secondary data analysis from a study examining brain-state dynamics during anaesthesia in children. Previous articles on EEG patterns during anaesthesia on selected patients are reported elsewhere, specifically a cohort of infants 0 to 6 months of age (*n* = 40)<sup>1</sup> and the assessment of EEG discontinuity during deep levels of anaesthesia over 0 to 3 years of age (*n* = 68).<sup>18</sup> The current study was a descriptive analysis and had no power calculation performed *a priori*.

## Results

Continuous video and EEG recordings were collected from the start of administration of sevoflurane general anaesthesia until recovery from sevoflurane general anaesthesia ( $\pm$ N<sub>2</sub>O) in 112 children aged 0 to 3 years. Data are presented from 95 patients. Patients were divided into two groups according to the combination of anaesthetic agents used for emergence: sevoflurane in air/O<sub>2</sub> (*n* = 64) and sevoflurane in N<sub>2</sub>O/O<sub>2</sub> (*n* = 31). Patient characteristics, clinical characteristics and medications prescribed (Table 1) and study profile details (Fig. 1) are provided.

### Characteristics of clinical-behavioural signs

First body movement was recorded in 97% children (*n* = 92/95), coughing in 86% (*n* = 76/88) and facial grimacing in 90% (*n* = 55/61) (Fig. 1).

First body movement, cough and grimace occurred close together in time and generally followed an orderly sequence of events across all ages. Eye signs showed no systematic pattern (see below). Children who emerged from sevoflurane in air/O<sub>2</sub> exhibited a median time from end of surgery to body movement of 6.4 min (95% CI, 4.5 to 8.9 min, *n* = 61/64) cough at 5.5 min (95% CI, 4.3 to 8.3 min, *n* = 50/60) and grimace at 9.3 min (95% CI, 7.8 to 16.0 min, *n* = 34/39) (Fig. 2a).

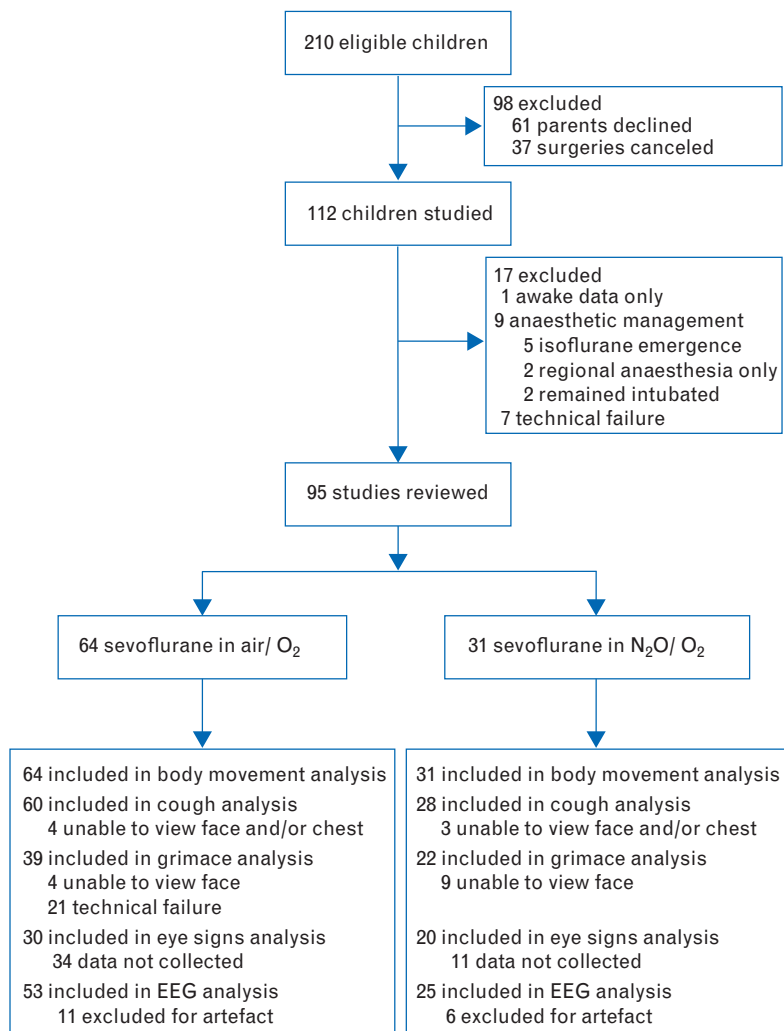
N<sub>2</sub>O was most commonly administered briefly around the end of surgery, and very few children had high expired N<sub>2</sub>O concentrations (>50%) when body movement, cough or grimace were observed (Table 2, Fig. 2a). There were no significant differences in the time of events with or without N<sub>2</sub>O.

There were no differences between children who emerged from sevoflurane in air/O<sub>2</sub> and children who emerged from sevoflurane in N<sub>2</sub>O/O<sub>2</sub> in total time from end of surgery until patient departure from the operating room to the PACU [air/O<sub>2</sub> 12 min (95% CI, 10 to 14 min)

**Table 1** Patient and clinical characteristics

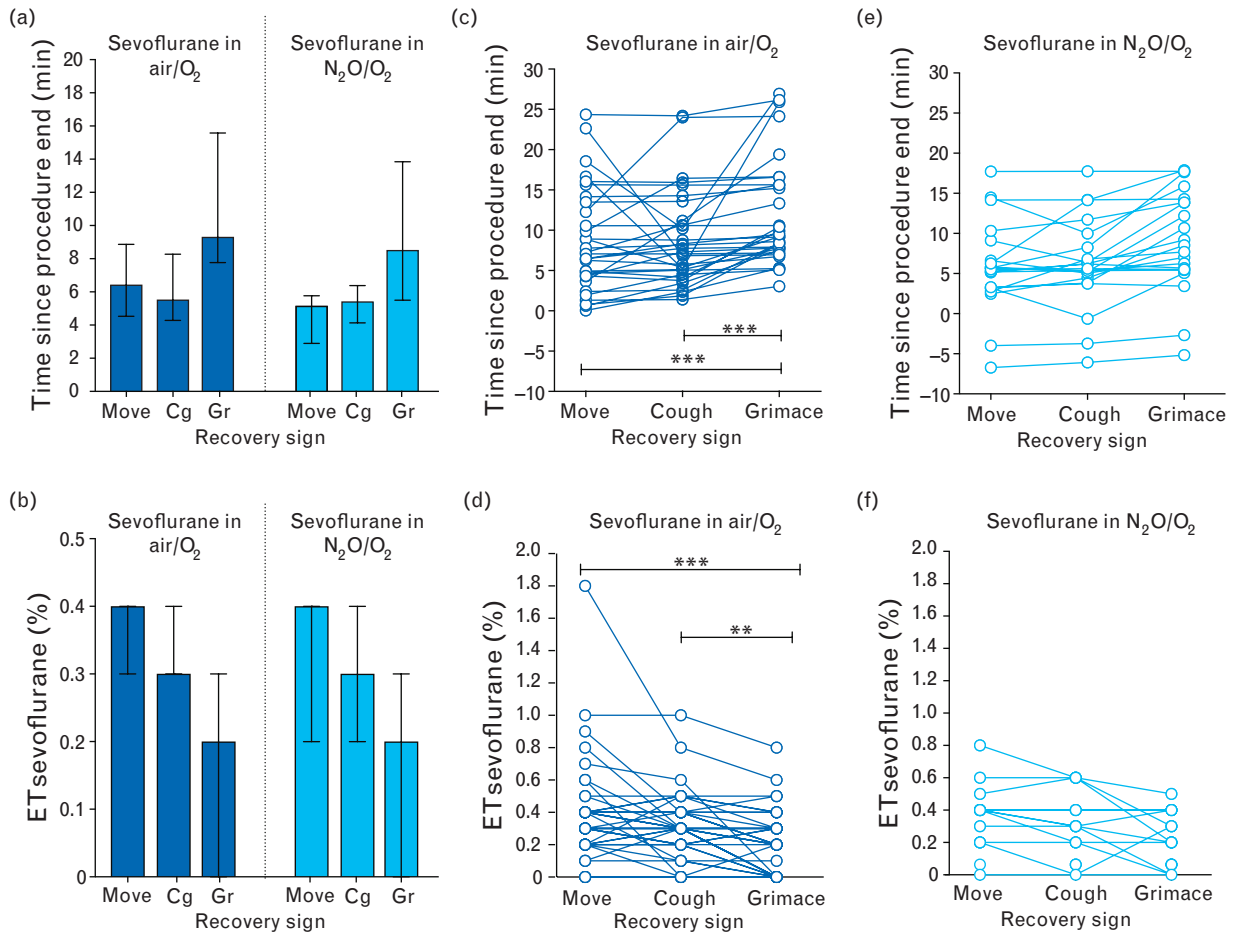
	Sevoflurane in air/O <sub>2</sub> , n = 64	Sevoflurane in N <sub>2</sub> O/O <sub>2</sub> , n = 31	P
Male [% (n)]	64% (41)	77% (24)	0.2 <sup>a</sup>
PMA at birth (weeks)	39 (CI, 39 to 39); range: 34 to 41	39 (CI, 39 to 39); range 33 to 42	0.8 <sup>b</sup>
PNA at study (months)	6.7 (CI, 6 to 12); range 1.4 to 40	10 (CI, 7 to 14); range 1.4 to 37	0.2 <sup>b</sup>
Mean weight at study (kg)	9.2 (CI, 8.4 to 10); range 3.2 to 17	9.2 (CI, 8 to 11); range 5 to 16	0.2 <sup>b</sup>
Duration of surgical procedure (min)	55 (CI, 44 to 64); range 2 to 189	66 (CI, 40 to 112); range 16 to 246	<b>0.004<sup>b,c</sup></b>
Duration of anaesthesia (min)	95 (CI, 86 to 114); range 33 to 301	119 (CI, 88 to 189); range 30 to 318	<b>0.02<sup>b,d</sup></b>
Airway			
Endotracheal tube [% (n)]	66% (42)	71% (22)	0.5 <sup>a</sup>
Laryngeal mask [% (n)]	28% (18)	26% (8)	0.8 <sup>a</sup>
Face mask [% (n)]	6% (4)	3% (1)	0.5 <sup>a</sup>
Anaesthetic management			
Sevoflurane + N <sub>2</sub> O/O <sub>2</sub> induction	78% (50)	100% (31)	<b>0.004<sup>a</sup></b>
Regional anaesthesia [% (n)]	53% (34)	77% (24)	<b>0.02<sup>a</sup></b>
Opioids [% (n)]	64% (41)	87% (27)	<b>0.02<sup>a</sup></b>
NSAID [% (n)]	45% (29)	48% (18)	0.2 <sup>a</sup>
Propofol [% (n)]	39% (25)	52% (16)	0.2 <sup>a</sup>
Neuromuscular block [% (n)]	33% (21)	48% (15)	0.1 <sup>a</sup>

Data are given as median with 95% CI and range, unless otherwise stated. 95% CI, 95% confidence interval limit. Bold typeface indicates statistically significant difference between groups. n, number; N<sub>2</sub>O/O<sub>2</sub>, nitrous oxide in oxygen; NSAID, nonsteroidal anti-inflammatory drug; O<sub>2</sub>, oxygen; PMA, post-menstrual age; PNA, postnatal age. <sup>a</sup>Chi-squared test. <sup>b</sup>Mann-Whitney U test. <sup>c</sup>Difference between medians: 21.5 min (95% CI, 6 to 40). <sup>d</sup>Difference between medians 24.5 min (95% CI, 3 to 44).

**Fig. 1**

Study profile.

Fig. 2



Clinical-behavioural signs of emergence from sevoflurane general anaesthesia. (a) Group-average median time since procedure end, or (b) group average median end-tidal sevoflurane when first body movement, cough or grimace were observed. Within-patient time from surgical procedure end and within patient End-tidal sevoflurane concentration for children who exhibited all clinical-behavioural signs during emergence from sevoflurane in air/oxygen (c and d) or from sevoflurane in nitrous oxide in oxygen (e and f). Negative times indicate the event occurred before the end of surgery. \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ . Cg, first cough; ETsevoflurane, end-tidal sevoflurane concentration; Gr, first grimace; Move, first body movement;  $N_2O/O_2$ , nitrous in oxygen;  $O_2$ , oxygen.

vs.  $N_2O/O_2$  12 min (95% CI, 10 to 14 min),  $P = 0.5$ , Mann-Whitney] or in the time of extubation [air/ $O_2$  8.3 min (95% CI, 5.9 to 10.0 min) vs.  $N_2O/O_2$  8.1 min (95% CI, 5.5 to 14.0 min),  $P = 0.7$ ; Mann-Whitney].

Time taken to exhibit first clinical-behavioural sign during emergence was independent of postnatal age. There were no associations between age and ETsevoflurane in air/ $O_2$  for body movement ( $F_{1,59} = 0.9$ ;  $P = 0.3$ ), cough

( $F_{1,48} = 0.1$ ;  $P = 0.7$ ) or grimace ( $F_{1,32} = 0.04$ ;  $P = 0.9$ ), or with ETsevoflurane in  $N_2O/O_2$  for body movement ( $F_{1,29} = 1.1$ ;  $P = 0.3$ ), cough ( $F_{1,24} = 0.6$ ;  $P = 0.4$ ) or grimace ( $F_{1,19} = 0.3$ ;  $P = 0.6$ ); (Supplemental Digital Content 1, <http://links.lww.com/EJA/A135>).

First appearance of body movement, cough and grimace endpoints occurred over a narrow ETsevoflurane range across all ages. In children who emerged from

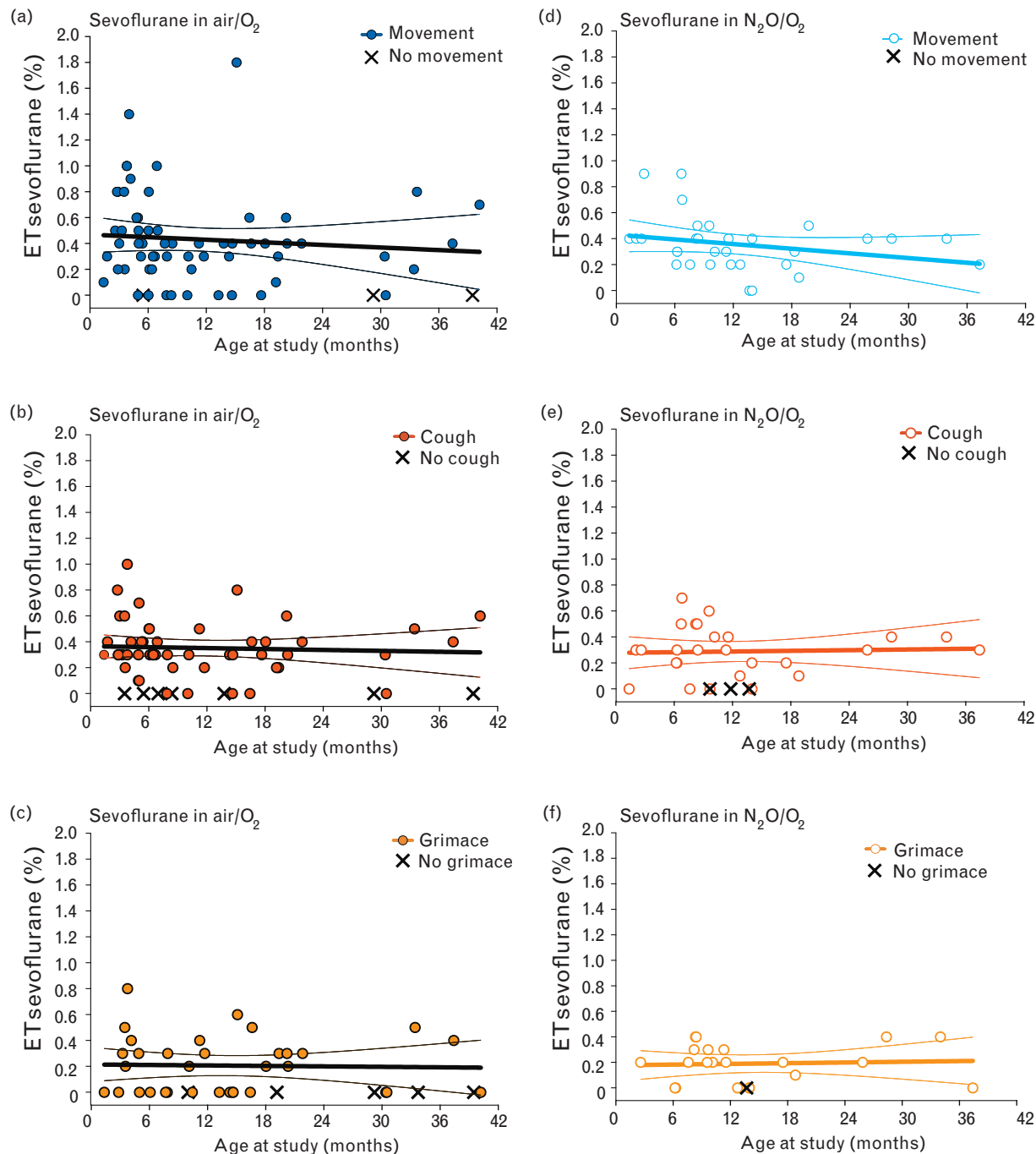
**Table 2** End-tidal nitrous oxide concentration at each clinical-behavioural sign ( $n = 31$ )

	End-tidal Sevoflurane (%)	End-tidal $N_2O$ (%)	Distribution of end-tidal $N_2O$		
			<20% [% (n)]	20 to 40% [% (n)]	≥50% [% (n)]
Gross body movement	0.4 (CI, 0.2 to 0.4); range 0 to 0.9	11 (CI, 7 to 15); range 0 to 73	84% (26)	10% (3)	6% (2)
Cough	0.3 (CI, 0.2 to 0.4); range 0 to 0.7	9.5 (CI, 6 to 14); range 2 to 50	88% (23)	8% (2)	4% (1)
Grimace	0.2 (CI, 0 to 0.3); range 0 to 0.4	6 (CI, 3 to 10); range 0 to 15	100% (21)	(0)	(0)

Data are shown as median with 95% CI limit and range, unless otherwise stated. CI, 95% confidence interval limit; n, number;  $N_2O$ , nitrous oxide.



Fig. 3



Relationship with clinical signs, end-tidal sevoflurane concentration and age in children during emergence from sevoflurane general anaesthesia. Individual end-tidal sevoflurane when first body movement, cough or grimace were observed for patients who emerged from sevoflurane in air/oxygen (a to c) or in nitrous in oxygen (d to f). Top panel illustrates first gross body movement; middle panel illustrates first cough; bottom panel illustrates first grimace. Data points represent individual patients. Solid line represents linear regression; shaded area represents 95% confidence interval. ETsevoflurane, end-tidal sevoflurane concentration; M, months; *n*, number; N<sub>2</sub>O/O<sub>2</sub>, nitrous in oxygen; O<sub>2</sub>, oxygen.

sevoflurane in air/O<sub>2</sub>, first body movement occurred at 0.4% (95% CI, 0.3 to 0.4%), cough at 0.3% (95% CI, 0.3 to 0.4%) and grimace at 0.2% (95% CI, 0 to 0.3%) (Fig. 2b).

In children who emerged from sevoflurane in N<sub>2</sub>O/O<sub>2</sub>, first body movement occurred at ETsevoflurane of 0.4% (95% CI, 0.2 to 0.4%), cough at 0.3% (95% CI, 0.2 to 0.4%) and grimace at 0.2% (95% CI, 0 to 0.3%) (Fig. 2b). There

were no significant differences in ETsevoflurane when each clinical-behavioural sign first occurred in children who emerged from sevoflurane in air/O<sub>2</sub> compared with sevoflurane in N<sub>2</sub>O/O<sub>2</sub> (body movement,  $P = 0.4$ ; cough,  $P = 0.3$ ; grimace,  $P > 0.99$ ; Mann-Whitney).

Forty children who emerged from sevoflurane in air/O<sub>2</sub> exhibited all three clinical-behavioural signs. Within-patient comparisons indicated that body movement and cough occur very close together in time ( $P > 0.9$ , Dunn's), followed by grimace (vs. body movement,  $P < 0.0001$ ; vs. cough,  $P < 0.0001$ , Dunn's) (Fig. 2c). Grimace occurred at a lower ETsevoflurane than did body movement ( $P < 0.001$ , Dunn's), and compared with cough ( $P < 0.01$ , Dunn's) (Fig. 2d). Within-patient comparisons of children who emerged with sevoflurane in N<sub>2</sub>O/O<sub>2</sub> ( $n = 12$ ) indicated no difference in time or ETsevoflurane for each clinical sign ( $P < 0.01$ , Dunn's) (Fig. 2e and f).

ETsevoflurane for all clinical-behavioural signs was independent of age, both for children receiving sevoflurane in air/O<sub>2</sub>, [body movement ( $F_{1,59} = 0.5$ ;  $P = 0.5$ ), cough ( $F_{1,48} = 0.1$ ;  $P = 0.7$ ) or grimace ( $F_{1,32} = 0.03$ ;  $P = 0.97$ ) (Fig. 3a to c)], and for children receiving sevoflurane in N<sub>2</sub>O/O<sub>2</sub> [body movement ( $F_{1,29} = 2$ ;  $P = 0.2$ ), cough ( $F_{1,24} = 0.04$ ;  $P = 0.8$ ) or grimace ( $F_{1,19} = 0.06$ ;  $P = 0.8$ ) (Fig. 3d to f)].

Eye positions were assessed an average of five times per patient (95% CI, 4 to 5). Dysconjugate eye gaze was observed between ETsevoflurane 1 to 0%, and was poorly correlated with the appearance of clinical signs and ETsevoflurane in either air/O<sub>2</sub> or N<sub>2</sub>O/O<sub>2</sub> (Fig. 4). Individual eye gaze assessments are shown in Supplemental Digital Content 2, <http://links.lww.com/EJA/A135>.

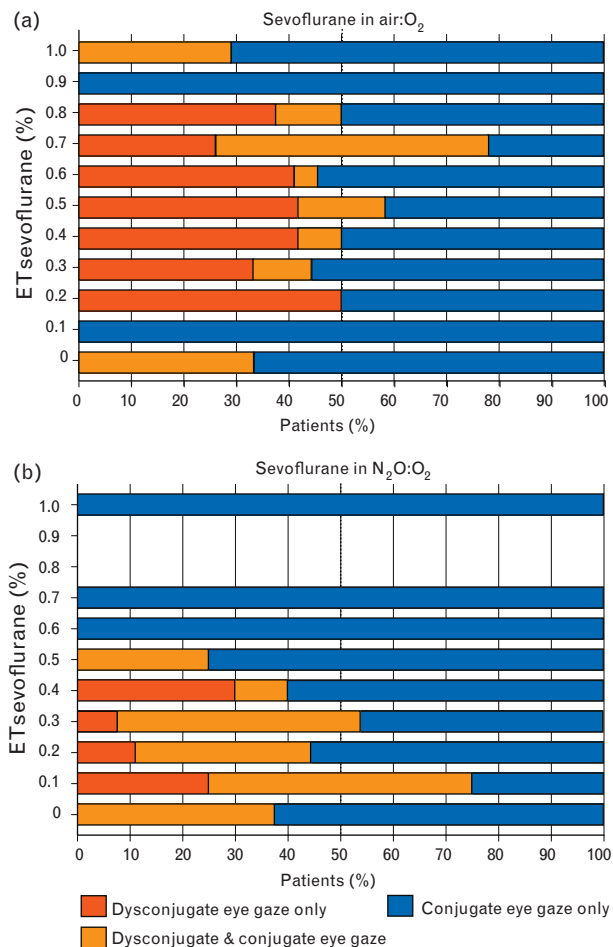
### Characteristics of frontal electroencephalographic frequency bands

Individual frontal EEG spectrograms computed at F7 are shown in age-matched patients (Fig. 5). The relative time course of clinical-behaviour recovery and ETsevoflurane are illustrated in the same figure.

Frontal slow-delta (0.1 to 4 Hz) oscillations were present from ETsevoflurane 2.0% and throughout emergence in children of all ages. Frontal alpha (8 to 12 Hz) oscillations were present during ETsevoflurane 2.0% – suitable for maintenance of a surgical state of anaesthesia – in all 63 children who were older than 3 months. In children less than 3 months, frontal EEG frequency bands shifted in power with decreasing ETsevoflurane. Specifically, frontal alpha power decreased with a simultaneous, but transient, increase in beta oscillations (13 to 30 Hz); (Fig. 5).

In children who emerged from sevoflurane in air/O<sub>2</sub>, alpha oscillations disappeared before the start of body movement in 73% of children ( $n = 30/41$ ; body movement was not observed in one patient). The time between the

Fig. 4

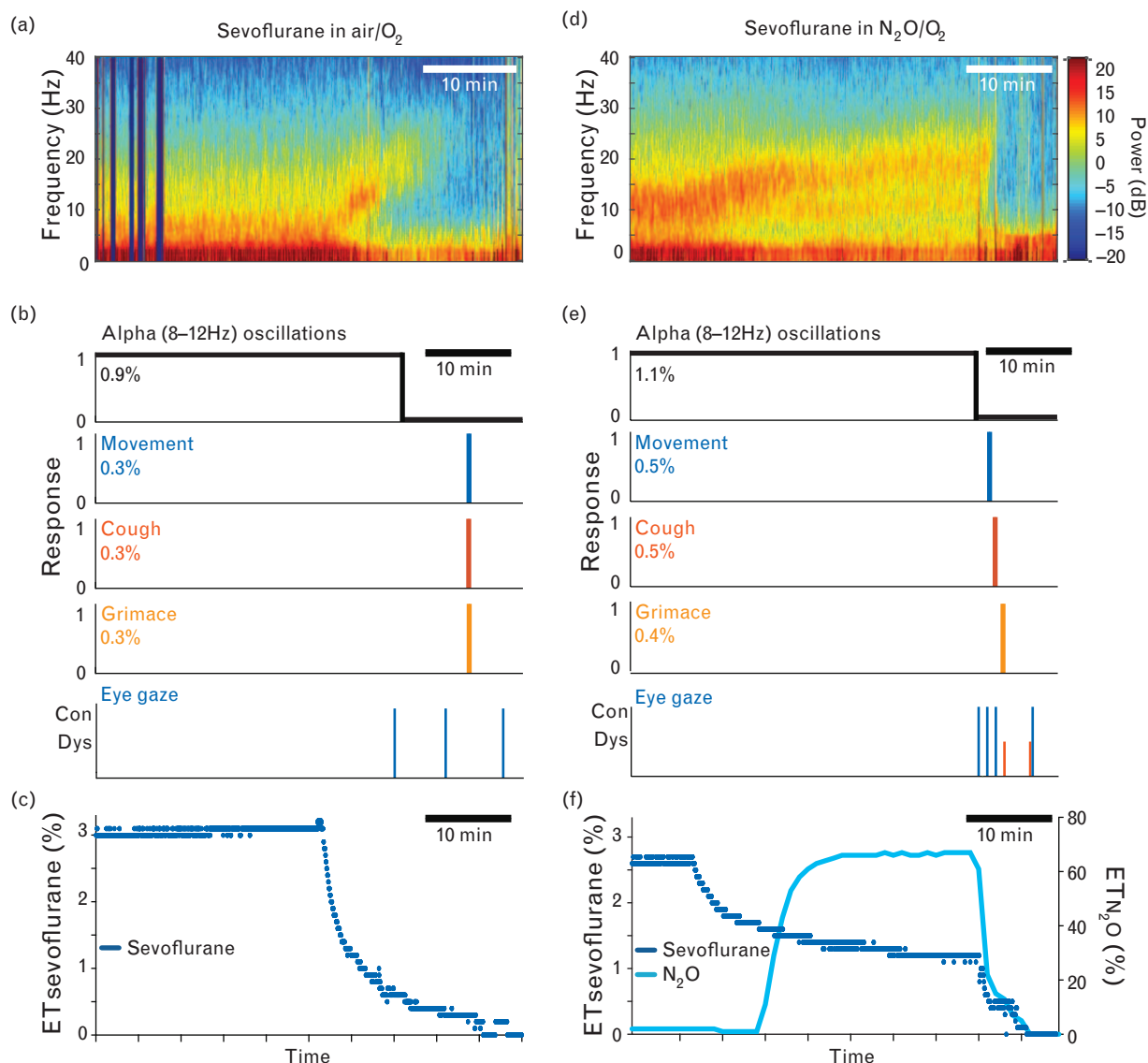


Relationship with eye gaze and end-tidal sevoflurane concentration during emergence from sevoflurane general anaesthesia. Dysconjugate eye gaze was observed between end-tidal sevoflurane 1 to 0%, and was poorly correlated with appearance of clinical signs. The percentage of patients with dysconjugate eye gaze at each end-tidal sevoflurane decrement in children who emerged from (a) sevoflurane in air/oxygen ( $n = 31$ ) and (b) from sevoflurane in nitrous in oxygen ( $n = 16$ ). ETsevoflurane, end-tidal sevoflurane concentration. Individual eye gaze assessment results are given in Supplemental Digital Content 2, <http://links.lww.com/EJA/A135>.

disappearance of alpha oscillations and the onset of body movement was 2.2 min (95% CI, 0.6 to 3.7 min). In 99% of patients, body movement occurred within 5 min of loss of alpha oscillations. The time between the disappearance of beta oscillations and the onset of body movement was 0.9 min (95% CI, 0.2 to 2.3). Both frontal alpha and beta oscillations disappeared at ETsevoflurane 0.5% (95% CI, 0.4 to 0.6%).

Frontal EEG in children who emerged from sevoflurane in N<sub>2</sub>O/O<sub>2</sub> followed a similar pattern. Alpha oscillations disappeared before the start of body movement in 95% of children ( $n = 19/20$ ). The time between disappearance of alpha oscillations and onset of body movement was 6.3 min (95% CI, 2.2 to 8.7 min). Body movement

Fig. 5



Time–frequency frontal electroencephalographic properties during emergence from sevoflurane general anaesthesia. Individual frontal electroencephalographic spectrograms computed at F7, clinical–behavioural signs and end-tidal sevoflurane in two infants aged 8 months old. (a to c) Infant 1 with sevoflurane in air/oxygen and (d to f) Infant 2 with sevoflurane in nitrous in oxygen. Top panel (a and d) illustrates individual frontal spectrograms; middle panel (b and e) illustrates presence of alpha oscillations, first body movement, first cough or first grimace (in which '1' indicates response, '0', no response) and eye gaze position (in which vertical line indicates when an eye gaze assessment was made); and bottom panel (c and f) illustrates end-tidal sevoflurane and ETN<sub>2</sub>O over time. Conj, conjugate eye gaze; Dys, dysconjugate eye gaze; ETsevoflurane, end-tidal sevoflurane concentration; ETN<sub>2</sub>O, end-tidal nitrous oxide concentrations; N<sub>2</sub>O, nitrous oxide; O<sub>2</sub>, oxygen.

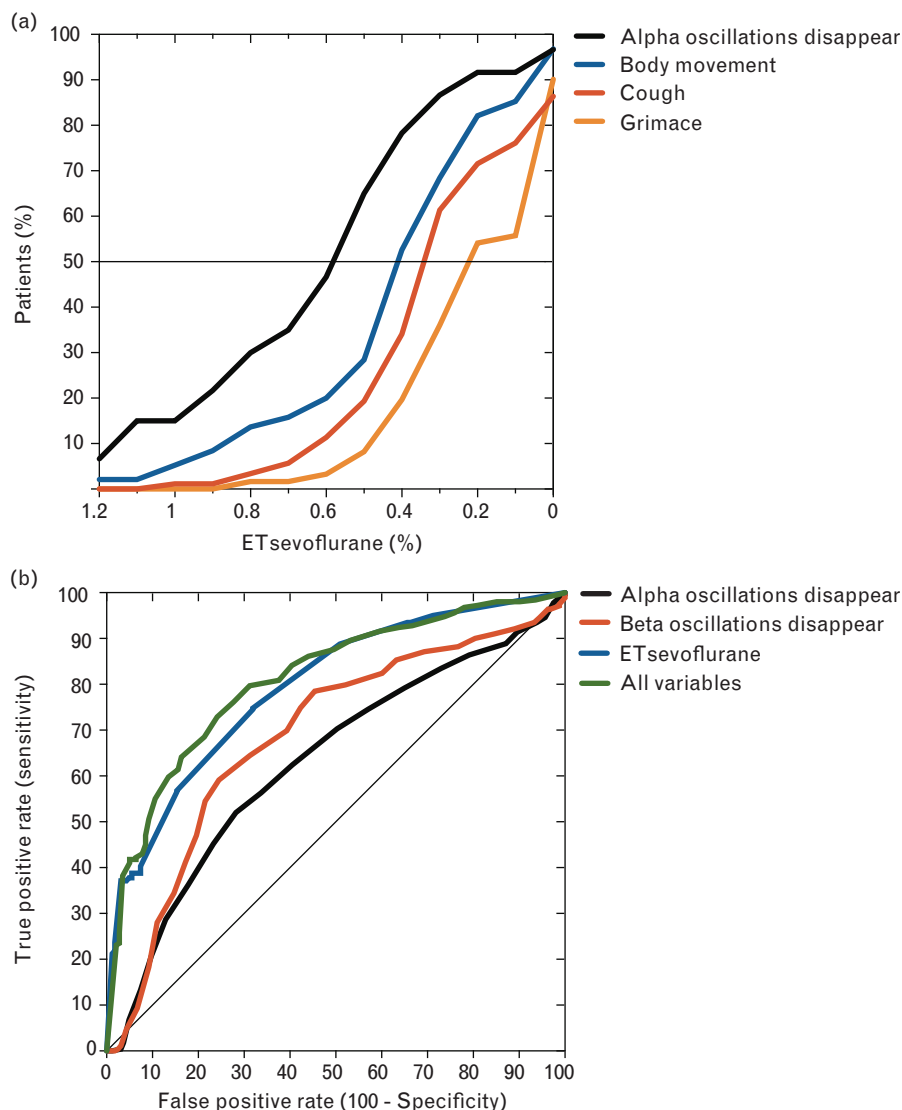
occurred within 5 min of loss of alpha oscillations in all patients. The time between disappearance of beta oscillations and onset of body movement was 2.1 min (95% CI, 0.6 to 7.1 min). Frontal alpha oscillations disappeared at a median ETsevoflurane of 0.6% (95% CI, 0.5 to 0.6%), and beta oscillations disappeared at a median ETsevoflurane of 0.5% (95% CI, 0.4 to 0.6%).

For children more than 3 months of age (who exhibit alpha oscillations), the cumulative percentage who

exhibited recovery of body movement, cough, grimace and alpha oscillation disappearance and the associated ETsevoflurane are summarised in Fig. 6a. Exploratory calculations were performed to estimate sensitivity and specificity of ETsevoflurane, frontal alpha EEG power and frontal EEG beta power in predicting the occurrence of body movement. By incorporating all variables into the ROC model, the area under the curve (AUC) was 81 (95% CI, 77 to 85) (Fig. 6b). Independent AUC values were 81 (95% CI, 77 to 85) for ETsevoflurane, 64 (95% CI, 5 to 69)



Fig. 6



Summary of clinical behavioural signs, electroencephalographic power and end-tidal sevoflurane concentration during emergence in children. (a) Percentage of children who exhibited recovery of body movement, cough, grimace and alpha oscillation disappearance and the associated end-tidal sevoflurane. (b) Receiver operating curve model to estimate sensitivity and specificity of end-tidal sevoflurane, frontal alpha electroencephalographic power and frontal electroencephalographic beta power in predicting the occurrence of body movement. Data shown for children more than 3 months of age with and without nitrous oxide exposure. ETsevoflurane, end-tidal sevoflurane concentration.

for alpha EEG power and 69 (95% CI, 64 to 74) for beta EEG power (Fig. 6b). At ETsevoflurane 0.4%, the probability of body movement occurring can be predicted with 75% sensitivity and 68% specificity. Significantly, when ETsevoflurane was more than 0.5%, and alpha oscillations disappeared, body movement had a positive predictive value of 0.75.

## Discussion

Three clinical-behavioural signs, namely gross body movement, cough and grimace, generally occurred in a close sequence and over a narrow range of ETsevoflurane

during the time course of clinical signs and their dependence on ETsevoflurane did not vary with postnatal age. Dysconjugate gaze can occur over a wide range of ETsevoflurane and can either precede or follow the occurrence of body movement, cough or grimace. EEG alpha power decreases around the time of body movement in children aged more than 3 months. Finally, N<sub>2</sub>O administration at the end of surgery had a negligible effect on the time course or ETsevoflurane at which children showed body movement, grimace or cough.

Early studies of sevoflurane in children showed a weak age dependence of minimum alveolar concentration

(MAC) to prevent response to surgical incision.<sup>7</sup> In one of the first studies evaluating sevoflurane in children, Lerman *et al.*<sup>7</sup> demonstrated rapid emergence, with a mean time from the end of sevoflurane administration to spontaneous eye openings reported as 9.6 and 10.8 min at 6 to 12 months and 1 to 3 years, respectively; no data were available for neonates. Previous studies that examined emergence have reported a limited number of clinical signs, narrower age ranges or grouped data across ages.<sup>8–15</sup>

Few studies have evaluated age-specific recovery characteristics of sevoflurane in children younger than 6 months of age, and analyses were not stratified by age.<sup>7,13–15</sup> Although the age dependence of sevoflurane MAC for surgical incision was reported previously,<sup>7</sup> we found that there were no significant age-related differences in the dependence of behavioural signs of emergence on ETsevoflurane. We have provided novel data on the eye gaze position during emergence in this population and showed wide variability in its time course and relationship to ETsevoflurane.

Similar to the findings in a previous study,<sup>9</sup> N<sub>2</sub>O administration at the end of surgery had no significant impact on the time course of clinical–behavioural signs. Also, N<sub>2</sub>O had no discernible impact on EEG patterns during emergence (see below).

In adult volunteer studies with sevoflurane or propofol anaesthesia, recovery of consciousness is associated with a reduction in alpha power, an increase in peak alpha frequency and an increase in beta power,<sup>19–21</sup> although individual patients can show variable patterns.<sup>21</sup> Emergence involves re-establishment of cortical and thalamocortical connection strength.<sup>20–23</sup> Alpha oscillations during general anaesthesia have been interpreted mathematically in models that emphasise inhibitory thalamocortical circuitry.<sup>24,25</sup>

The normal infant EEG during sleep and wakefulness changes rapidly during the first year of life, coincident with maturation and refinement of cortico-cortical and thalamocortical circuits.<sup>26–30</sup> Previous paediatric studies of EEG during anaesthesia have used variable designs and analytical methods, which may account for some of the discrepancies in their conclusions.<sup>1–6</sup>

Davidson *et al.* evaluated spectral edge and integrated EEG total power over the entire 2 to 20 Hz range at 2 min after the time at which anaesthetic gas was turned off, and before and after the first purposeful movement in 64 children aged 0 to 12 years. Children at 6 months to 12 years exhibited significant decreases in forehead power during emergence compared with children at 0 to 6 months.<sup>3</sup>

Sury *et al.* evaluated central–parietal EEG power in the 5 to 20 Hz range in 20 infants aged 0 to 10 months during sevoflurane emergence. They reported that in infants

older than 3 months, decreases in power occurred in the 5 to 20 Hz range before awakening occurred.<sup>4</sup>

Previous work by our group investigated age-varying EEG properties in 30 infants 0 to 6 months of age during sevoflurane anaesthesia.<sup>1</sup> Frontal alpha EEG power is present during maintenance of surgical anaesthesia in infants older than 3 months of age, and decreases through emergence.<sup>1</sup> Akeju *et al.*<sup>2</sup> also reported similar findings in their study of 54 children and young adults during sevoflurane anaesthesia.

In the current study, and similar to the adult studies of EEG dynamics under general anaesthesia,<sup>19–21</sup> we found that reductions in frontal alpha oscillatory power and increases in frontal beta oscillatory power occurred nearly coincident with clinical–behavioural signs of emergence in most infants older than 3 months of age (Figs. 5 and 6). In contrast to our work and the studies cited above, Lo *et al.*<sup>5</sup> reported that global alpha power *increased* during emergence. The reasons for this discrepancy are not clear.

Our interpretation of the ROC models is that, overall, ETsevoflurane is a good predictor of the first body movement during emergence from sevoflurane anaesthesia in infants and young children. Future studies may clarify whether the addition of EEG indices such as the disappearance of frontal alpha oscillations or increase in beta oscillations may improve prediction compared with ETsevoflurane alone, especially for the subset of infants and children whose first movement occurs at above-average ETsevoflurane.

Age-related differences in the raw EEG have been shown in several studies of children receiving general anaesthesia, with respect to sevoflurane<sup>1,2</sup> and more recently with propofol.<sup>31</sup> Many clinically available perioperative brain monitors of anaesthetic depth, such as bispectral index, are based on algorithms derived from adult data and may not accurately represent brain state in the youngest paediatric patients.<sup>32</sup> Children less than 3 months of age show different EEG signatures compared with older children, for example a lack of alpha oscillations, and these features cannot predict onset of emergence. Future studies that use systems-neuroscience-based strategies and incorporate features of brain development to accurately define anaesthetic depth are warranted in these young patients.

### Study limitations

Anaesthetic management was given according to the discretion of the anaesthesiologist according to clinical need and consequently included combinations of anaesthetic agents and techniques. There was variability in the time course of the reduction in inspired sevoflurane concentration, in the flow rates and in the use of N<sub>2</sub>O during emergence. Our analysis stratified patients based on whether they received N<sub>2</sub>O exposure during

emergence. Measuring anaesthesia recovery or recovery of consciousness in nonverbal populations is indirect in nature, and unlike adults, cannot be assessed using a response to a verbal command. Observation of clinical-behavioural signs is a useful alternative although scoring of video data is subjective. To overcome this pitfall, three cameras were time-locked and positioned in locations in the operating room to detect subtle body movement and facial expression from several camera angles. Eye signs assessments were intermittently evaluated when clinically permitted.

## Conclusion

The current study characterised clinical-behavioural features of emergence from sevoflurane anaesthesia in children 0 to 3 years and correlated these features with continuous EEG spectra. Our results demonstrate that clinical-behavioural signs tend to occur sequentially with ETsevoflurane, and are independent of postnatal age and exposure to N<sub>2</sub>O. Eye gaze assessments are variable across a wide range of ETsevoflurane. Although current EEG indices provide information regarding maturation of information processing during anaesthesia in young children, the clinical use of paediatric brain monitors remains contentious.<sup>32</sup> Further investigation is required before these, or other mathematically derived measures, can be recommended as a unitary clinical monitor of unconsciousness or an anaesthetic state in infants and children.

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