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Clinical Investigation

CLINICAL INVESTIGATION

# Electroencephalographic markers of brain development during sevoflurane anaesthesia in children up to 3 years old

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## Abstract

**Background:** General anaesthetics generate spatially defined brain oscillations in the EEG that relate fundamentally to neural-circuit architecture. Few studies detailing the neural-circuit activity of general anaesthesia in children have been described. The study aim was to identify age-related changes in EEG characteristics that mirror different stages of early human brain development during sevoflurane anaesthesia.

**Methods:** Multichannel EEG recordings were performed in 91 children aged 0–3 yr undergoing elective surgery. We mapped spatial power and coherence over the frontal, parietal, temporal, and occipital cortices during maintenance anaesthesia.

**Results:** During sevoflurane exposure: (i) slow–delta (0.1–4 Hz) oscillations were present in all ages, (ii) theta (4–8 Hz) and alpha (8–12 Hz) oscillations emerge by ~4 months, (iii) alpha oscillations increased in power from 4 to 10 months, (iv) frontal alpha-oscillation predominance emerged at ~6 months, (v) frontal slow oscillations were coherent from birth until 6 months, and (vi) frontal alpha oscillations became coherent ~10 months and persisted in older ages.

**Conclusions:** Key developmental milestones in the maturation of the thalamo-cortical circuitry likely generate changes in EEG patterns in infants undergoing sevoflurane general anaesthesia. Characterisation of anaesthesia-induced EEG oscillations in children demonstrates the importance of developing age-dependent strategies to monitor properly the brain states of children receiving general anaesthesia. These data have the potential to guide future studies investigating neurodevelopmental pathologies involving altered excitatory–inhibitory balance, such as epilepsy or Rett syndrome.

**Keywords:** anaesthesia; general; child; development

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### Editor's key points

- Multichannel EEG recordings from 91 children aged 0–3 yr were used to map spatial power and coherence during sevoflurane anaesthesia.
- Age-dependent changes detected in brain oscillations might reflect cortical maturation and integration.
- These findings demonstrate the importance of age-dependent strategies for monitoring the brain states of children receiving general anaesthesia.

Each year, millions of children receive general anaesthesia for surgery. Sevoflurane is one of the most commonly used vapour anaesthetics in children because of its rapid induction, emergence, and recovery profile. Clinical studies using non-invasive brain monitoring show general anaesthetics and hypnotic agents produce EEG oscillations with specific spatial organisation that relate fundamentally to neural-circuit architecture and function.[1,2] For example, in adults under propofol anaesthesia, specific EEG patterns are observed, consisting of incoherent slow oscillations distributed across the entire head and strongly coherent alpha oscillations located across only the front of the head.[3,4] The association of unconsciousness with frontal alpha oscillations is a fairly consistent finding, although there are counterexamples.[5]

Prior studies suggest that neurophysiological response to sevoflurane changes as a function of age.[6–10] However, these studies lack the detailed characterisation of anaesthesia-associated neural-circuit activity particularly at specific developmental ages associated with critical periods of heightened brain plasticity because of (i) low numbers of patients enrolled, (ii) grouped analysis over a broad age range that involves key developmental changes, (iii) limited electrodes and lack of spatial mapping, and (iv) use of EEG-derived algorithms that can lose valuable information.

The study aim was to investigate whether there are systematic changes in sevoflurane-induced brain oscillations that might mirror different stages of human brain development. We used multichannel EEG recordings in children up to 3 yr of age undergoing sevoflurane general anaesthesia for elective surgery. We mapped spatial power and coherence over the frontal, central, parietal, temporal, and occipital cortices. Our results suggest key developmental milestones in the assembly and maintenance of sevoflurane-induced circuit activity in the human brain.

## Methods

### Ethics approval

This study was approved by the Boston Children's Hospital Institutional Review Board (Protocol Number: P000003544) and classified as 'no more than minimal risk'. Informed written consent was obtained from the parents/legal guardians. The study conformed to the Declaration of Helsinki.

### Patient population

Children who were scheduled for an elective surgical procedure were recruited from the preoperative clinic at the Boston Children's Hospital from December 2011 to August 2016. The inclusion criteria consisted of 0–3 yr old and requiring surgery below the neck. All children were clinically stable on the day of study and ASA Physical Status I or II. The exclusion criteria were (i) born with congenital malformations or other genetic conditions thought to influence brain development, (ii) diagnosed with a neurological or cardiovascular disorder, or (iii) born at <32 weeks postmenstrual age.

### Study design

Multichannel EEGs were recorded during the administration of sevoflurane general anaesthesia. The end-tidal anaesthetic gas concentration was time locked to the EEG recording. The spatial properties of the EEG were evaluated during a sevoflurane-maintained surgical state of anaesthesia.

### Anaesthetic management

Anaesthetic management was adjusted per the anaesthetist's impression of clinical need. Each patient received anaesthesia induced with sevoflurane alone, or a combination of sevoflurane and nitrous oxide in oxygen. Nitrous oxide was added at the discretion of the anaesthetist ($n$=66). Nitrous oxide was discontinued after placement of a tracheal tube or laryngeal mask. Tracheal tube ($n$=62), laryngeal mask ($n$=24), or face mask ($n$=5) were used. Propofol bolus was used to facilitate tracheal intubation or to suppress motor reflexes in 44 subjects [median dose: 2.4 mg $kg^{-1}$ [inter-quartile range (IQR): 1.7–3.3 mg $kg^{-1}$]. Seven subjects were prescribed midazolam premedication on the day of surgery.

### Data acquisition

All subjects were in the supine position throughout the study. Each subject was studied once.

#### *EEG recording*

An EEG cap was used to record the EEG activity (waveguard EEG cap; Advanced NeuroTechnology, Enschede, Netherlands) with 33 or 41 recording electrodes positioned per the modified international 10/20 electrode placement system. For 33-channel recording, the electrodes were positioned at FPz, FP1, FP2, F3, F4, F7, F8, FC1, FC2, FC5, FC6, Cz, CPz, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, T7, T8, M1, M2, POz, Oz, O1, and O2. For 41-channel recordings, additional electrodes were positioned at AF7, AF8, PO7, PO8, FT7, FT8, TP7, and TP8. Reference and ground electrodes were located at Fz and AFz, respectively. Impedance of the electrode–skin interface was minimised using an EEG prepping gel (Nuprep gel; Weaver and Company, Aurora, CO, USA), and conductive EEG gel was used to optimise electrode contact (OneStep clear gel; H + H Medical Devices, Dülmen, Germany).

The EEG activity from 0 to 500 Hz was recorded (EMU40EX; Natus Medical Incorporated, Oakville, ON, Canada). Signals were digitised at a 1024 Hz sampling rate (or 256 Hz in five patients) and 16-bit resolution.

#### *Clinical data collection*

Clinical information was collected from the electronic medical records and from the in-house anaesthesia information management system. End-tidal sevoflurane, oxygen, and nitrous oxide concentrations were downloaded from the anaesthetic monitoring device (Dräger Apollo; Dräger Medical