

Alterations in the Functional Connectivity of Frontal Lobe Networks Preceding Emergence Delirium in Children

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ABSTRACT

Background: This study aimed to characterize the electroencephalogram in children who emerged with emergence delirium (ED) compared with children without ED using methods that involved the assessment of cortical functional connectivity.

Methods: Children aged 5 to 15 yr had multichannel electroencephalographic recordings during induction and emergence from anesthesia during minor surgical procedures. Of these, five children displayed ED after sevoflurane anesthesia. Measures of cortical functional connectivity previously used to evaluate anesthetic action in adults were compared between ED and age-, sex-, and anesthetic-matched non-ED children during emergence from anesthesia.

Results: At the termination of sevoflurane anesthesia, the electroencephalogram in both ED and control patients showed delta frequency slowing and frontally dominant alpha activity, followed by a prolonged state with low-voltage, fast frequency activity (referred to as an *indeterminate state*). In children with ED, arousal with delirious behavior and a variety of electroencephalogram patterns occurred during the indeterminate state, before the appearance of normal wake or sleep patterns. The electroencephalogram in children without ED progressed from the indeterminate state to classifiable sleep or drowsy states, before peaceful awakening. Statistically significant differences in frontal lobe functional connectivity were identified between children with ED and non-ED.

Conclusions: ED is associated with arousal from an indeterminate state before the onset of sleep-like electroencephalogram patterns. Increased frontal lobe cortical functional connectivity observed in ED, immediately after the termination of sevoflurane anesthesia, will have important implications for the development of methods to predict ED, the design of preventative strategies, and efforts to better understand its pathophysiology. (**ANESTHESIOLOGY 2014; 121:740-52**)

EMERGENCE delirium (ED) is a significant problem, particularly in children.^{1,2} Numerous potential contributory factors have been identified,³⁻⁸ especially the use of sevoflurane.⁹⁻¹¹ However the incidence, preventative strategies, and management of ED remain unclear, partly due to inconsistencies in defining ED and uncertainty about the pathophysiology of the phenomenon.^{12,13} Rapid emergence has been suggested as an underlying mechanism; however with nonvolatile anesthetics, rapid emergence is not associated with an increased risk of ED.¹⁴ Understanding the pathophysiology of ED may inform strategies for prevention.

Multichannel electroencephalogram is a recognized tool for identifying neurophysiologic states during anesthesia, sleep, and arousal. Due to the logistical difficulties in using it in the operating room environment, there are comparatively few studies that describe the spatiotemporal patterns of electroencephalogram activity observed during anesthetic emergence and induction. This is particularly the case for pediatric studies. However, a range of recent studies involving healthy adult populations have revealed that anesthetic

What We Already Know about This Topic

- Emergence delirium often occurs in children during emergence from anesthesia. Functional cortical connectivity and characteristics of the electroencephalogram in children who undergo emergence delirium are not well defined.
- Multichannel electroencephalogram recordings were obtained during emergence in children who underwent minor surgical procedures under general anesthesia.

What This Article Tells Us That Is New

- In children without emergence delirium, an electroencephalogram pattern of sleep or drowsy states was observed before peaceful awakening.
- In children with emergence delirium, arousal with clinical delirium occurred before observation of electroencephalogram patterns of sleep.
- Frontal regional functional connectivity was significantly elevated in emergence delirium compared with that of matched controls shortly after discontinuation of anesthesia.

action is associated with quite specific topological rearrangements of cortical level neural activity.¹⁵⁻¹⁷ Typically, such studies have quantified changes in functional connectivity

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that attend both induction and emergence from anesthesia and have suggested that it is these functional alterations that are causally responsible for hypnosis and other anesthetic-induced alterations in behavior. On this basis, we speculated that differences in functional connectivity would be observed between children having a normal anesthetic emergence from those suffering ED.

In this study, we compare the electroencephalogram in children who awoke from anesthesia peacefully and those with ED by visual analysis of time domain electroencephalogram patterns in addition to the well-described functional connectivity measures of Global Efficiency (GE) and Global Coherence (GC). Patterns of dissociated electroencephalogram activity (some brain areas being more active while others are less active) were found using both methods.

Materials and Methods

Subject Population

After institutional ethics approval (Royal Children's Hospital Human Research Ethics Committee, Melbourne, Victoria, Australia) and parental consent, 60 children with American Society of Anesthesiologists physical status I or II were recruited into an observational study which monitored multichannel electroencephalogram during rest, induction, and emergence of anesthesia. The study was nested within a larger study describing the topographic characteristics of multichannel electroencephalogram in children at rest (baseline), during induction, and emerging from anesthesia. We studied children aged between 5 and 15 yr listed for minor elective surgery procedures. Children with neurological disease or developmental delay and children undergoing cranial or otolaryngological procedures were not recruited. In the course of this study, five children (8%) experienced a delirious state with emergence. We were able to select a total of seven "normal" control (NC) subjects with the same anesthetic and sex distributions to compare electroencephalogram and clinical characteristics of children with and without delirium (table 1). Children were age matched to minimize the effects of any confounding developmental changes in the electroencephalogram.

Anesthetic Protocol

Sedative premedication was not administered to study participants. Anesthesia was induced with sevoflurane in oxygen using a circle breathing circuit ($n = 10$) or by a propofol bolus with supplemental sevoflurane ($n = 2$; NC4, ED4). Nitrous oxide was added to the circuit at the discretion of the anesthesiologist. A laryngeal mask airway was used without neuromuscular-blocking agents. Physiological monitoring of vital signs was conducted as per standard clinical practice.

Analgesia was provided with caudal local anesthetic block or intravenous opioid bolus (table 2). During surgery, anesthesia was maintained with sevoflurane. The child was observed continuously for delirium during recovery from the anesthetic.

Electroencephalogram Acquisition

Electroencephalogram data were acquired using a battery-powered asalab 64-channel electroencephalogram recording system (Advanced Neuro Technology, Enschede, The Netherlands) and WaveGuard 10/5 standard montage pediatric electrode cap (Advanced Neuro Technology) (fig. 1). This recording system is well suited to the electrically noisy operating room environment due to active electrode shielding, inherent $10^{12} \Omega$ input impedance and 24 bit resolution. Data from the electroencephalogram recording system were continuously logged *via* a universal serial bus connection to a battery-powered laptop computer.

Conductive electroencephalogram gel (OneStep Cleargel; H + H Medical Devices, Münster, Germany) was injected into the gap between the electrode and the subject's scalp.¹⁸ When electrode impedances were acceptable ($<40 \text{ k}\Omega$),¹⁹ an elastic net bandage (Surgifix Tubular Bandage; Smith and Nephew, London, United Kingdom) was placed over the top of the cap to keep electrodes close to the scalp. Electroencephalogram recordings were acquired continuously with a sample rate of 512 Hz.

A 5 min, baseline, eyes-closed recording was conducted before surgery when the child was at rest. Recording of electroencephalogram was commenced before the start of anesthetic induction and was stopped before the commencement of any surgery. These data were not analyzed any further for the current study. When sevoflurane was discontinued, a timer was started and the time noted, with electroencephalogram recording starting at or before this point in 8 of the 12 ($n = 5 \text{ ED}$, $n = 7 \text{ NC}$) children studied. For one child (ED2), electroencephalogram recording was abandoned as their surgery was brought forward reducing the time necessary for adequate electrode preparation. In the three other children (NC3, NC2, and NC5), electroencephalogram was recorded immediately after the child had been transferred to recovery. These children were recruited at older hospital premises with an adjacent recovery suite. The start of one recording was delayed due to a technical issue and has been excluded from the quantitative analysis (NC5).

Electroencephalogram Data Analysis

Electroencephalogram was visually inspected offline and any sizeable artifacts rejected manually using Advanced Source Analysis (Advanced Neuro Technology) software package. Noisy channels were removed, and the remaining channels were high-pass filtered above 0.3 Hz for the visual analysis and bandpass filtered between 1 and 40 Hz for quantitative analysis. Any remaining classifiable artifact was identified and removed using independent component analysis *via* EEGLAB scripting.²⁰ We defined delta (1 to 3 Hz), theta (4 to 7 Hz), alpha (8 to 12 Hz), and beta (13 to 40 Hz) frequency bands. Transverse and longitudinal bipolar montages were used for visual analysis. Each recording was visually scanned to identify transient abnormalities and/or epileptiform disturbances.

Table 1. Participant Demographics

Subjects	Normal Control	Emergence Delirium
Number of subjects in subset	7	5
Median age at recording (yr ± SD)	6.6 ± 0.8	5.7 ± 0.9
Median weight (kg ± SD)	22.0 ± 5.4	22.0 ± 3.4
Male sex	5	4
Sevoflurane induction (+propofol)	6 (1)	4 (1)
Urological/medical procedures	6/1	4/1
Posterior dominant rhythm (Hz ± SD)	8.50 ± 1.25	8.00 ± 1.5 Hz
Length of surgical procedure (min ± SD)	25 ± 15	22 ± 11

Cortical level functional connectivity analysis was conducted using the previously described GE and GC measures on artifact corrected data using customized MATLAB scripts (The MathWorks, Inc., Natick, MA). These electroencephalogram-derived measures identify genuine functional alterations in network topology and connection strength and have been previously applied to characterizing the actions of propofol and nitrous oxide anesthetic agents in adults.^{15–17} GE is a graph theoretic measure calculated on time domain electroencephalogram data and can be broadly understood as the average surrogate-corrected zero lag cross correlation over a defined undirected network of electroencephalogram sensors. In contrast, GC is a measure calculated from frequency domain electroencephalogram data and is calculated from the eigenvalues of the complex cross-spectral matrix. Specifically, GC is defined as the ratio of the largest eigenvalue to the sum of all eigenvalues of the cross-spectral matrix and is evaluated for each frequency bin of the corresponding discrete Fourier transform. For subsequent comparisons, the mean value of GC calculated over the frequency range 5 to 15 Hz, which encompasses the peak GC magnitude, was used. All measures are defined on the interval [0 1] with larger values corresponding to increased functional connectivity in a defined network. Detailed mathematical derivations of these measures can be found in the studies reported by Kuhlmann *et al.*,¹⁶ Lee *et al.*,¹⁷ and Cimenser *et al.*¹⁵ and are omitted here for brevity.^{15–17} The data were rereferenced to 42 channels to calculate

the small surface Laplacian derivation, with peripheral channels excluded due to an insufficient number of neighboring electrodes.²¹ Each frontal network was calculated from nine channels: AF3, AF4, Fz, and F1 to F6 channels. The parietal network involved seven channels: Pz and P1 to P6. The full brain network involved all 42 channels. These groupings were chosen to define equivalent pediatric functional regions to those described in adults. Thus functional connectivity analysis was calculated at essentially two different spatial scales by using either the common average or Laplacian rereferenced electroencephalogram data. The surface Laplacian limits electrode sensitivity to local and superficial cortical activity, thus revealing brain dynamics at smaller spatial scales compared with common average reference derivations. The Laplacian also has the additional advantage of minimizing electromyographic artifact. The time when sevoflurane was switched off in each patient was denoted as time = 0 min, ensuring a comparison across subjects could be made. The final GE and GC data were segmented into 5-min time bins for subsequent statistical analysis.

Statistical Analysis

Normally distributed data were summarized as mean ± SD. Omnibus tests were performed using ANOVA or the Kruskal–Wallis test appropriately based on the results of the Levene test for homogeneity of variance. The significance of any changes in functional connectivity measures GE and GC was evaluated using repeated-measures (mixed-effects) ANOVA with time as the within-subjects factor and ED status as the between-subjects factor. All statistical analyses were performed using SPSS for Windows (version 16; SPSS Inc., Chicago, IL). A value of *P* less than 0.05 was considered statistically significant.

Clinical Behavior Assessment

The behavior and responsiveness of each child during recovery from anesthetic was marked against the electroencephalogram at corresponding times. Delirium was assessed using parameters previously developed by our research group.¹³

Table 2. Patient Summaries; NC Group

Subject	Procedure	Nitrous Oxide	Propofol Bolus at Induction	Analgesia	Dose, µg	EEG	Posterior Dominant Rhythm* (Hz)	Surgical Time (min)
NC1	Cystoscopy	Yes	No	None		Yes	8.75	26
NC2†	Diagnostic laparoscopy and cystoscopy	No	No	Fentanyl‡	25 µg	Yes	9.25	22
NC3†	Correction of hypospadias	No	No	Caudal		Yes	8.25	55
NC4	Hallux nail excision	No	Yes	Fentanyl	30 µg	Yes	8.50	11
NC5†	Circumcision	Yes	No	Caudal		Yes	6.50	29
NC6	Circumcision	Yes	No	Fentanyl	35 µg	Yes	10.00	21
NC7	Open rectal biopsy	Yes	No	Fentanyl	25 µg	Yes	7.50	10

* Derived from occipital channel spectrum in resting eyes-closed data; 4-s windowing. † Electroencephalographic recording started when patient in recovery, otherwise starting prior or when sevoflurane was switched off. ‡ Medication given during surgical plane, otherwise given during induction. EEG = electroencephalogram; NC = normal control.

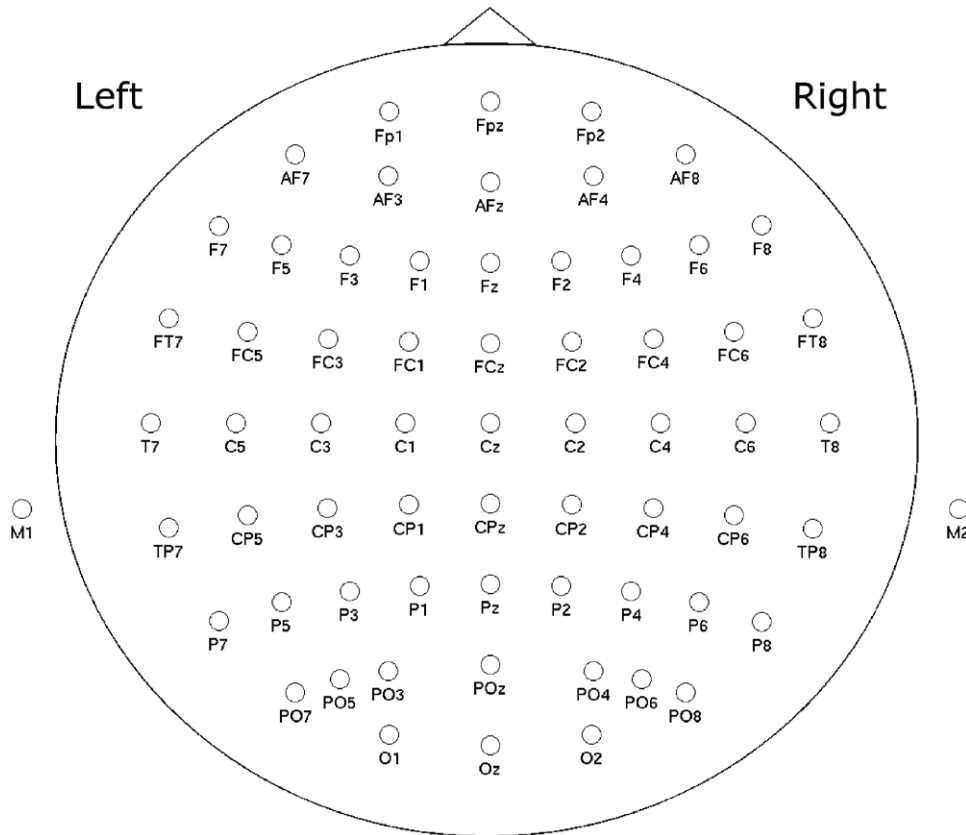


Fig. 1. Location and nomenclature of a 64-channel cap according to the 5% electrode placement scheme: frontal pole (Fp), antero-frontal (AF), frontal (F), central (C), parietal (P), temporal (T), occipital (O), and mastoid (M). The numbering starts at the midline (z for zero) increasing with distance. Even numbers indicate right-sided placement with odd numbers on the left.

Results

Clinical Characteristics

Subject characteristics, which included steady-state concentration of maintenance sevoflurane in the preceding minutes before sevoflurane being switched off, heart rate, and oxygen saturation, did not differ between the NC and ED groups.

After discontinuation of anesthesia, all children aroused with behaviors that included eye opening, head elevation, staring, and face rubbing. The mean time after sevoflurane was discontinued to the onset of ED was 10.1 ± 2.8 min (table 3).

Five children without ED roused further to normal wakefulness naturally and two roused after stimulation by the

Table 3. Patient Summaries; Emergence Delirium Group

Subject	Procedure	Nitrous Oxide	Propofol Bolus at Induction	Analgesia	Dose	EEG	Posterior Dominant Rhythm* (Hz)	Surgical Time (min)	Time from sevo-off to ED Episode (min)
ED1†	Circumcision	Yes	No	Caudal		Yes	7.00	17	9.1
ED2	Cystoscopy with retrograde pyelogram	No	No	Morphine	2 g	No	Not recorded	40	Not recorded
ED3†	Urethral meatotomy	Yes	No	Fentanyl	25 µg	Yes	7.00	22	12.1
ED4†	Removal of foreign body from foot	Yes	Yes	Infiltration		Yes	10.00	13	12.6
ED5†	Excision biopsy of perineal naevus	No	No	Fentanyl‡	20 µg	Yes	7.50	17	6.5
								Mean	10.1 ± 2.8

* Derived from occipital channel spectrum in resting eyes-closed data; 4-s windowing. † Electroencephalographic recording started when patient in recovery, otherwise at or before sevoflurane switched off. ‡ Medication given during surgical plane, otherwise given during induction. ED = emergence delirium; EEG = electroencephalogram; NC = normal control.

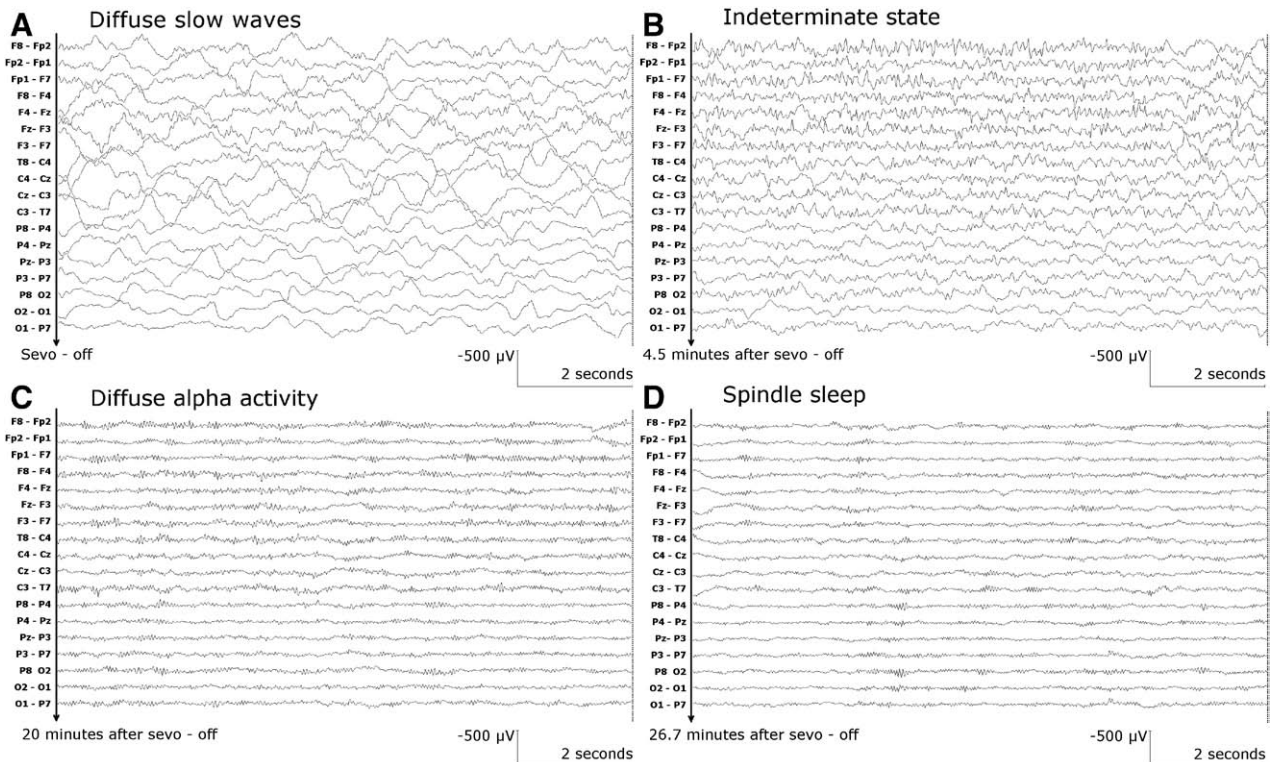


Fig. 2. Electroencephalogram transverse bipolar montage time series from a representative normal control patient (patient NC4). All displayed time series data were bandpass filtered between 0.3 and 70 Hz. (A) Diffuse slow-wave activity seen immediately after sevoflurane switched off. (B) Indeterminate state characterized by diffuse, mixed alpha and beta frequency activity. (C) Diffuse mixed frequency and voltage alpha activity. (D) Spindle sleep patterns before awakening.

recovery nurse after a prolonged period of sleep (NC7 and NC4). Three children without features of ED woke upset but were responsive, oriented, coherent, and could articulate the cause of their concern (usually postoperative pain or nausea; NC1, NC3, and NC4).

Five children with ED opened their eyes, were unresponsive to calling their name, disoriented, confused, and exhibited gross motor behaviors that included rolling over, grabbing bedrails, and sitting upright. Onset was typically accompanied by confused mumbling with progression to distressed speech and inconsolability in two children (ED1 and ED2). Both children showed signs of anxiety and distress, with fearful behavior, agitation, and evasiveness. Complex motor behavior was also displayed, with attempts by ED1 and ED2 to jump out of bed, prompting physical restraint by nursing staff. ED1 injured their surgical site, requiring reevaluation by the surgeon. This patient eventually responded to their name, became oriented, and settled after 10 min.

Qualitative Electroencephalogram Analysis

Electroencephalogram was of inadequate quality in one child as their surgery was brought forward without sufficient time

to prepare all electrodes (ED2). In another child (ED1), the electroencephalogram was unable to be recorded after the delirium event as the electrode cap became dislodged as a consequence of their highly agitated state.

In children with electroencephalogram recordings beginning at the time of the discontinuation of sevoflurane,* the electroencephalogram showed typical patterns previously reported during emergence from anesthesia: diffuse, slowing at 2 to 3 Hz, and frontally dominant, mono-rhythmic alpha frequency activity between 8.5 and 11.5 Hz (fig. 2A). The delta activity attenuated 12 min on average after ceasing inspired sevoflurane and was followed in all cases by an often prolonged, *indeterminate state* characterized by diffuse, mixed alpha and beta frequency activity (fig. 2B). This fast activity remained diffuse in distribution but gradually reduced in voltage and became intermittent and amplitude modulated (fig. 2C). There was no difference in the appearance or duration of this state in the ED and control patients.

In the seven age-matched children without ED, the indeterminate state progressed to a variety of electroencephalogram patterns before emergence. In all children, there was the reappearance of slower frequencies, either theta activity typical of drowsiness (NC1) or slower delta activity with vertex waves and spindles typical of sleep (NC4, NC3, NC2, NC5, NC7, and NC6) (fig. 2D). From this point, some patients remained asleep, either with (NC2 and NC7) or

* Electroencephalogram recordings for NC2, NC3, and NC5 did not start when sevoflurane was turned off. Recording for these children began upon reaching recovery approximately 20 s after sevoflurane switched off in NC2 and NC3. Thus, the period of diffuse slowing may have been present, but was not captured.

without (NC4 and NC5) intermittent arousals, whereas others subsequently awoke with appearance of their posterior dominant rhythm and low-voltage activity anteriorly (NC3, NC6, and NC1).

In contrast, the children with ED became aroused during the indeterminate state, with slightly differing electroencephalogram patterns. In three children with ED, patterns characteristic of arousal were seen. In one child (ED3), the indeterminate state was followed by diffuse, bilateral theta slowing at 6 Hz lasting approximately 4 min, synchronous with the delirious behavior (fig. 3A). In another child (ED4), alpha activity typical of their posterior dominant rhythm appeared in the occipital region with prominent bifrontal 15 to 16 Hz beta and bilateral centrotemporal 5 to 6 Hz theta, synchronous with the delirious behavior (fig. 3B). In another patient (ED5), a brief arousal pattern of diffuse 6 Hz theta and frontocentral alpha was seen for 52 s (fig. 3C). This was synchronous with the brief episode of delirious behavior and occurred before the appearance of sleep with spindles and midline sharp waves when they settled and later woke after a similar arousal pattern. In the child with the most dramatic

delirious behavior (ED1), the electroencephalogram immediately before ED showed diffuse, low-voltage anterior and posterior alpha activity with intermittent midline slow-wave transients suggesting drowsiness (fig. 3D). During ED, this child's electroencephalogram showed only low-voltage, desynchronized activity with superimposed artifacts. After ED, two patients subsequently roused with appearance of their posterior dominant rhythm and low-voltage mixed frequency activity (ED3 and ED4), one patient slept then awoke (ED5), and one patient had their leads immediately removed (ED1) (fig. 4).

Quantitative Electroencephalogram Analysis: GE and GC Measures of Functional Connectivity

Functional connectivity in full brain and frontal and parietal subnetworks was calculated using the GE and GC measures to characterize any differences between children with ED, before the manifestation of behavioral abnormalities, and their matched controls. In figure 5, GE was plotted for each individual for full, frontal, and parietal networks using common and Laplacian derivation schemes aligned to the point in time when sevoflurane was switched off. Each datum

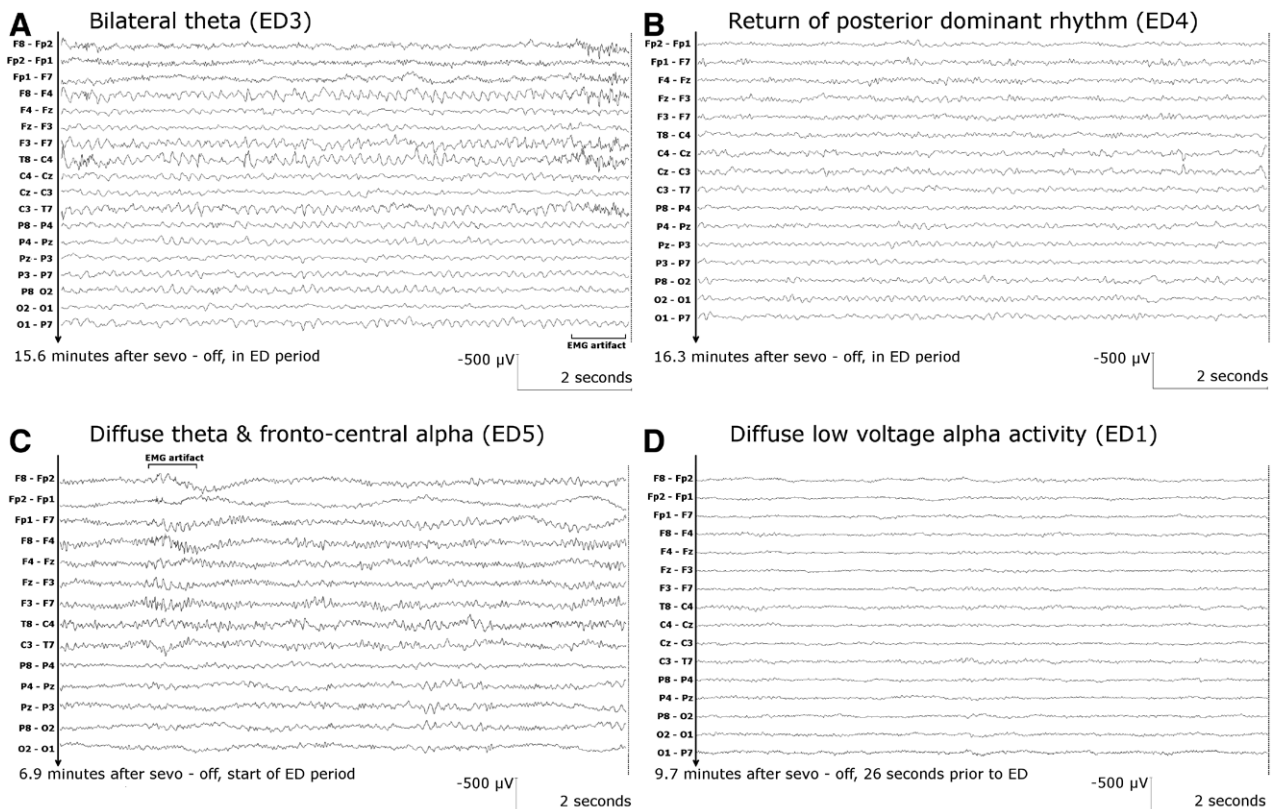


Fig. 3. Electroencephalogram transverse bipolar montage time series data from patients with emergence delirium (ED) during or just before the onset of ED. All displayed time series data were bandpass filtered between 0.3 and 70 Hz. (A) Diffuse bilateral theta slowing with frontal electromyographic artifact during delirious behavior (patient ED3). (B) Return of posterior dominant rhythm and frontal beta activity (patient ED4). Bipolar pairs involving F8 were removed from montage display due to poor data quality. (C) Diffuse 6 Hz theta and frontocentral alpha (patient ED5). Bipolar pairs involving P7 and Cz removed from montage display due to poor data quality. (D) Diffuse low-voltage anterior and posterior alpha activity (patient ED1). Bipolar pairs involving P3 removed from montage display due to poor data quality.

point was colored according to group, with blue points denoting the period of ED in the overall time series of the ED group. The common average exhibited higher values of GE in all three regional networks compared with the Laplacian derivation.

The data from each participant were binned into 5-min epochs to ensure a sufficient number of points to fairly calculate the mean, withstanding data loss from artifact rejection. Because the prediction of ED in children would be of clinical benefit, the time windows between sevoflurane being switched off and the mean onset of ED were of particular interest.

For full and parietal brain networks, there was no significant deviation in mean GE between the groups in time. However, in both common average and Laplacian derivations, differences between ED and NC frontal networks were seen after sevoflurane had been switched off (fig. 6). Data were further analyzed using a mixed-effects design ANOVA which revealed a significant difference in mean GE between the 0 and 5 min and 5 and 10 min time windows (for the Laplacian montage: $F(1, 8) = 7.475$, $P < 0.05$ partial $\eta^2 = 0.483$). For children with ED, a substantial decrease was shown in mean GE between the two time windows, whereas the control subjects showed no significant variation ($F(1, 8) = 5.883$, $P < 0.05$ partial

$\eta^2 = 0.424$). This result was also reproduced between the two groups using the common average montage ($F(1, 8) = 19.664$, $P < 0.05$ partial $\eta^2 = 0.711$). Also, a between-group effect was also significant in both Laplacian and common average derivations, suggesting that children with ED had higher mean GE values in frontal networks than controls (tables 4 and 5).

Global Coherence spectra obtained in figure 7 for control patient NC4 demonstrated higher values of GC using common average *versus* Laplacian montage (denoted by warmer colors). Alpha band activity was shown to begin approximately 11 Hz, with the peak magnitude reached in the frontal region 15 min after sevoflurane had been switched off. This band of activity quickened toward a plateau value of approximately 14 Hz toward the end of the recording. This trend in parietal network connectivity was muted in the Laplacian derivation, suggesting that smaller spatial scales are associated with reduced correlation using this montage, a trend substantiated in the study by Kuhlmann *et al.*¹⁶ Due to changes in GE-based frontal networks discussed above, frontal GC figures for all ED subjects are presented in figure 8. In the 5-min period before the onset of ED, a shift in the peak frequency of alpha band GC was shown to occur across all subjects. An independent-samples *t* test confirmed a significant increase in mean GC in the

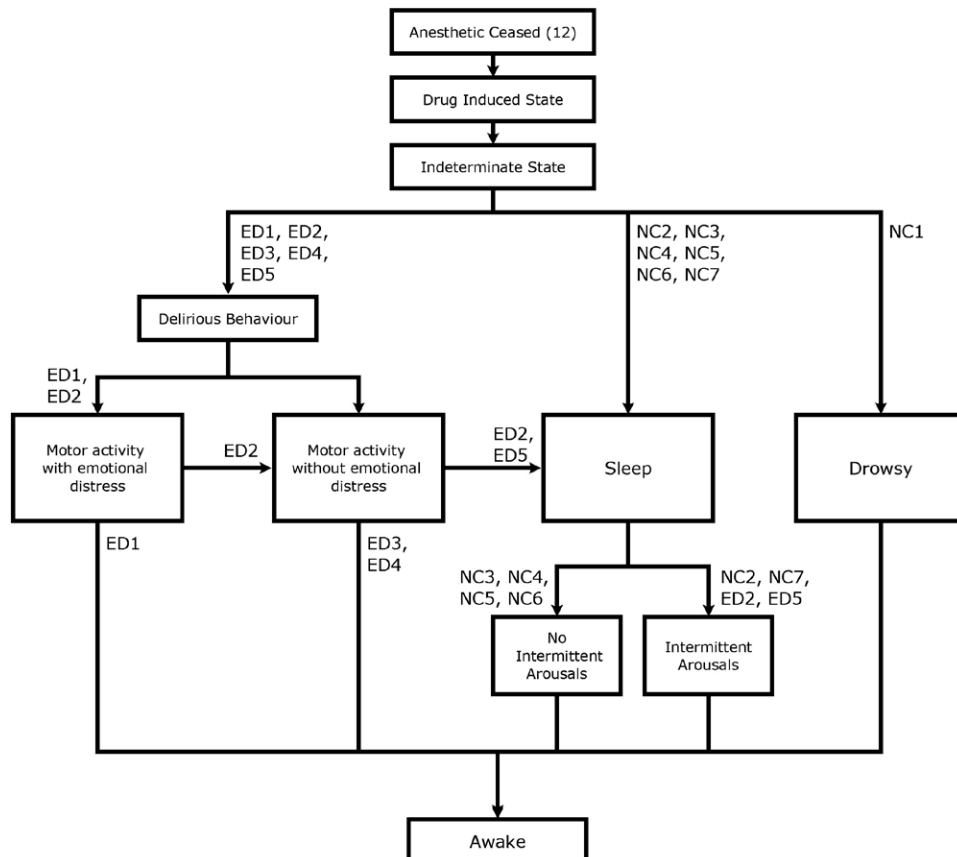


Fig. 4. State transitions of normal control (NC) children compared with those with emergence delirium (ED), from the termination of sevoflurane to awakening. State transitions are categorized according to behavioral and electroencephalographic patterns.

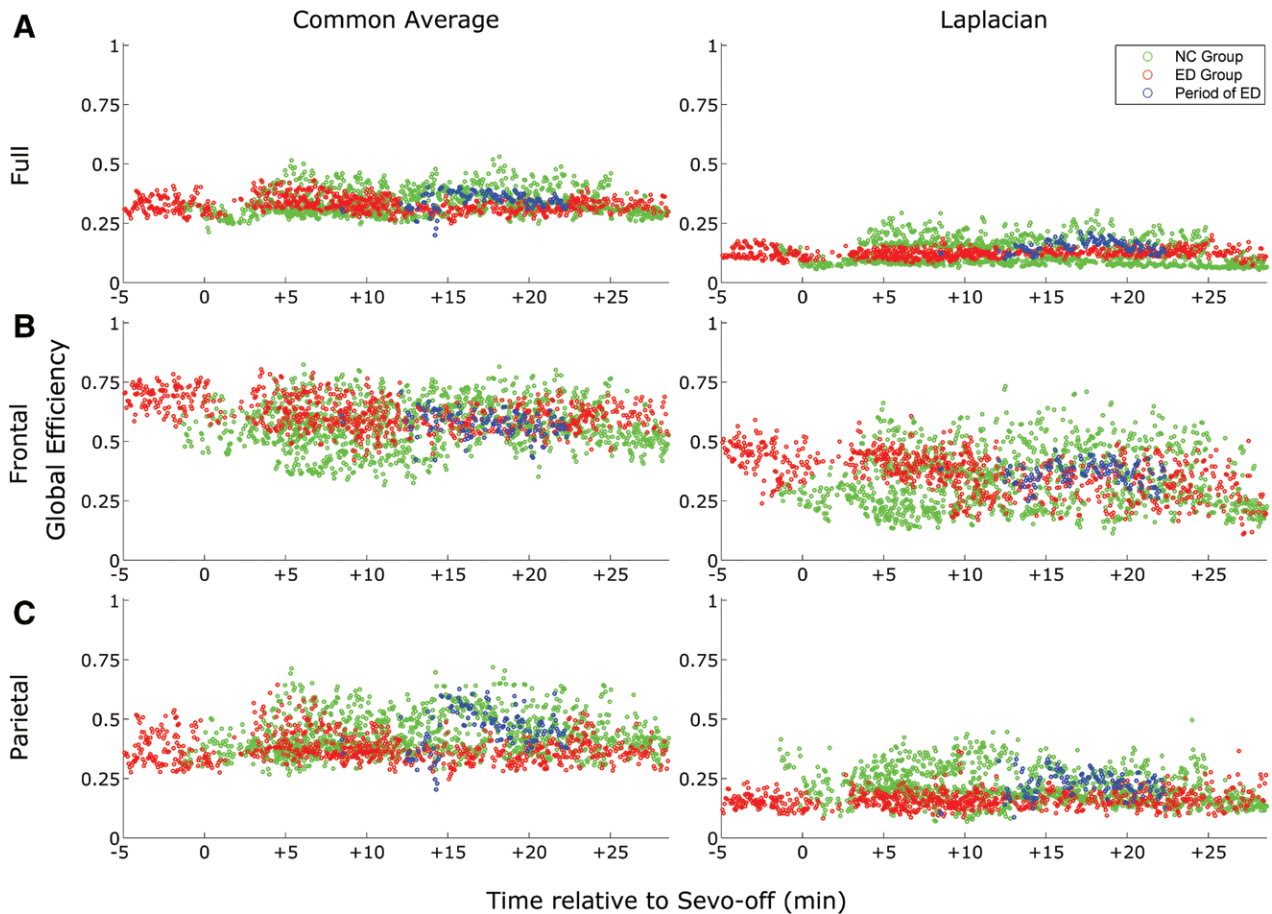


Fig. 5. Time series for Global Efficiency functional connectivity measures for Normal Control (NC) (green) and emergence delirium (ED) groups (red, ED period in blue). Values calculated for (A) full brain, (B) frontal, and (C) parietal networks with either common average (left column) or Laplacian rereferencing (right column).

alpha band for frontal networks between ED and NC in both derivations (tables 6 and 7).

Discussion

In this study, we investigated whether multichannel electroencephalography was able to reveal differences between children exhibiting ED from a set of matched controls who recovered from anesthesia without any complications (NC). In particular, it was hypothesized that alterations in functional connectivity, assessed through the respective time and frequency domain measures GE and GC, would be observed between the two groups.

Based on a cohort of 60 children who had their electroencephalogram collected during induction and emergence from anesthesia, we found an incidence of ED of 8.3%, a figure consistent with previous reports.²² Of the five ED cases observed, all were in children who had received sevoflurane, an outcome compatible with the established propensity of sevoflurane to increase the risk of ED.⁴

Since its initial articulation,²³ the concept of functional connectivity has proven usage in the descriptive characterization of the spatiotemporal variations in large-scale neural activity recorded during anesthesia.²⁴ Functional

connectivity is typically defined in terms of quantifying statistical dependencies between spatially remote neurophysiological events.²³ In our case, these neurophysiological events were the electroencephalogram recorded at different scalp locations. Although the choice of these locations is to some extent arbitrary, their dense and orderly coverage ensures that cortical activity is spatially well sampled and systematically recorded. This allows quantitatively legitimate comparisons to be made between differing physiological states and patient cohorts. For this reason, functional connectivity is an admissible observable phenomenon.²³ We chose time domain correlation and frequency domain cross-spectrum as measures of statistical interdependency from which we derived the network- and subnetwork-based estimates of functional connectivity GE and GC. Although other measures could have been used, we chose these quantities as they have already been used successfully in the cortical level characterization of anesthetic action.^{15,17} Consistently and methodically defining some measure of functional connectivity allows us to avoid the otherwise subjective assessment of alterations in spatiotemporal neural activity. Although anatomical (structural) connectivity undoubtedly constrains functional

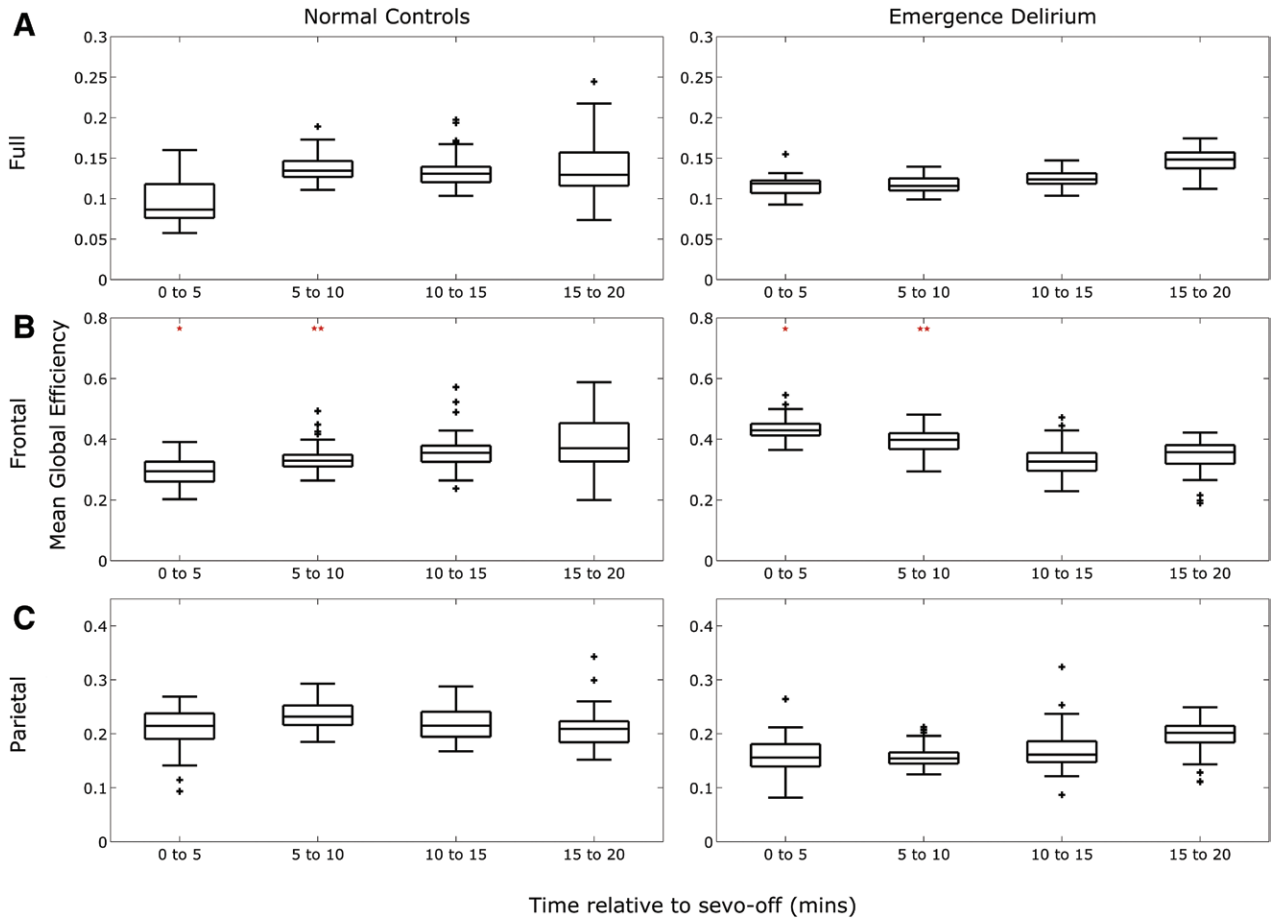


Fig. 6. Box-whisker plots illustrating the time course of changes in mean Global Efficiency calculated in 5 min time bins for (A) full brain, (B) frontal, and (C) parietal networks either normal controls (NC) (left column) or children with emergence delirium (right column). Similar temporal trends with respect to clinical grouping and brain network were also observed using the common average derivation (results not shown). Stars indicate bins that were significantly different between emergence delirium and NC groups. Boxes represent interquartile ranges, lines enclosed within boxes (and connected lines) median values, whiskers represent the largest (smallest) nonoutlier, and crosses represent outliers (defined as values extending further than 1.5 times the interquartile range—equivalent to approximately 3 SD for normally distributed data).

connectivity, it is not capable of providing either a sufficient or a complete description of activity-dependent spatiotemporal neural activity.

The significant result of this study was that the GE and GC measures of frontal lobe functional connectivity (figs. 5–8) were different in magnitude and time course between ED and NC patients after the termination of anesthesia. The fact that frontal lobe network changes were observed is consistent with the semiology of ED and is likely to have important implications for the pathophysiology of other disorders of anomalous arousal such as nonrapid eye movement parasomnias. In particular, in the first 5 min after the termination of anesthesia, frontal lobe network functional connectivity was elevated in patients with ED compared with their matched controls, which subsequently followed a different time course: decreasing in patients with ED, but increasing in the NC group. This behavior was seen in both common-reference and Laplacian derivations, implying that the source of such differences is not of extracortical

origin. Although in general common-reference electrode derivations are sensitive to spatially widespread and temporally coherent sources of activity (which may include electrocardiogram, electrooculogram, electromyogram, and eye-blinks), Laplacian reference electrode derivations are generally understood to focus on superficial, small-scale cortical level activity. Higher values for GE and GC were seen in the common average *versus* Laplacian derivation. This is attributed partly to volume conduction effects of the common average montage and reinforces the finding that the surface Laplacian enhances electrode sensitivity to more local and superficial sources.²¹ The implication of varying peak alpha band GC-based functional connectivity measures across time in ED subjects remains unknown.

One interpretation of this observed increase in frontal lobe network functional connectivity is that it represents a state of cortical hyperexcitability, as greater network connectivity would imply an enhanced ability to react to internally and externally imposed stimuli. On this basis,

Table 4. Means and SDs: Mean Global Efficiency

			Laplacian			Common Average			N*
			Full (M ± SD)	Frontal (M ± SD)	Parietal (M ± SD)	Full (M ± SD)	Frontal (M ± SD)	Parietal (M ± SD)	
Time (referenced to sevo-off)	0–5 min	Normal controls	0.12 ± 0.05	0.31 ± 0.10	0.24 ± 0.06	0.32 ± 0.04	0.55 ± 0.07	0.40 ± 0.06	6
		Emergence delirium	0.12 ± 0.02	0.43 ± 0.02	0.15 ± 0.02	0.34 ± 0.03	0.65 ± 0.06	0.38 ± 0.06	4
	5–10 min	Normal controls	0.12 ± 0.05	0.31 ± 0.12	0.23 ± 0.06	0.33 ± 0.04	0.55 ± 0.08	0.43 ± 0.08	6
		Emergence delirium	0.12 ± 0.01	0.37 ± 0.05	0.15 ± 0.03	0.34 ± 0.02	0.61 ± 0.05	0.38 ± 0.05	4

Data are presented as mean (M) ± SD; N = sample size. Global Efficiency ranges from 0 to 1.

* Patient NC5 was excluded from the analysis as first 5 min of electroencephalogram during emergence was not recorded.

NC = normal control.

we might speculate that patients with ED are more likely to be triggered to an anomalous state of arousal. Significantly, these results mirror Choi *et al.*'s,²⁵ who investigated functional connectivity in delirium using functional magnetic resonance imaging, finding of increased functional connectivity between prefrontal cortex and posterior cingulate cortex.

Our finding that changes in frontal lobe connectivity precede the expression of ED suggests that the methods outlined here may find practical usage in the monitoring of postoperative state such that appropriate surveillance and care can be assigned based on a better defined level of risk. Clearly for this to be a reality, larger studies of the type we have described here will have to be performed to both corroborate and extend our results. However, a recent study by van Dellen *et al.*²⁶ of adult patients aged 50 yr or older undergoing cardiac surgery who exhibited postoperative delirium found, on the basis of 21-channel electroencephalography, reduced functional connectivity in the alpha band. The authors speculated that delirium emerged as a consequence of functional *disconnection*. Discrepancies between their results and ours may reflect (1) differences in the methods used to evaluate functional connectivity, (2) the different patient cohorts, and (3) differences in the pathogenesis of the hyperactive and agitated delirium we observed compared with the more common hypoactive and lethargic delirium that characterized the van Dellen *et al.* patient cohort.

In addition to quantifying alterations in functional connectivity, this study also classified the behavioral and electroencephalographic features of children emerging from anesthesia. Children with quiet arousal awoke from states characterized by typical sleep patterns with theta activity typical of drowsiness or slower delta activity with vertex waves and spindles. In contrast, in children experiencing ED, the state before arousal was the same as the indeterminate state seen before “sleep-like” patterns in children with quiet arousal. These children did not have normal sleep rhythms and transients before ED. The indeterminate state may be an electroencephalogram state resulting from residual drug without clear sleep-like patterns.

One interpretation of this finding is that the indeterminate electroencephalogram represents a state of residual anesthesia and delirium occurs when children arouse from such a state. As a corollary, ED is less likely if the child progresses from the indeterminate state through sleep to arousal. This fits with the clinical observation that delirium may be due to “rapid awakening” with less time to develop normal sleep states. Pain may increase the risk of delirium; this is consistent with the hypothesis that pain will increase the chance of a child awakening when deep, without progressing to a sleep state (children in pain are unlikely to remain asleep). If the incidence of ED is less when a child progresses to sleep, this would imply that the risk of ED is clinically reduced if every attempt is made to allow a child to awaken in a quiet environment without stimulation. Such an idea is

Table 5. Repeated-measures Mixed ANOVA: Mean Global Efficiency

		Laplacian						Common Average					
		Full		Frontal		Parietal		Full		Frontal		Parietal	
Time	ED Status	Time	ED Status	Time	ED Status	Time	ED Status	Time	ED Status	Time	ED Status	Time	ED Status
Significance	<i>P</i> = 0.67	<i>P</i> = 0.18	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> = 0.45	<i>P</i> = 0.93	<i>P</i> = 0.20	<i>P</i> = 0.22	<i>P</i> < 0.01	<i>P</i> < 0.01	<i>P</i> = 0.07	<i>P</i> = 0.21	

Time: within-subjects effect; 0–5 min, 5–10 min after sevoflurane switched off. ED status: between-subjects effect; normal controls, emergence delirium. Data are presented as mean (M) ± SD; N = sample size. Global efficiency ranges from 0 to 1. Patient NC5 was excluded from the analysis as first 5 min of electroencephalogram during emergence was not recorded. Bold indicates values that reached statistical significance using a mixed-effects ANOVA statistical test.

ED = emergence delirium; NC = normal control.

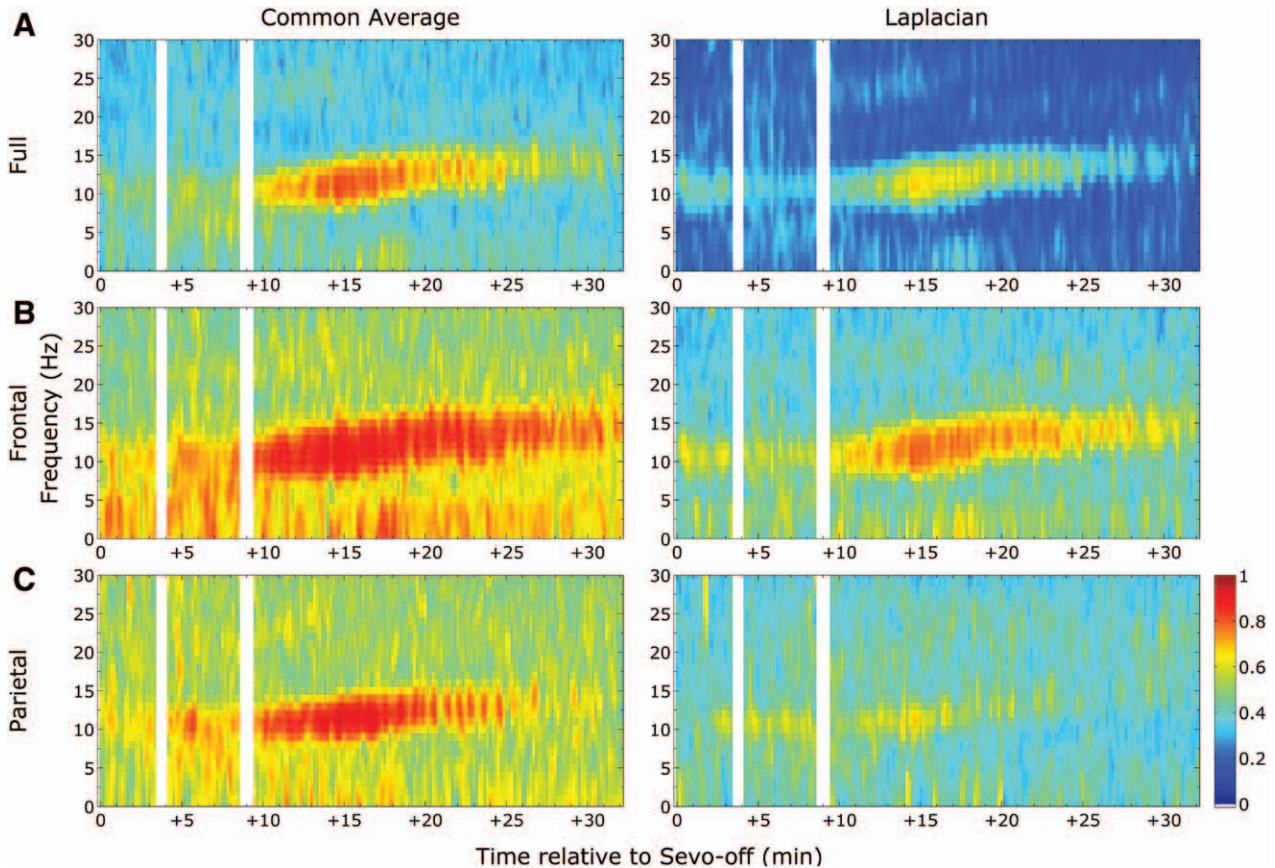


Fig. 7. Time series for Global Coherence functional connectivity measures for the same normal control subject (NC4) for (A) full, (B) frontal, and (C) parietal networks calculated using either common average (left column) or Laplacian rereferencing (right column). Vertical white spaces indicate the time intervals in which data contained artifact.

also supported by the results of our functional connectivity analysis. Further clinical studies are required to see whether this is indeed clinically apparent.

There are a number of limitations associated with our study. In cases of ED, the assessment of behavioral characteristics may have been better with video recording and offline analysis. Although the clinical drug regimen was not standardized across the sample, use of age-, sex-, and anesthetic-matched controls ensured equal representation of these potential confounders in the two groups. Also the “indeterminate” state was unable to be classified using classical sleep staging due to the residual effect of sevoflurane which made interpretation of results in relation to night terror problematic. Due to inhomogeneity in normal limits of children’s electroencephalograms, individual variability can heavily influence small studies such as ours making it difficult to draw any conclusions about the magnitude of the aforementioned effects in the population. Although we observed clear differences in electroencephalogram-derived measures after the cessation of sevoflurane, due to logistical constraints and preoperative variations in drug regimens, we did not investigate whether they were preexisting during the earlier phases of anesthesia or indeed in the preanesthetic

state. Clearly, future studies will need to clarify this as it has important implications for the pathophysiological mechanisms underlying ED and clinical efforts to ameliorate it. Despite clear technical challenges in studying pediatric ED, further high-density electroencephalogram studies are advocated to clarify our functional connectivity findings.

Finally, in this study, children awoke from sevoflurane anesthesia. ED is unusual with propofol total intravenous anesthesia even though children may have rapid arousal. It would be informative to extend our study to propofol total intravenous anesthesia to see whether these children without ED having total intravenous anesthesia arouse from sleep-like or indeterminate patterns.

In conclusion, this observational study found that ED occurred when children roused during an electroencephalogram without evidence of sleep. In contrast, age-matched children who awoke during an electroencephalogram with sleep-like patterns did not have ED. Quantitative results demonstrate significant frontal GE network changes in the ED group in the time immediately after sevoflurane being switched off, thus supporting the findings of dissociative patterns seen qualitatively. This provides some insight into the possible mechanisms underlying ED.

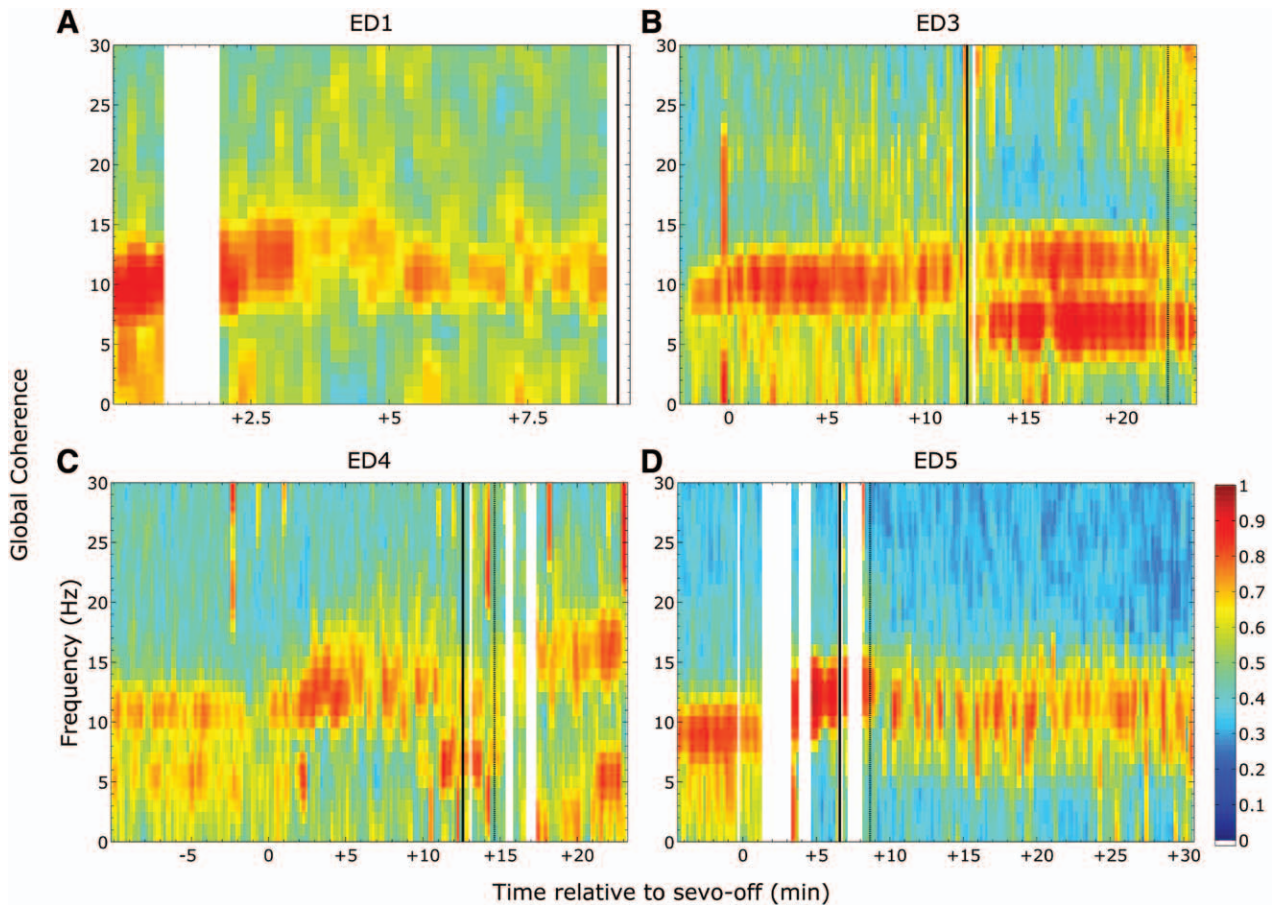


Fig. 8. Time series for estimated functional connectivity using the Global Coherence measure calculated using Laplacian rereferenced electroencephalogram data for frontal networks of patients with emergence delirium (ED) (A) ED1, (B) ED3, (C) ED4, and (D) ED5. In each subfigure: vertical solid black line = onset of ED episode, vertical dashed black line = end of ED episode (where applicable). White spaces indicate time intervals in which data contained artifact preventing the meaningful calculation of Global Coherence.

Table 6. Means and SD: Mean Global Coherence (5–10 min after Sevoflurane Switched Off)

	Laplacian			Common Average			N
	Full (M ± SD)	Frontal (M ± SD)	Parietal (M ± SD)	Full (M ± SD)	Frontal (M ± SD)	Parietal (M ± SD)	
Normal controls	0.39 ± 0.10	0.59 ± 0.10	0.54 ± 0.10	0.52 ± 0.06	0.72 ± 0.03	0.65 ± 0.08	7
Emergence delirium	0.44 ± 0.14	0.74 ± 0.05	0.50 ± 0.09	0.62 ± 0.16	0.85 ± 0.04	0.76 ± 0.11	4

Data are presented as mean (M) ± SD; N = sample size. Global coherence ranges from 0 to 1.

Table 7. Independent-samples *t* test: Mean Global Coherence (5–10 min after Sevoflurane Switched Off)

	Laplacian			Common Average		
	Full	Frontal <i>t</i> (9) = -2.59	Parietal	Full	Frontal <i>t</i> (9) = -5.51	Parietal
Significance (two tailed)	<i>P</i> = 0.58	<i>P</i> < 0.05	<i>P</i> = 0.57	<i>P</i> = 0.16	<i>P</i> < 0.05	<i>P</i> = 0.12

Bold indicates values that reached statistical significance using an independent-samples *t* test.

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Competing Interests

Dr. Liley has a nonequity shareholding in, as well as being a co-founder of, the medical device company Cortical Dynamics Ltd. (Perth, Western Australia, Australia). The other authors declare no competing interests.

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