Characterisation of awakening from anaesthesia in infants

A thesis submitted by
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Abstract

There is uncertainty about the doses of anaesthetic drugs required for unconsciousness in infants. It is important to both avoid inadequate doses leading to intraoperative awareness and also excess doses that may harm the developing brain. Depth of anaesthesia monitoring has been developed in adults based upon electroencephalography (EEG). The EEG of infants is different and few data are available. Heart rate variability (HRV) using the ECG is another non-invasive tool that could be used in infants. The hypothesis of this thesis is that EEG and HRV could help predict or warn of awakening after anaesthesia. Awakening was defined by a panel of experts as at least 2 of crying, coughing, vigorous limb movements, eyes open or looking around. A suitable clinical model of awakening from anaesthesia was determined in a series of pilot studies. Intubated infants anaesthetised with sevoflurane were studied after surgery. Tickling the foot proved a reliable stimulus to cause awakening. EEG and HRV were monitored at the end of surgery during emergence. Events and behaviour were videoed and characteristics of EEG and HRV were identified. After awakening began EMG and other interference made signals difficult to interpret. In all infants there was negligible EEG power in frequencies higher than 20Hz and most power was in frequencies less than 5Hz. Infants older than 52 weeks post menstrual age (PMA) had an oscillatory characteristic within the 5 to 20 Hz range during anaesthesia that reduced in power appreciably as sevoflurane levels decreased; power in 5-20 Hz reduced to less than 100 μV^2 before awakening began which may provide a potential warning of awakening. Infants less than 52 weeks PMA had low EEG power in 5-20 Hz throughout. EEG power in this frequency band during anaesthesia increases with age. HRV was low during anaesthesia but increased before awakening began. HRV low frequency power increased in bursts as anaesthesia levels decreased. A case report demonstrated the potential value of P5-20Hz and LF HRV band power in the development of intraoperative depth of anaesthesia monitoring in infants older than 52 weeks PMA.

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Symbols, abbreviations and units

Abbreviation	Description
AB	awakening began
AEP	auditory evoked potential
alpha	EEG frequency 8-13Hz
ANOVA	analysis of variance
AW	awakening
BAT	Behavioral Arousal Threshold
beta	EEG frequency 14-30Hz
BIS	A commercial EEG monitor
bAB	60 second period before awakening began
bSO	60 second period before sevoflurane turned off
CFM	Cerebral Function Monitor
CFAM	Cerebral Functioning Analysing Monitor
Cz	EEG channel, midline central
CP3 and CP4	EEG channels, centro-parietal, left and right of midline

Abbreviation	Description
Delta	EEG frequency <4Hz
EC50%	median effective concentration
EEG	Electroencephalography
epochXL	2^{nd} epoch of raw band power exceeding mean + 2SD of baseline
FFT	Fast Fourier Transformation
FPR	False positive rate
F_{res}1Hz	frequency resolution one Hz
F_{res}0.2 Hz	Frequency resolution 0.2 Hz
Fz	EEG channel, midline frontal
GABA	γ-aminobutyric acid
gamma	EEG frequency >30 Hz
GCS	GLASGOW COMA scale
GTF	Grass Telefactor
HF	high frequency

Abbreviation	Description
HR	heart rate
HRV	heart rate variability
Hz	Hertz
IFT	isolated forearm technique
Kg	kilogram
kPa	kilopascal
l/min	litres per minute
LF	low frequency
LOC	level of consciousness
MAC	minimal alveolar concentration
μV^2	microvolts squared (unit of EEG power)
MF	median frequency
Mg	milligram
MSSD	mean SSDiffNN
M1	First limb movement
NMDA	N-methyl D-aspartate
NN	interval between normal beats
NN25	the number of pairs of adjacent beats with an absolute difference more than 25 milliseconds

Abbreviation	Description
OAS/S	Observer's Assessment of Alertness/Sedation Scale
Oz	EEG channel, midline occipital
P	Probability statistic
P5-20Hz	EEG power in frequencies 5 to 20 Hz
P_{et}	end tidal pressure (% of atmospheric pressure)
P_{et}Sevoflurane	percentage of Sevoflurane in expired gas
PET	positron emission tomography
PMA	post menstrual age
pNN25	percentage of NN interval that differ by more than 25 milliseconds
PK	probability
PSD	power spectrum density
PTT	pulse transit time
ROC	Receiver Operating Characteristic

Abbreviation	Description
RMSSD	square root of MSSD
RR interval	interval between successive ECG R waves
s^2	seconds squared (unit of HRV power)
SD	standard deviation
SDHR	SD of HR
SDiffNN	difference between each successive adjacent pair of NN intervals
SDNN	standard deviation of NN
SEF	spectral edge frequency
SIDS	sudden infant death syndrome
SO	Sevoflurane turned off
SSDiffNN	square of the difference between each successive adjacent pair of NN intervals
Theta	EEG frequency 4-7Hz
TP	total power
TPR	True positive rate
T7	EEG channel, left temporal
UMSS	University of Michigan Sedation scale
vHF	Very high frequency

Abbreviations grouped by theme

EEG channels	
Cz	midline central
Fz	midline frontal
Oz	midline occipital
T7	left temporal
CP3 and CP4	centro-parietal, left and right of midline

EEG frequency bands	
gamma	> 30 Hz
beta	14-30 Hz
alpha	8-13 Hz
theta	4-7 Hz
delta	< 4 Hz

Events	
SO	sevoflurane turned off
M1	first limb movement
AB	awakening began
AW	full awakening
bSO	60 seconds before SO
bAB	60 seconds before AB

HRV time domain	
HR	heart rate
SDHR	standard deviation of HR
NN	interval between normal beats
SDNN	standard deviation of NN
SDiffNN	difference between each successive adjacent pair of NN intervals
SSDiffNN	square of the difference between each successive adjacent pair of NN intervals
MSSD	mean SSDiffNN
RMSSD	square root of MSSD
NN25	the number of pairs of adjacent beats with an absolute difference more than 25 milliseconds
pNN25	percentage of NN interval that differ by more than 25 milliseconds

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Declaration

I, Michael Roy Joseph Sury, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Except for some EEG data in Chapter 8, all data presented has been obtained by the author according to the ethical standards of the Institute of Child Health. Dr Dylan Bould assisted in obtaining feedback and analysis of the results of the survey of opinion presented in Chapter 5.

1 Introduction, objective and outline

Anaesthesia has been defined as a combination of unconsciousness, amnesia and immobility.[1] Three types of drugs, or components, are used to create a state of anaesthesia. The most important drug is a hypnotic which causes unconsciousness but also necessary are an analgesic to prevent pain, and a muscle relaxant to prevent reflex movement. Each component has an effect upon the others. For example a high dose of a hypnotic drug can be used to suppress wakefulness and movement to painful surgery but its dose can be reduced by the addition of analgesia and muscle relaxation. An ideal anaesthetic therefore is a balanced technique in which the doses of the three components are minimised. Nevertheless, the primary endpoint is unconsciousness and the focus of this thesis is to measure it.

During surgery the dose of a hypnotic needs to be adjusted to control the arousal of the central nervous system and to prevent the return of consciousness. Inadequate dosing could lead to awareness and distress whereas excessive dosing may cause unwanted side effects. Purposeful movement or increases in heart rate and blood pressure may indicate awareness but these features are not specific to consciousness. Movement can be a feature of spinal reflex activity and sympathetic cardiovascular responses are not necessarily related to conscious level. High heart rate and blood pressure can occur even with high doses of hypnotic drugs, and conversely can be absent in an awake patient given high doses of opioids. In adults consciousness is demonstrated by the ability to communicate and the dose of hypnotic that causes unconsciousness has been estimated. In infants however the dose is uncertain and is based upon an assumption that it relates to the dose that prevents movement.

Avoiding excessive doses may be important, because hypnotic drugs have effects on major organ function. Infants may be vulnerable to drug toxicity because of immature drug metabolism and excretion, and acute cardiovascular and postoperative respiratory dysfunction may also be problematic. Furthermore, high doses of hypnotic agents cause apoptosis in the developing brains of laboratory animals and could occur in humans also.

In patients who cannot communicate, a monitor of conscious level could help to prevent both inadequate and excessive doses in the dynamic situation of anaesthesia for a surgical procedure. Such a monitor would need to be practical in a wide variety of situations and be able to rapidly process signals from non-invasive skin sensors.

Cerebral cortical electrical activity is assumed to be related directly to conscious level and is measured using the electroencephalograph (EEG). Hypnotic drugs have dose dependent effects upon the EEG in adults and, although its reliability is debated, the EEG may be used to estimate depth of anaesthesia. Adult EEG data may be applicable in children but not in infants because the normal EEG of infants is different. There are few EEG data from infants during anaesthesia.

Autonomic nervous system activity is indirectly affected by conscious level. Change in heart rate is controlled by the autonomic system and is easily and rapidly detected by electrocardiography (ECG). In health there is beat to beat variation in heart rate related to autonomic function. The effect of anaesthesia depth on heart rate variability (HRV) has been investigated in adults but few data exist to determine its value in infants.

Any monitor of conscious level, direct or indirect, needs to be validated against accepted behavioural markers of consciousness. In adults communication can be used, but in infants surrogate markers are necessary.

This thesis investigates the EEG and HRV in infants during recovery from anaesthesia with the prime objective of identifying and testing characteristic features of awakening that could be used to develop a monitor of conscious level to help guide the dose of anaesthesia in order to prevent both inadequate and excessive dosing. The following chapters are concerned with two main themes: the development of a model to test conscious level during anaesthesia in infants, and the investigation of characteristics of the EEG and HRV that may detect or predict of awakening.

1.1 Objective

To identify and investigate EEG and HRV characteristics that may warn or predict awakening from anaesthesia in infants

1.2 Outline

Table 1-1 provides an outline of the main contents of each section.

Table 1-1: Thesis outline

Section	Main contents
1.	Introduction and objective
2.	Background
3.	Hypothesis and plan of investigation
4.	Methods – general aspects and equipment
5.	Development of the model of awakening from anaesthesia
6.	Characterisation of EEG changes
7.	Characterisation of HRV changes
8.	Further observations
9.	Discussion and future directions
10.	Appendices
11.	References

1.3 Summary of the aims, outputs and dates of each study

A summary of the studies in this thesis is presented below in Table 1-2.

Table 1-2. Summary of the aims, outputs and dates of each study in infants

The aims and outputs of each study are in the first and second columns respectively

5.1. Assessment of arousal and stimuli in non-intubated infants (Protocol 03AR16 versions 2 and 3; 20 infants studied, Mar 04 – Aug 05)	
• to determine the reliability of loud noise as a stimulus to rouse an infant from anaesthesia • to assess the feasibility of using a model of awakening from anaesthesia in which the infant is breathing spontaneously without a tracheal tube • to examine responses (including EEG changes) associated with arousal or awakening	• Loud noise is not a reliable stimulus • The model of awakening from anaesthesia in which the infant is breathing spontaneously without a tracheal tube is associated with airway and breathing problems. • There may be age related EEG power spectrum changes associated with awakening
5.2 Defining awakening by consensus (Feb 07 – Aug 08)	
To determine working criteria of awakening in a neonate or infant the opinion of a group of Paediatric Anaesthetists was determined by a questionnaire survey. Questions asked were: • Is it possible to define	29 respondents agreed that awakening in neonates after anaesthesia is a combination of at least 2 of 6 behaviours and these could reasonably be reduced to 5. For the purposes of this thesis the working criteria of awakening in a neonate or infant is combination of at least 2 of: • crying or attempting to cry

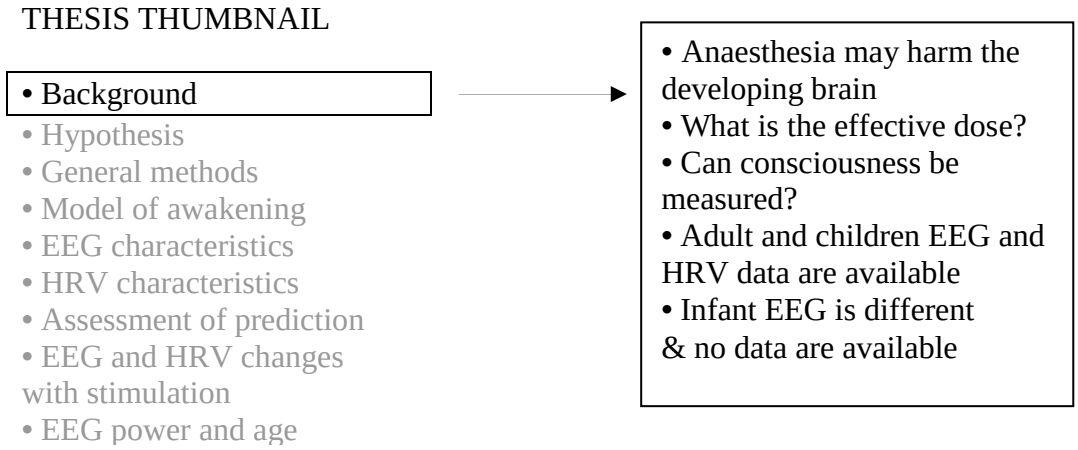
awakening from anaesthesia in neonates? • What are the observable phenomena that can be used to describe awakening from anaesthesia in neonates? • What stimulus should be used to test rousability in sleeping neonates at the end of anaesthesia?	• vigorous limb movements • gagging on a tracheal tube • eyes open • looking around There was less agreement about testing rousability. Of the three interventions suggested (removal adhesive tape, light touch and oral suction) only light touch was considered reasonable to use repeatedly.
5.3 Assessment of awakening in unstimulated intubated infants (Protocol 03AR16 version 4; 9 infants studied, Feb 08 – July 08)	
• To further investigate the characteristics of EEG changes during awakening from anaesthesia • To determine which EEG channels may be most useful to detect changes during awakening	• High power and a prominent frequency within the range of 5-20Hz is a feature of the EEG in anaesthetised infants older than 52 w PMA. • One minute before movement or awakening power within 5-20Hz decreases. • Younger infants do not have this feature. • It is most obvious in frontal, central and centro-parietal channels. • Unstimulated infants may take too long to awaken spontaneously • A stimulus should be applied to intubated infants to test the sequence of behavioural changes that may be predicted by changes in EEG and HRV.

5.4 Assessment of awakening in stimulated intubated infants (Protocol 03AR16 version 5; 20 infants studied, Jan 09 – Sept 09)	
• To determine the reliability of skin stimulation in causing gradual arousal or awakening • To observe the timing of behavioural changes during awakening provoked by skin stimulation	• In an intubated infant, in which sevoflurane is being washed out, tickling the feet produces a progression of responses, beginning with movement, then cardiorespiratory changes and culminating in awakening. • Awakening did not begin until P_{et}Sevoflurane was approximately 0.5%
6. Characterisation of EEG changes (infants studied are those of section 5.4)	
• To determine EEG characteristics during awakening from anaesthesia after surgery. • To compare EEG characteristics during awakening after surgery with those during anaesthesia before surgery. • To determine if EEG characteristics of awakening can be reversed when anaesthesia is re-established.	• EEG power was larger in the centro-parietal than the frontal channels. • The EEG after awakening is difficult to interpret because of interference. • Before awakening most EEG power lies in the low frequency range. • EEG characteristics during anaesthesia before and after surgery are similar • In the range 5-20 Hz EEG power during sevoflurane anaesthesia increases with age • In infants less than 52 weeks PMA the power is negligible • In infants older than 52 weeks PMA the EEG power is greater than100 μV^2 • This band power decreases during sevoflurane wash-out and before awakening began. • Awakening did not begin until P5-20 was

	less than 100 μV^2. • Parents would not consent to allow anaesthesia to be re-established for research
7. Characterisation of HRV changes (infants studied are those of section 5.4)	
• To determine HRV characteristics during awakening from anaesthesia after surgery	• HRV frequency domain band power changes in a characteristic fashion after sevoflurane is turned off. • Power in LF increases considerably more that HF and vHF but the increase appears in bursts. • Measurement and comparison of LF power at specific times may not describe the change in LF power in a sequence of data. • The identification and quantification of bursts may be more useful.
8.1 Assessment of prediction (infants included in analysis are those of section 5.4)	
• Statistical assessment of the ability of EEG HRV and ET sevoflurane to predict a true sleep state using o Receiver operating characteristics o Prediction probability	• ROC analysis: prediction of a sleep state was highest using end-tidal sevoflurane • PK analysis: prediction of change in conscious level was similar in all variables except EEG power in infants less than 52 weeks PMA
8.2 Potential value of EEG P5-20Hz and HRV LP (Protocol 03AR16 version 5; one infant observed in Oct 09)	
This is case report of an infant who required re-establishment of anaesthesia for clinical reasons	• P5-20Hz decreased and HRV LP increased during sevoflurane wash-out o These changes were reversed when

• To investigate how P5-20Hz and HRV LP react to intraoperative stimuli and changing P_{et}Sevo • Do P5-20Hz and HRV LP have the potential to monitor depth of anaesthesia?	sevoflurane anaesthesia was re-established. • P5-20Hz decreased and HRV LP increased in reaction to a painful stimulus o These changes could be reversed by both intravenous fentanyl and an increase in P_{et}Sevoflurane • P5-20Hz and HRV LP have the potential to monitor depth of anaesthesia
8.3 The relationship between age and P5-20Hz during anaesthesia (Infants included in analysis are those of sections 5.3 and 5.4 and also 14 infants and children from Royal Melbourne Childrens Hospital in Australia).	
• To confirm and further investigate the association between age and P5-20Hz	• The combined data support the initial finding that P5-20Hz is related to age.

2 Background



2.1 Why do infants need conscious level monitoring?

The dose of the hypnotic component of anaesthesia needs to be adjusted to induce and maintain adequate "depth" in response to varying stimulation and it is important to avoid the consequences of both excessive and inadequate doses. Gas sampling monitors the expired concentration of anaesthetic vapour and this is assumed to be the concentration achieved within the brain. The concentration of anaesthetic needed to prevent movement in adults and infants has been estimated from limited data. There are no data to measure the effect of anaesthesia on conscious level in infants. The evidence for these statements is presented below.

2.1.1 Problems of excessive anaesthesia

2.1.1.1 Cardiovascular depression

Excess doses of almost all anaesthesia drugs cause dangerous cardiorespiratory depression. Cardiac function in neonates is more vulnerable than in adults because the maximum tension created per unit cross-sectional area of myocardium is less[2] and the depressant effects of inhaled anaesthetics are greater.[3-5] In comparison with adults,

tissue solubility of inhaled anaesthetics is decreased in infants so that equilibration between inspired and tissue concentrations takes place sooner.[6] Sevoflurane is the current preferred inhalational induction agent because of its low blood solubility and least unpleasant smell. It reduces systemic vascular resistance and depresses cardiac contractility.[7;8]

2.1.1.2 Respiratory effects

Anaesthesia in infants often causes appreciable slowing of the respiratory rate and reduction in the functional residual capacity and tidal volume.[9] During the early phase of recovery from anaesthesia the oxygen saturation of blood is commonly less than 90%[10] and this is thought to be caused by pulmonary atelectasis[9;11] which probably persists if consciousness is slow to return. Post-operative apnoea is common in preterm babies[12] and its incidence decreases in time after anaesthesia administration ends.[13]

2.1.1.3 Neurological effects

In laboratory rat pups, combinations of large doses of midazolam, isoflurane and nitrous oxide cause permanent brain damage by widespread neuronal apoptosis.[14] The cause may be related to both GABA receptor agonism (an action of isoflurane and midazolam) and NMDA receptor antagonism (an action of nitrous oxide). Minor apoptosis is a feature of normal refinement of neuronal circuitry in the developing brain.[15] Widespread apoptosis could be triggered by blocking synaptic transmission at a critical stage of rapid brain growth and there is concern that anaesthetics in infants could also damage the developing brain.[16] The age at which the primate or human brain development matches that of rodents is uncertain[17;18] and although there are data showing the cortical apoptotic effect of prolonged exposure to ketamine in infant monkeys[19], there are no comparable data in humans.[20]

Evidence is being sought to show the effect of anaesthesia on the developing human brain.[20] There have been two retrospective audits of children who had had surgery before the age of 3 years. Wilder and colleagues found that the incidence of learning disability was associated with the number of anaesthetics,[21] and Kalkman and colleagues showed an association between anaesthesia and subsequent abnormal

behaviour of children assessed by their parents and recorded in a questionnaire.[22] Neither study could specify anaesthesia over any other potential confounding factors such as hospital admission and therefore cannot be considered as reliable evidence of harm caused by anaesthesia; although these studies are not reassuring of "no harm done". A multicentre randomised controlled trial is underway in preterm infants having inguinal hernia repair to compare the effects of sevoflurane anaesthesia versus spinal local anaesthesia on neurological development.[23]

2.1.2 Problems of inadequate anaesthesia

Movement and cardiorespiratory signs of sympathetic nervous activation can be reduced or prevented by analgesia and muscle relaxation. These reduce the dose requirement of hypnotic drug,[24;25] but potentially increases the possibility of intraoperative awareness. Despite modern drugs and practices, intraoperative awareness occurs in adults and in children.

2.1.2.1 Evidence of awareness and recall

Intraoperative awareness is a conscious appreciation of intraoperative events and is either detected during surgery or reported postoperatively.[26] It is under-reported because sub-anaesthetic doses affect memory and recall.[27] Depression of the central nervous system is dose dependent and memory loss may be one of the first modalities to be suppressed.[28]

If a patient is not sufficiently anaesthetised, and if muscle relaxants are not used, movement should be possible. If muscle relaxants are used communication is possible by using the isolated forearm technique (IFT) in which a tourniquet isolates the forearm from the remainder of the circulation so that it's muscles are not paralysed by the relaxant drug. The patient therefore has the capacity of non-verbal communication and awareness can be tested during surgery. In studies using the IFT intraoperative awareness has been demonstrated that cannot be recalled by patients later.[29;30] The method can only be used for a limited period because it causes ischaemia of the arm, and it relies on cooperation. Nevertheless it has been used successfully in children over the age of 5y[31] and in a study of 184 children 2 responded during anaesthesia.[32]

Even though anaesthesia can cause amnesia, the incidence of intraoperative awareness is usually estimated by assessment of postoperative recall. Recall of events can be either explicit or implicit.[33] Implicit recall involves the triggering of thought or behaviour without any appreciation of the reason for it.[26;34;35] Explicit recall is a clear memory of real events and can be measured using questionnaires presented at various times after the return of consciousness.[36;37]

2.1.2.1.1 Recall in adults and children

In adults, explicit recall after all types of anaesthesia is approximately 1 in 500[38] but can be as high as 1% if anaesthesia doses are limited (for example in patients with poor health).[39;40] In children, memory for real events has been recorded and may be linked to dreaming.[41-43] However recent studies have found that postoperative interviews detected recall in approximately 0.6-0.8% of children aged between 5 and 18 years;[44;45] the incidence may have been higher if the questioning was modified to be appropriate to the age of the child.[46] Fortunately few of these children were distressed by their intraoperative memories. Adults seem to be less fortunate and some remember extreme intraoperative pain and distress which often leads to post traumatic stress disorder.[47-51] Children who have had pain during intraoperative awareness seem to have less psychological disturbance than adults.[48]

2.1.2.1.2 Recall in infants

Recall may be assessed in infants by changes in behaviour or later when they are older and able to communicate. There are reports of young adults who can remember their hospital admission when they were aged 2 years[52] but adults generally do not remember their childhood events before the age of 3 to 4 years old (this is termed infantile amnesia). At age 2 to 3 years language and a *sense of self* develop and both of these are important in the formation of explicit memory.[53] Nevertheless evidence of recall can be found in infants of 7 to 8 months old who are able to find hidden objects. Such memory is retained for longer with increasing age and is also affected by the type of the experience, the number of times it occurs and by reminder cues.[54] At the age of 9 months information can be retained for 4 weeks , at age 10 months for up to 6 months,[55] and at age11 months up to 12 months.[54;56]

An event may alter complex behaviour without involving conscious thought. Implicit memory has been demonstrated in toddlers (2-3 years old) who were more familiar with auditory tests if they had had the tests before at the age of 6-7 months.[57] There is also evidence of neonatal memory; behaviour can be modified by stories read out loud during the last weeks of pregnancy,[58] newborns can recognise and their mother's voice,[59] and neonates prefer new rather than familiar images.[60;61] Neonates and young infants may learn from the pain of heel pricking because, on repeated stimuli, there is anticipatory distress.[62]

2.1.2.1.3 What is consciousness in infants?

Consciousness is difficult to define precisely and its application in infants is discussed comprehensively by Davidson.[63] Common definitions use the words awareness or wakefulness but these may be little more than synonyms. Philosophical and psychological considerations expose the complex and elusive nature of the concept of consciousness. For the practical problem of anaesthesia, evidence of consciousness in patients relies on communication and this is not possible in infants.

While few would disagree that the terms "awake", "sleepy" and "asleep" can be applied to infants, it could be argued that these behaviours are reflex. Behavioural changes in response to pain however, even in pre-term infants of 24 weeks gestation, are not considered to be reflex activity.[64-66] Foetuses and infants as young as 20 weeks gestation have the neurological structures and connections that enable them to feel pain.[67-69] In the past anaesthesia was considered to be too dangerous and possibly unnecessary for premature infants undergoing major surgery[70] but for the past 2 decades the principle of humane use of anaesthesia and analgesia has been applied to all infants irrespective of their maturation[71] and even to foetuses undergoing surgery before birth.[72]

2.1.3 Uncertainty of pharmacokinetics

2.1.3.1 Intravenous anaesthesia

Propofol is the only intravenous hypnotic suitable for maintenance of anaesthesia because, within recommended dose ranges, it is non-cumulative. Blood concentrations achieved after a single intravenous dose of propofol are available in infants[73] but data are sparse about the concentrations required to maintain anaesthesia. The volume of distribution is larger, and rates of clearance and elimination are higher and more variable in infants than in children.[74] The time taken to achieve effect-site concentration also varies with age.[75]

Remifentanil, an ultra-short acting potent opioid, is ideal for infusion in combination with propofol and its kinetic characteristics are less variable than propofol.[76]

2.1.3.2 Inhalational anaesthesia

In comparison with intravenous drugs, the kinetic characteristics of inhalational agents are much less variable. Provided that they are insoluble, inhaled vapours and gases can approach equilibrium in tissues that have a good blood supply. Within approximately 10 minutes of inhalation of a constant concentration of sevoflurane the end-tidal concentration reaches a plateau and is close to the inspired concentration. A small difference between inspired and expired concentrations remains because some sevoflurane is redistributed to tissues with poor blood supply and there is some clearance by metabolism and non-pulmonary excretion.

End-tidal concentration at equilibrium therefore approximates closely to the concentration within the brain. End-tidal concentration can be measured by standard infrared continuous gas analysis. The accuracy of the sampling depends on obtaining an end-tidal sample with a plateau. A plateau is difficult to achieve in spontaneously breathing infants who have a high respiratory rate. In rabbits and in newborn infants,[77] the maximum end-tidal carbon dioxide concentration measured over one minute is almost equivalent to the arterial carbon dioxide concentration. This relationship is true even at high respiratory rates.

2.1.4 Uncertainty of efficacy

A sleeping person who has been given a dose of hypnotic could either be sleeping "lightly" and be readily awakened by a stimulus, or be unrousable and therefore anaesthetised. In the context of anaesthesia, *depth*, with its extremes of *bottom* and *surface*, is a useful descriptor for conscious level which has the equivalent extremes of coma and alert states. In coma the brain is unresponsive even to pain compared to the alert state that is responsive to trivial stimuli. It is the stimulus therefore that helps to define conscious level during anaesthesia.

The response however may be difficult to define also. The response may be brief or sustained, partial or full. It is possible to arrange the various types of responses into a hierarchical scale so that a graded response to a stimulus can be described in a scale. A scale however has problems of validity and reliability (see section 2.3.1) and it is simpler to define a single response that does or does not occur. Such an *all or none* response is used in dose studies to determine the proportion of individuals who do, or do not, respond to a stimulus. This is known as a quantal response. If several doses are tested a regression coefficient can be calculated and used to estimate the likelihood of individuals responding. If the intensity of a stimulus is gradually increased, rather than the dose, a relationship between stimulus and effect can be estimated. Testing anaesthesia depth therefore could be approached by considering minor stimuli and progressing to more painful stimuli to test deeper levels of unconsciousness.

Nevertheless, there are several common problems in estimating effect. They include the reproducible nature of the stimulus, the definition of effect and the reliability of the observation. The following stimuli and observations have been used, or could reasonably be used, to determine the effect of hypnotic drugs on conscious level.

2.1.4.1 Stimuli used to test efficacy

2.1.4.1.1 Application of a face mask or insertion of an oral airway

The motor response to application of an anaesthesia face mask has been used to determine the induction doses of thiopentone[78] and propofol[73] that are effective

enough to prevent a motor response. The stimulus may be difficult to standardise because the application of a face mask can be painless or painful depending upon the anaesthetist's skill. The response outcome was acceptance of the mask by the infant i.e. lack of "avoidance movement of the head and hand movement to prevent mask application". The authors inferred that the distinction between acceptance and non acceptance was clear. Insertion of a finger or oral airway into the mouth has been used to test rousability in infants breathing sevoflurane but the authors found that some infants tolerated oral stimulation and would suckle without being otherwise disturbed.[79;80]

2.1.4.1.2 Skin incision

Skin incision is an accepted stimulus because it is simple, relevant to surgery, and can be standardised. It has been termed "maximal" on the assumption that that no other stimulus is as painful. The response of interest is the prevention of gross and purposeful movements, but it may be difficult to distinguish these from reflex movements.

Even purposeful movements however can be caused by reflex spinal cord responses that may be unrelated to cortical activity. This has been demonstrated in rats in whom the dose required to prevent movement to skin incision was the same in decorticate and intact animals.[81] Antognini has used a goat model to explore the effects of anaesthesia on the spinal cord. In the goat, the blood supply to the brain can be isolated so that anaesthetic can be delivered to the spinal cord and brain separately. He found that anaesthetic levels in the spinal cord were more important than those in the brain in preventing both movement and cortical arousal[1] which suggests that the spinal cord is not only responsible for reflex movement but also influences cortical arousal. Antognini also found that spinal cord suppression reduces cortical arousal caused by midbrain electrical stimulation and therefore has an indirect cortical suppressive effect.[82;83] The sedative effect of spinal anaesthesia is well known in adults and has been described recently in infants also.[84]

2.1.4.1.3 Noise or verbal command

Young infants do not respond reliably to verbal stimuli, and this makes it difficult to define any other end point that could be related to conscious level. As infants mature to over 6 months of age most will respond to verbal stimulus during recovery from anaesthesia: Davidson and colleagues found that 19 of 25 infants (the youngest was 5m old) responded and the remainder woke up spontaneously.[85] Response to noise may be affected if there is hearing impairment or if anaesthesia has a direct effect on hearing. In adults, the dose of anaesthetic required to prevent awakening to verbal command has been found to be 10% of the dose needed to prevent movement to skin incision.[86]

2.1.4.2 Estimation of minimal alveolar concentration

The minimal alveolar concentration (MAC) of a drug is the concentration which prevents a response to a stimulus in a specified proportion of subjects. The MAC 50% is the most common term in use and it sometimes called the median effective concentration (EC50%).[87] Response to skin incision is the most common test of efficacy but other endpoints can be used also. To estimate the MAC, ideally, a large number of similar individuals are subjected to various doses and the number who respond to a chosen stimulus at each dose is determined.[88] Logistic regression estimates not only the MAC (or EC50%) but also the EC95%, and from these the likelihood of a chosen dose being effective can be estimated by interpolation. Inhalational vapours are potent and the differences between EC50% and EC95% are small.[1]

The MAC required to prevent response to skin incision has been estimated in infants for inhalational anaesthetics. Since large numbers of infants are not readily available for study a different method of estimating MAC has been used. MAC can be estimated in small samples of individuals using the *up and down* method.[89] This involves the administration of one concentration of vapour only to each infant and testing whether there is a response. In a series of infants, perhaps as few as 12, the concentration given to each successive infant depends on the response of the previous

one; if an infant rouses, the next one receives a higher concentration, or if there is no response the next infant receives a lower concentration. When the series has equal numbers of responders and non responders, the EC50% can be estimated from the mean of the concentrations used.[88] Close examination of results, for example those testing isoflurane, reveals that there is a wide spread of effective and ineffective doses and therefore the precision of the measurement is in doubt.[90] Furthermore, the statistical methods by which MAC is calculated varies between authors and has been reviewed recently.[91] Nevertheless studies using MAC methodology have yielded interesting results.

2.1.4.2.1 Variation with age

Using the *up and down* method, the MAC (immobilisation to skin incision) of halothane, isoflurane and sevoflurane have been measured in infants of various ages. The MAC of isoflurane and halothane increases from birth, peaks at 3-6 months and decreases thereafter whereas the MAC of sevoflurane decreases as age increases (Table 2-1):[92-94]

Table 2-1: Age and MAC of sevoflurane

Age	0–1 months	1–6 months	6–12 months	12 months
MAC of sevoflurane	3.3	3.2	2.5	2.3

2.1.4.3 Assessment during muscle relaxation

2.1.4.3.1 Sympathetic nervous system activation

Sympathetic nervous system activation produces increased heart rate, blood pressure, breathing rate, sweating and lacrimation and these are potential indicators of awakening. Such autonomic changes are not specific to awakening and are likely to

be associated with pain or distress. It is unethical to test this in a conscious patient in a clinical trial.[24-26] Sympathetic activation in response to laryngoscopy has been used to test the efficacy of an anaesthetic in children[95] but not in infants.

2.1.4.3.2 The isolated forearm technique

The isolated forearm technique could be used to determine the dose required to cause unconsciousness. If this technique was applied to infants, movement of the arm would not necessarily signify consciousness but, in combination with sympathetic activation and other physiological measurements, may support the possibility of awareness.

2.1.5 Potential advantages of level of conscious monitoring in infants

The following are potential advantages.

- A monitor to guide dosage

A monitor of conscious level or awakening would be useful because the dose of anaesthetic varies between individuals and circumstances. Reduction in dose reduces cost and atmospheric pollution.

- Reduced anaesthesia toxicity

By reducing the dose cardiorespiratory depression, prolonged recovery and potential apoptotic brain damage could be minimised.

- Investigation of effective *light* or *minimal*[96] anaesthesia and sedation techniques

There is a demand for sedation techniques that ensure immobility for painless imaging. Sedation however is unpredictable in young infants. If anaesthesia is contemplated its risks should not outweigh the potential benefit of the imaging. New, effective and safe sedation techniques are needed.[97]

2.2 Potential monitors of conscious level

The last decade has seen the development of several conscious level monitors for anaesthesia although they are not yet used widely.[98] The evidence of the usefulness of the monitors of EEG and other potentially useful modalities is explored below.

2.2.1 Monitors using EEG signals

The cerebral cortex, thalamic nuclei and the ascending arousal pathways of the brainstem and midbrain are important in the control of consciousness.[1;99-101] This is accepted for two reasons. First, patients with diffuse cortical damage or focal lesions of the ascending arousal thalamic nuclei or pathways become unconscious, and secondly, functional magnetic resonance scanning[102] and positron emission tomography[103;104] show that anaesthesia depth is associated with suppression of metabolism in the cortex and ascending arousal pathways.

In adult volunteers PET scanning has shown that global cerebral glucose metabolism in the awake baseline state decreases during propofol anaesthesia.[103] Moreover there are regional differences. Overall, metabolism decreases more in the cortex than subcortical structures yet, specifically, the greatest decreases occur in the midbrain and left anterior cingulated and inferior colliculus. PET assessment of regional blood flow has shown similar changes in the medial thalamus and midbrain.[105] EEG variables correlate approximately with the change in metabolic activity.[102]

The EEG, detected by scalp surface electrodes, measures the electrical activity of the outer layer of cerebral cortex. The recordable signals are likely to be due to post-synaptic potentials related to groups of axons and these last between 50 and 200 milliseconds. Axon action potentials produce smaller local current changes lasting less than 10 milliseconds and are unlikely to be detected. The EEG is a complex waveform of seemingly random nature. Its amplitude is variable but is usually less than 100 μV with visible oscillations between 1 and 20 Hz. EMG signals have a higher frequency pattern but because their amplitude is high (up to 500 μV) they can easily mask cortical signals. A true EEG recording in a patient who moves is consequently difficult to achieve.

The source of the EEG oscillations has been shown in cats to originate from both cortex and thalamus.[106] The EEG during sleep has slow waves that become flatter, more rapid and "desynchronize" during awakening. Electrical stimulation of the midbrain reticular formation changes the EEG from sleep to wake patterns.[107] This is seen both at the cortex and the midbrain in the cat showing that the rhythms are synchronised. Moreover a "gamma" faster rate of 30-40Hz is provoked and maintained after midbrain stimulation and may be a characteristic of "awake" coordinated EEG signalling between specific regions and nuclei. Power within high frequency gamma EEG rhythms provide the best band power discriminator of change of consciousness in humans (adults) related to anaesthesia.[108] Gamma can arise in both cortex and thalamus independently. Thalamic intralaminar nuclei receive input from many sources and activate the cortex. [107] During awakening the thalamic and cortex gamma oscillations become synchronised – linking the activity of the intralaminar nuclei and the cortex.[109]

Within the thalamus there is a biphasic rhythm of hyperpolarisation for approximately 10 milliseconds followed by depolarization.[110] As anaesthesia takes effect the phase of hyperpolarisation becomes longer. At medium anaesthetic doses the transition rate is approximately 1 Hz and this is manifest by the high amplitude low frequency cortical EEG. Higher doses cause longer periods of hyperpolarisation represented by *burst suppression*.

There is interplay between cortex and thalamus. The cortex stimulates the thalamus and the anaesthetic effects on the thalamus are abolished by removal of the cortex.[111] Yet ablation of the thalamus does not annul the EEG of the cortex.[112] Recordings from both scalp and thalamic electrodes (implanted into patients having deep brain stimulation for chronic pain syndromes) show that the cortical EEG changes promptly with awakening yet thalamic EEG changes take approximately 10 minutes longer.[113] Conversely, during dreaming the cortical EEG shows fast rhythms while the thalamus maintains its slow oscillation characteristic of sleep.

A plausible theory of the mechanism of anaesthesia is that key thalamic structures, responsible for excitation, become inhibited (by hyperpolarisation) and block thalamocortical neural transmission[99;114;115] The thalamic and midbrain nuclei have

both general and specialised functions and it is proposed that consciousness is maintained by the integration of these systems communicating with the cortex.[115] If communicating systems are inhibited by different anaesthesia drugs and doses this may account for the gradual loss of function seen in sedation rather than anaesthesia. That loss of consciousness is often sudden may be explained by a non-linear change in function.[115]

2.2.1.1 Unprocessed EEG

The EEG is not equal over the whole cortex and there is an international system of electrode positions.[116] Parietal, central and frontal positions are most accessible and the recommended channels for EEG monitoring of sleep used in polysomnography are 2 frontal and 2 central channels.[117-119]

The unprocessed EEG has been considered to be too complex to use during anaesthesia because of technical difficulties with electrode placement and electrical interference, and the changes may be too quick to appreciate and interpret in a clinical scenario.[25] Nevertheless, the raw EEG signal should be understood, before interpreting the result of any processing method. The EEG can have 3 components:[120] a continuous waveform, transients, and periods of electrical silence. Electrical silence is observed during deep levels of anaesthesia (and coma) and transients are associated with natural sleep. In anaesthesia, it is the continuous waveform that has been studied to help determine the level of consciousness (LOC).[25] The following is a description of the EEG first in natural sleep and then in anaesthesia both in adults and infants.

2.2.1.1.1 Natural sleep in adults

EEG oscillations can be counted over a few seconds to give an estimate of their frequency. In the relaxed awake state *alpha* oscillations (between 8 and 13 Hz) are common and during the alert state these disappear and the EEG becomes low amplitude and disorganized with frequencies between 30 and 50Hz. By convention, frequency bands have been categorized as *gamma* (> 30 Hz), *beta* (14-30 Hz), *alpha* (8-13 Hz) *theta* (4-7) *and delta* (< 4 Hz).[120]

EEG studies of sleep are usually performed in a sleep laboratory and involve the application of multiple electrodes to the scalp and face to achieve not only EEG but

also electrooculographic (EOG) and EMG signals. The combination of these three signals were used to describe the classical stages of sleep in 1968[121] and are similar to those used for infants older than 6 months.[122] These are summarised in Table 2-2.

Sleep in adults has a temporal organization in which there are alternating periods of slow wave (SWS) and rapid eye movement sleep (REM).[120;122] Normal sleep begins with SWS and then changes to REM when SWS has become established. SWS has 4 stages. Stage 1 is the first stage of sleepiness in which alpha oscillations slow and become less regular and eventually disappear. The amplitude of the background pattern decreases. The appearance of well formed transients called sleep spindles characterizes stage 2; these are prominent and have an oscillation of 12-14Hz. Beta and theta activity becomes more obvious. Other transients appear: vertex sharp waves (V-waves) are sharp, spiky, last < 70 milliseconds, and appear in central channels; K-complexes are high amplitude, bi or tri phasic slow potentials lasting > 70 ms that can be detected in frontal and central channels. In stages 3 and 4 theta waves become the dominant pattern and their amplitude increases. In REM sleep there are movements of the eyes that are detected by large voltage shifts in the nearest frontal channels. The background oscillation in all channels is low amplitude gamma activity that mimics the pattern of an alert state.

Table 2-2: EEG during wakefulness and sleep after 6 months of age

State	**Dominant EEG oscillations (amplitude)**	**EOG**	**EMG**
Alert wakefulness	30-50 Hz (low amplitude)	Blinking	high
Relaxed wakefulness	8-13 Hz	Blinking	reduced
Non-REM Sleep stage 1	2-3s of 4-8 Hz and sharp waves over vertex	slow rolling eye movements	reduced
Non-REM Sleep stage 2	sleep spindles appear 1-3/min up to 20% of epoch high amplitude delta waves k complexes appear		minimal
Non-REM Sleep stage 3	20-50% of epoch delta waves	no movement	minimal
Non-REM Sleep stage 4	>50% of epoch delta waves	no movement	minimal
REM sleep	irregular 30-50 Hz (low amplitude) sharp waves replaced by saw tooth waves at 2-5 Hz	2 states: - tonic REM (absent eye movements) - phasic REM (eye movements present)	sporadic bursts

An epoch is usually 30 or 60 seconds. Adapted from Handbook of Sleep Medicine by Shneerson [122]

2.2.1.1.2 Natural sleep in infants

Infants younger than 6 months have a sleep pattern less well defined than in adults. Instead of SWS and REM stages, sleep is separated into quiet (QS) and active sleep (AS).[123] In their circadian sleep rhythm infants tend to sleep more, at different times and with frequent naps.[124] The ultradian rhythm is also different. Newborns begin sleep with AS, have more AS than QS, and also shorter AS and QS cycle lengths.[125] Naps gradually lengthen into organized sleep periods. By approximately 3 months of age sleep begins with QS.

Non-REM and REM sleep develop gradually from 3 months of age from QS and AS respectively. Only after 6m of age can non-REM sleep be readily sub-divided into 4 stages. Before 6m the EEG during QS/non-REM sleep is a single pattern of high amplitude low frequency oscillation. Sleep spindles, which are characteristic of non-rapid eye movement (non-REM) sleep, appear by 4 weeks of age but become characteristic of non-REM sleep by the age of 3 months; K complexes appear by 6 months.[120]

Zampi and colleagues have studied the EEG immediately before arousal (a change in heart rate or breathing pattern – rather than awakening). In neonates and infants they found that there was desynchronisation and an increase in amplitude in all frequencies during QS/non-REM sleep, but no change during AS/REM-like sleep.[126] Compared with neonates, infants had more rapid desynchronisation.[127] Desynchronisation however did not always lead to awakening.

Beyond infancy the EEG changes with age. In a 3 year old theta oscillations are established and by 6 years alpha oscillations are commonly seen but at a slower frequency than in adults. By 7 or 8 years the alpha frequency has increased to 10 Hz.[120] The dominant posterior oscillation is an oscillation recognized in parietal and posterior channels during relaxed wakefulness and it changes with age:[128] 3.5-4.5 Hz in 75% infants who are 4 months old, 5-6 Hz in most infants by 6 months, 8 Hz in most children by 3 years, 9 Hz in 9-year-olds, and 10 Hz by 15 years.

2.2.1.1.3 Natural sleep in foetuses and preterm infants

Non-invasive EEG recording of a foetus is possible, trans-abdominally, from approximately 12 weeks gestation and there is continuous low amplitude irregular activity unrelated to body movement.[129-133] Different patterns appear at 24 weeks but sleep or waking states cannot be distinguished by EEG until the foetus is about 32 weeks old. At 28 weeks fast waves appear superimposed on slow waves in temporal and occipital areas. From 24-27 weeks the *tracé discontinu* pattern appears; this is a pattern of bursts of high amplitude slow waves lasting 2-6 seconds mainly over the occipital cortex followed by depressed activity lasting 4-8 seconds, and it becomes associated with quiet sleep between 32 and 36 weeks gestation. After 36 weeks (either before of after birth) *tracé discontinu* is replaced by a *tracé alternant* pattern which consists of 3 to 8 second bursts of high-amplitude slow frequency activity interspersed with low-amplitude mixed frequency oscillations. *Tracé alternant* disappears by 2 months of age. REM-like EEG activity can be detected from 28 weeks gestation onwards by bursts of low amplitude high frequency oscillations that become more continuous and associated with eye movements by 37 weeks.

There may be an effect of preterm birth. By convention, the developmental age of an infant who was born preterm is called the post-menstrual age (PMA = gestation at birth + age after birth).[134] In studies comparing preterm and term infants of equal PMA, term infants had higher amplitude EEG especially in frequencies less than 8 Hz.[135;136]

2.2.1.1.4 Anaesthesia

The type of anaesthesia affects the EEG differently however the changes during propofol,[28;137] sevoflurane[138] and isoflurane[139] anaesthesia are broadly similar. Initially there is low amplitude desynchronisation and disappearance of any prominent oscillations. As anaesthesia is established an oscillation in the range of 8-20Hz appears that increases in amplitude. In the past this was known as a Widespread Anterior Rapid (WAR) pattern and considered to be present at sub-MAC levels of anaesthesia – that is, concentrations less than that required to prevent movement to

surgery. As anaesthesia deepens slow waves become prominent. At deeper levels *burst suppression* replaces other patterns.[140] Burst suppression is an alternating pattern of high amplitude bursts followed by near electrical silence every few seconds. Deepest levels of anaesthesia result in electrical silence. These characteristics are reversed as the anaesthesia dose and effect decrease. Surgical stimulation causes a degree of reversal of these EEG changes.

The characteristics of raw EEG in neonates and infants during anaesthesia have not been described in detail. In 1986 James and colleagues noted that the EEG of some children (not infants) having isoflurane anaesthesia for cardiac surgery had episodic oscillations within the alpha range.[141] In 1990 Kitahara and colleagues found that infants less than 6 months old had dominant slow waves during halothane anaesthesia that did not change with depth of anaesthesia.[142]

In 2008 Davidson and colleagues recorded EEG from infants and children during anaesthesia and emergence but, rather than comment on raw EEG changes they calculated power changes within the frequency range 2-20 Hz. [143] They noted also that some of their youngest infants had a discontinuous EEG pattern throughout emergence similar to the tracé alternant pattern of natural sleep.

In 1999 Constant and colleagues studied the changes in EEG during induction of anaesthesia in children aged 2 to 12 years; they compared sevoflurane and halothane.[144] Both agents caused similar changes to the EEG. After induction oscillations in the 14-30 Hz range were common although sevoflurane caused oscillations that were “spiky”. As anaesthesia progressed there was a gradual increase in the presence and amplitude of delta oscillations. There have been case reports of seizure and EEG seizure-like activity associated with sevoflurane,[145] but none were reported in the aforementioned studies.

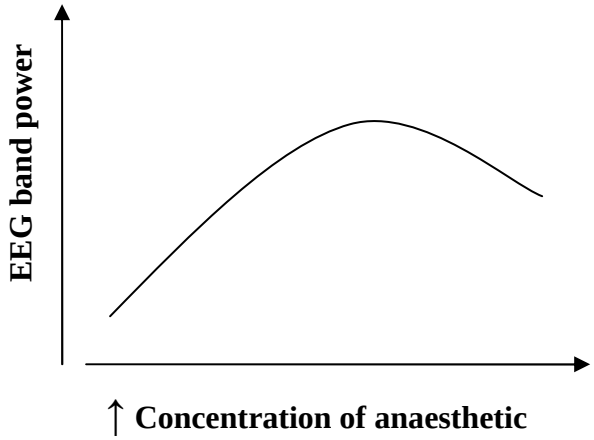
2.2.1.2 Processed EEG - power spectrum

Any complex waveform can be considered to be a construct of many sinusoidal waves of varying frequency, amplitude and phase. The EEG signal can be deconstructed into constituent frequencies either by a system of filters at source or after digitisation and subsequent processing by various methods including Fast Fourier Transformation

(FFT). A power spectrum can then be generated and the power within selected frequency bands can be calculated.

The first EEG monitors, in the 1980s, used filters to exclude unwanted low and high frequencies and then measure the amplitude of the remaining signal (known as amplitude integration). They included the Cerebral Function Monitor (CFM) which measured the minimum and maximum amplitude of a wide frequency band [146-148] and a modification of the CFM, the Cerebral Functioning Analysing Monitor (CFAM), which quantified the amplitude of frequency bands.[149] Since the development of personal computers, digitisation and FFT have become accessible so that digital signals can be processed and descriptors calculated off-line. These descriptors include the power within selected frequency bands, the median (MF) and the spectral edge (SEF) frequencies, and the total power. None of these variables predict movement to surgical stimuli and so have not been sufficiently valuable during anaesthesia.[147;149-155]

Figure 2-1: Common relationship of EEG band power to concentration of anaesthetic



The main problem with power derived variables is that they decrease initially and then increase as anaesthesia deepens (see Figure 2-1). For example both MF and SEF decrease as sevoflurane concentration increases but then with further increases of sevoflurane concentration MF and SEF begin to increase.[152] Power within frequency bands have a similar problem. Kuizenga and colleagues showed that sevoflurane has a

similar biphasic effect on SEF and power in 2 frequency bands (2-5 and 11-20 Hz).[156] Nevertheless studies of power changes within frequency bands have yielded interesting results.

2.2.1.2.1 Power spectrum in anaesthetised adults

In adults the change in power within frequency bands has been measured both during induction of and awakening from anaesthesia. In all the following studies the EEG was recorded from either frontal or central channels. During induction of propofol anaesthesia Koskinen and colleagues found that the power between 12 and 28Hz frequencies increased first and then decreased.[137] During awakening from isoflurane in adults, Long and colleagues found that although there were obvious power changes occurring both before and during return of consciousness no single variable was predictive in all patients except for an abrupt decrease in power in the 1-4Hz frequency band.[157] During awakening from either sevoflurane or propofol (both combined with remifentanil) Dressler and colleagues[108] calculated signal power in frequency bands of 1Hz and showed that the prediction probability for detecting awakening was highest for both a reduction in the power in low frequencies (<15Hz) and for an increase in power in high frequencies (>26Hz).

2.2.1.2.2 Power spectrum in anaesthetised infants and children

In 1989 Sugiyama and colleagues found that EEG power in slow frequencies in infants was associated with arterial halothane concentration; of all the recording channels this association was strongest for occipital channels. They also showed that the youngest infants had power in only the slow frequncies.[158]

With sevoflurane Constant and colleagues anaesthetised children older than 2 years and found that induction was associated with an increase in the power of low frequencies.[144]

Two recent studies have presented EEG data from infants recovering from sevoflurane anaesthesia. In 2008 Davidson and colleagues recorded forehead and parietal EEG in 3 age groups: infants less than 6 months (n=17), toddlers 6months to 2 years old (n=19), and children 2 to 10 years old (n=21).[143] This was a descriptive study and the type of anaesthesia drug and technique varied (some children had

sevoflurane others had isoflurane, some had opioids, and some were breathing spontaneously). They found that forehead power was higher than parietal and that power within 2–20 Hz range decreased during emergence in all age groups except in infants less than 6 months old. The EEG power increased with age.

Lo and colleagues studied multi-channel EEG recording of infants and children (age range 22 days to 3.7 years) recovering from anaesthesia by either sevoflurane or isoflurane alone.[159] Surgery was mainly inguinal or genital and analgesia was provided by local anaesthesia. Anaesthesia was maintained at 1.4 MAC (age adjusted) which, for sevoflurane, is approximately 4% for infants. All patients were intubated and their ventilation was controlled. It is not clear from their methods whether children were undisturbed before extubation and the criteria for extubation and emergence are not described. Children also received reversal of muscle relaxation with neostigmine and glycopyrrolate. Extubation occurred at less than 0.5 MAC (approximately 1.2% sevoflurane for infants). They found that power in frontal channels was always greater than that in occipital and the power within alpha and beta frequency ranges increased when sevoflurane concentrations decreased before extubation. Any relationship between age and power was not examined.

The ratio between the powers of various frequency bands may be useful. In a pilot study of 10 children (youngest age 5m) recovering from propofol anaesthesia the ratio of high frequency to low frequency band power tended to be proportional to sedation scores and plasma propofol concentrations. The ratio was lowest just before awakening.[160]

In summary (Figure 2-2), these studies suggest that neonates and infants less than 6 months old tend to have low power EEG signals during anaesthesia. Older infants seem to have changes similar to those seen in adults, in that power in frequencies in the alpha and beta range are present during maintenance doses of both sevoflurane and isoflurane. However, as anaesthetic vapour is washed-out the power decreases or increases depending on the study. The difference may relate to the dose of sevoflurane and the presence of opioids; Davidson's infants had opioids and had less sevoflurane or isoflurane during steady state anaesthesia. At high doses of anaesthesia, as in Lo's study, the EEG may be suppressed and therefore as anaesthesia washes-out EEG

power increases. If the steady state anaesthesia dose is low, made possible by the analgesic effect (and possibly sedative effect) of an opioid, an infant may remain still and comfortable at much lighter levels of anaesthesia than otherwise. In these circumstances, just before awakening, the decrease in EEG power will be apparent. Neither Davidson's nor Lo's studies conclusively demonstrate a clear temporal relationship of EEG power in relation to anaesthesia dose. Further work is indicated to demonstrate what happens to the EEG during specified and controlled conditions of recovery. Neither study defined criteria for awakening.

Figure 2-2: Summary of published EEG characteristics during anaesthesia washout

- Infants > 6m old have changes similar to adults[143]
- Frontal channels have highest power[143;159]
- Power in 8-30 Hz ↑[159] or ↓[143]
- HF/LF power ratio ↓[160]

2.2.1.3 Processed EEG - BIS

In the last decade several EEG monitors have been developed. The "BIS", "Entropy" and the "Narcotrend" monitors are 3 examples and all three use forehead electrodes and process the EEG with a combination of algorithms to obtain a score from 0 to 100 representing the extremes of coma and alert states. The mathematical derivation of their scores is different but all three use the power in various frequency bands. The BIS (Bispectral index) also measures phase synchronization between common frequencies.[161-164] Entropy measures the predictability (or the sinusoidal nature[165]) of 2 wide EEG frequency bands; 0.8-30 Hz for "state entropy" and 0.8-47 Hz for "response entropy"; the latter incorporates the frontalis EMG.[166] The Narcotrend algorithm has not been published.[167]

These monitors have been called “black boxes” because their algorithms are either complex and not readily understood, or unpublished. Nevertheless the algorithms have been developed to produce scores that decrease with both decreasing conscious level (as defined by a validated scale of behaviour)[152;168] and also with increasing doses of propofol and concentrations of common inhalational agents.[139;154;169] The BIS, for example, has been designed so that a score between 40-60 is compatible with absence of explicit recall. On the assumption that this is true, BIS has been used to aid the reduction of doses of anaesthetics and allow more rapid recovery.[170;171]

BIS and Entropy scores have been developed to match sedation and light anaesthesia and may therefore predict awakening from painless stimuli.[169] However they are poor predictors of movement during surgery possibly because pain either activates spinal reflexes that mimic awakening or because pain causes true awakening by activation of both spinal and cortical systems. Consequently the role of BIS and similar monitors is uncertain and they are not widely used.

There is evidence showing that BIS-directed anaesthesia can reduce the incidence of explicit recall. In a study of adults who were at risk of awareness Myles and colleagues randomised patients to receive either anaesthesia directed by BIS or anaesthesia controlled only by clinical judgment. BIS reduced explicit recall from 11 in 1238 patients to 2 in 1225.[39] In a similar study by Avidan and colleagues, patients were randomised to receive either BIS-directed anaesthesia or anaesthesia in which end-tidal anaesthesia vapour concentration was maintained greater than 0.7 MAC.[172] In each group of almost 1000 patients, 2 had explicit recall, and it may be concluded that either BIS-directed or MAC-directed anaesthesia are equally effective.[23]

There is however a distinction between explicit recall and awareness and Russell has demonstrated that when the BIS (or the Narcotrend) monitor is tested with the isolated forearm technique, neither monitor is able to distinguish between patients who can communicate and those who cannot.[173-175] Russell tested various anaesthesia drugs and altered their doses so that patients could communicate by their isolated forearm. Although all the patients communicated with him none could recall it later. An important detail is that he made sure his patients were pain free by using both extradural analgesia and intravenous remifentanil infusions. In summary BIS helps to

reduce explicit recall but not true intraoperative awareness in patients who are pain free. There are no studies demonstrating the effect on the EEG of awareness during painful surgery.

There are other circumstances when processed EEG can mislead. Changes in processed EEG scores may not be specific to the cortical effects of anaesthetic drugs. BIS changes during epileptiform activity[176] decreases due to the effects of muscle relaxants without anaesthesia[177] and can also change with glucose metabolism.[102] In addition ketamine[178] and nitrous oxide[179] do not depress the EEG or the BIS in proportion to their conscious level effects.

A major consideration is that an anaesthesia drug can have an immobilising effect at the spinal cord in addition to cortical effects.[1] For example in a study, comparing the effects of equi-MAC doses of halothane and sevoflurane, the BIS scores were higher during halothane[180] and this may be due to halothane having a greater immobilizing action at the spinal cord than sevoflurane rather than halothane having a different effect on the EEG and BIS.[181-183] This means therefore that movement may not be related to cortical function if the anaesthetic has a direct immobilizing effect on the spinal cord. Moreover where there is direct immobilization, EEG, processed or otherwise, may be more closely related to the prevention of explicit recall and possibly more useful than formerly realised.

Although most studies of processed EEG monitoring in children concern BIS several investigated other monitors. One study found that Narcotrend has a high prediction probability of recovery in children older than 1y[184] and 3 studies showed that Entropy is similar to BIS in monitoring conscious level in children older than one year.[166;185;186] The following is a brief review of BIS monitoring of sevoflurane anaesthesia.

2.2.1.3.1 BIS and sevoflurane in infants

The BIS and Entropy scores in children are similar to those in adults at equal sedation levels but several studies report that BIS scores are less reliable in infants and small children.[85;185-191] When infants and children are given MAC-equivalent concentrations of sevoflurane BIS levels are slightly higher in infants.[189] In a study of 3 end-tidal

concentrations of sevoflurane in children over 6m old, the highest BIS values tended to be in the youngest infants and BIS increased paradoxically when sevoflurane was increased from 3 to 4%.[192] These findings may be explained by an immobilizing action of sevoflurane related to age; the paradoxical rise of BIS is unexplained, but could be similar to the biphasic change of EEG power as anaesthesia dose increases.

In a study comparing 3-6 month-old with 7-12 month-old infants, given equal concentrations of sevoflurane, BIS scores were lower in the younger infants.[193] This may suggest a special feature of infants aged 3-6 months or it may simply indicate that the BIS algorithm is not applicable to young infants.

BIS correlates with sedation score poorly in infants[186] in children.[190] Infants who have a caudal local anaesthetic block need only low concentrations of sevoflurane to keep BIS low.[188] Davidson measured BIS and Entropy in children having cardiac angiography and found that widest variation of scores was in infants and awakening occurred at lowest scores in the youngest patients.[185] In a study in infants and older children recovering after circumcision (all children had had and effective penile block) sevoflurane was reduced in steps and patients were presented with a uniform auditory stimulus (calling the child's name). Often the infants awoke spontaneously demonstrating the difficulty of presenting a reliable stimulus to infants.[85]

Wodey and colleagues have submitted paediatric BIS recordings to complex statistical comparisons and have found that phase synchronization between EEG frequencies is dependant upon age.[194;195]

2.2.1.3.2 Other BIS studies in infants

BIS scores follow isoflurane anaesthesia in children older than 1 year similarly to adults.[196] In a study of 60 children receiving anaesthesia with propofol and remifentanil EEG variables were similarly predictive of awakening in children older than 1 year but were least reliable in infants.[197]

2.2.1.4 Processed EEG - Auditory evoked potential

The auditory evoked potential (AEP) is an EEG signal provoked by a noise stimulus (a click) and detected from scalp electrodes. It is caused by neural transmission

through the brainstem, the midbrain and the cortex. Background EEG is removed by averaging the recordings after many clicks. A typical recording may use 1024 clicks at 6 Hz and take 2-3 minutes to achieve. The resultant AEP waveform is an average of the recording after each click. The waveform has characteristic peaks and troughs that are temporally related to brainstem, early cortical and late cortical transmission.[198;199] The late cortical component disappears with low doses of anaesthetic and the brainstem is resistant to anaesthesia. The shape of the early cortical waveform however is suppressed by anaesthesia; peaks in the waveform are delayed in a dose-dependant manner.[198-200] The Alaris AEPTM monitor uses headphones and frontal EEG electrodes and can estimate the shape of the AEP within 2-6 seconds by a technique called autoregressive modeling.[201] From this estimation a mathematical algorithm calculates an index ranging from 0 to 100 representing deep coma and fully alert state respectively.

The main problem with this method is with non-EEG interference. EMG, in particular, caused by contraction of the posterior auricular muscle, is triggered by noise and therefore the AEP is least reliable when muscle relaxants are not used.[198] A study of children over the age of 2 years found that AEP was as reliable as in adults.[202] ECG interference is a problem in infants.[203]

2.2.2 Monitors of cerebral blood flow and metabolism

EEG derived variables have been found to correlate with changes in cerebral blood flow[204] and metabolism.[102] Near-infrared spectroscopy (NIRS) measures oxygen saturation of tissue and involves a non-invasive sensor placed on the head. It relies on the principles of light transmission and absorption to determine regional cerebral oxygenation.[205] Its ability to discriminate increased blood flow and by inference, cerebral activity and conscious level has not been tested during recovery from anaesthesia.

2.2.3 Monitors of autonomic activity

In natural sleep the effect of the parasympathetic nervous system predominates over the sympathetic and this balance is reversed in stressful situations.

2.2.3.1 Processed electrocardiography - HRV

Heart rate variability (HRV) is the beat-to-beat variation in heart rate and requires accurate measurement of the timing of R waves on an ECG trace. An increase in heart rate is not a specific feature of awakening or stress but the variability in heart rate is changed by autonomic tone. HRV therefore may be useful as an indirect and surrogate monitor of conscious level.[206-208]

The sequence of RR intervals can be analysed by simple statistics such as the mean and range (or standard deviation (SD)) of heart rate over a period of time,[65;209] but a more sophisticated method involves interpolating the plot of RR intervals to derive a waveform that can be further processed to achieve a power spectrum of constituent frequencies.[210;211] Two frequencies are prominent in normal RR sequences. The high frequency (HF, 0.15-0.4 Hz) component is associated with vagal parasympathetic tone and is synchronous with pulmonary ventilation. The low frequency (LF, 0.05-0.15 Hz) component may be related to sympathetic tone. Estimation of power within these frequency bands is feasible with an period of 20 seconds which allows a frequency resolution of 0.05 Hz and this is sufficient provided lower frequencies than LF are not studied.[210] Power spectrum analysis of HRV could therefore be used to generate a score over the previous 20 seconds of ECG recording.

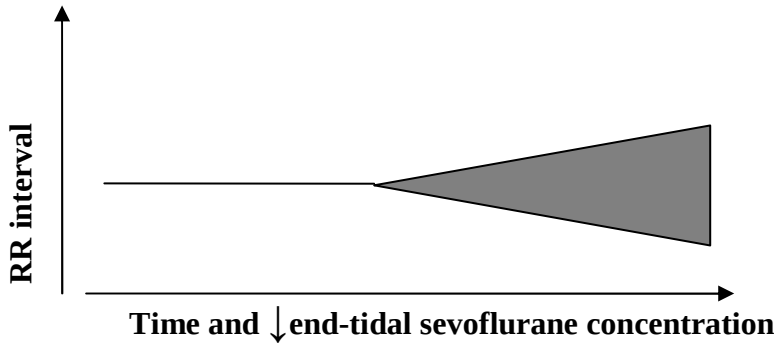
Precise measurement of the RR interval is crucial for HRV analysis and, if there is interference, it may be difficult to be certain of the fiducial point of an R wave. Automatic detection may detect false R waves or miss true ones and, mainly for this reason, real time HRV analysis may not be reliable. In infants, the difference between successive RR intervals may be less than 5 msec[210] and therefore a sampling frequency of at least 200Hz is necessary to determine the time of the fiducial point with sufficient precision. Even then, the RR interval is only an estimate of the true RR interval because the shape of the R wave may change. In health, HF and LF peaks are prominent. In stress, both peaks are reduced or disappear.[210] In natural sleep the HF increases and LF decreases whereas in anaesthesia both peaks are reduced.[212]

A research LOC monitor, called the Fathom, calculates the respiratory influence upon HRV.[213] The process involves the detection of the phase relationship of R waves to a

fixed point in the respiratory cycle. Vagal tone is proportional to the clustering of phases and a score can be calculated from data over approximately 10 breaths.

In adults power spectrum analysis studies of the effect of sevoflurane have found conflicting results; one study found no change in HRV,[214] and another found that LF power reduced.[215] In children older than 5 years Constant and colleagues found that HRV is minimal during anaesthesia and is mainly caused by the mechanical effect of breathing. However during recovery, HRV power increases in both HF and LF bands; the LF band increased by a factor of up to 40. In another group of children, between 21 months and 8 years old, Wodey and colleagues found similar results during withdrawal of sevoflurane anaesthesia:[216] in addition they found that the youngest children had the lowest baseline HF power and the least change in heart rate during sevoflurane washout. Figure 2-3 summarises the HRV changes known to take place during withdrawal of sevoflurane anaesthesia in children. HRV has not been studied in infants during recovery from anaesthesia. Normative data from 30 infants less than 12 hours old in natural sleep has been published by Doyle and colleagues.[217] They found that during QS, there is a prominent power in the HF band in 80% of babies that corresponds to the respiratory frequency, and that this disappeared during AS.

Figure 2-3: Pictorial summary of published evidence of HRV in children during sevoflurane washout



During sevoflurane washout

- **↑ LF and HF power**
- **↑ LF/HF ratio**

2.2.3.2 Other autonomic variables

Electromyography (EMG) is the measurement of the electrical activity generated by muscle. For skeletal muscles, activity is dependent upon both conscious and reflex control. The EMG has be used to detect awakening from anaesthesia but its changes are sudden and give little warning of impending return of consciouisness.[218;219] The forehead muscles are unusual because they have an autonomic component and an increase in EMG occurs even in the presence of muscle relaxants.[220] A ratio of the lower and upper facial EMG may be associated with painful or other stress related phenomena.[221]

Oesophageal motility is also under autonomic control and contractions are depressed during anaesthesia. It has not been found to be clinically useful in adults.[222]

Blood pressure variability has been measured using a continuous non-invasive monitor and the power spectrum that is similar to that of HRV.[212;220]

Pulse transit time (PTT) is the latency between the ECG and the corresponding pulse waveform. It is reduced during sympathetic arousal but is also affected by other cardiovascular factors.[223]

Electrical conductance of skin decreases with sweating caused by sympathetic arousal. With the pain of heel prick, for example, conductance increases in term neonates but not in those less than 36 weeks old (PMA).[224]

2.3 Defining behaviour of arousal and awakening

The terms arousal and awakening are common and their meanings are easily confused. Most authors have used arousal with reference to body systems (e.g. arousal of the autonomic nervous system) and therefore arousal may not be related to conscious level. Nevertheless, cortical arousal indicated by changes in the EEG may be related to conscious level. Awakening infers alertness arising from a sleep state and is usually used in reference to conscious level. Some authors have used arousal instead of awakening especially when they have used *roused* and *rousability* (probably, both of these refer to awakening). Whenever the author has used *arousal*, and it is obvious that they intended to describe conscious level, *awakening* has been used instead.

There are no agreed definitions or criteria of conscious level in anaesthetised infants. This section summarises first the problems of developing an observational tool and then reviews the observable behaviour and stimuli used in other scenarios and considers whether these are applicable to anaesthesia.

2.3.1 Observational scales – general aspects

Behaviour, either unstimulated or caused by stimulation, may be brief or sustained, partial or full. It may be possible to arrange the various types of responses into a hierarchical scale so that a graded response to a stimulus can be described in a scale. A scale however has problems of validity and reliability and it is simpler to define a single response that does or does not occur. Such an *all or none* response has been used in Minimal Alveolar Concentration (MAC) studies to determine the effective dose of anaesthesia.[91]

2.3.1.1 Validity and reliability

Validity, in terms of the range of descriptors in the scale, can be determined by agreement amongst experts.[225] Further supporting evidence of validity may then be sought by comparison with similar scales (criterion validity) and by testing the scale

against a hypothesis (construct validity). Reliability is the ratio of the inter-subject variation to the sum of the inter-subject variation and measurement error; a perfect scale has a reliability of 1. Allied to this measure are the within-observer (scores achieved at different times) and inter-observer reliability.

Two schools of thought have led to 2 types of scale. Detailed scaling tools with many items for assessment are developed to measure behaviour or to differentiate between behaviours. In principle the more items within the scale, the greater the accuracy of the measurement and the greater the potential for differentiating behaviours. If they are too detailed however they may be difficult to apply quickly in rapidly changing situations. Furthermore, complicated scales are unlikely to be reliable unless observers are well-trained. An alternative approach is pragmatic and limits the number of items. This is appropriate to situations in which the purpose of the scale is to make a decision rather than to make a measurement. For example a limited number of items could be used to construct a tool that has clinically relevant binary outcome. A binary outcome forms the simplest of scales [118;119] yet even these may not be reliable between observers.[226]

Only one sedation scale was developed for and has been validated in children[227] (similar to a scale used in adults[228]) but it was not intended for infants. Several scales have been developed to describe conscious level in infants but not in the context of anaesthesia. Their validity is therefore in doubt.

2.3.1.2 Problem of provocation

Arousal from sleep may be spontaneous but if not, there needs to be provocation stimulus. Cutaneous stimulation with pain, touch and temperature are potentially useful but these directly stimulate spinal reflex activity. Moreover there are ethical constraints in research using painful stimuli. Airway obstruction, hypoxia and hypercapnia are relevant stimuli to anaesthesia but cause arousal secondary to complex respiratory reflexes. In the context of anaesthesia, airway and breathing reflexes may be sufficiently suppressed so that tracheal intubation is required to maintain safe oxygenation. If so, the tracheal tube itself could be a painful stimulus especially when it is moved within the trachea. Consequently if the patient is immobile the tracheal tube may not be stimulating but once it is moved the patient

may be stimulated and awaken rapidly. The following methods of provocation have been published.

Temperature has been tested by using a cold metal disc on the abdomen of sleeping infants for 5 seconds but there was considerable variation between subjects.[229] Horne and colleagues used a jet of air (3 Hz for 5 seconds) directed into a nostril and this stimulates by irritation.[230] An arousal threshold can be identified and is defined as the mean jet pressure between *arousal* response and *no arousal* responses. The test is reproducible enough to determine a difference in arousal thresholds between sleep states. An auditory stimulus is potentially useful because loudness can be measured and increased until the infant responds.[231] Within safety limits, sound is harmless and not distressing. Furthermore, auditory processing does not directly involve the spinal cord. Hearing sensitivity may vary both between and within individuals. Chang and colleagues showed that a mixed frequency noise was a reliable provocation of autonomic arousal in young infants sleeping naturally.[118] Potentially important factors other than loudness, include pitch and the problems of hearing deficit, tolerance and habituation.[232] If habituation is caused by learning, sedation and anaesthesia drugs may prevent it and allow noise responses to be reproducible. Alternatively anaesthesia may affect the "hearing" process.

2.3.2 Observable behaviour and stimuli applicable to infants

2.3.2.1 Natural sleep

2.3.2.1.1 Sleep studies

In 1971 Anders and colleagues formed a committee to recommend a common description of natural sleep in normal full-term newborn infants.[123] They created a manual that has been a standard for sleep researchers ever since. An earlier committee had standardized a description of sleep in adults[121] but this needed modification for developing infants. Observations from foetuses and preterm infants have also been published. Anders and colleagues decided against developing a scoring system but rather to "code" or describe states that could be used to develop scoring systems in

other situations. They defined 7 states based on behavioural and physiological characteristics from polygraphic recordings (see Table 2-3). A time epoch of 20-30 seconds was recommended to code the "state" which was the dominant behaviour in that time. The primary criterion to define sleep is sustained eye closure (transient eye openings in one epoch per minute may be ignored depending on other observations). Three secondary behaviour observations are facial and body movements, and vocalization. The number, combination and weighting of coded observations can be varied and consequently researchers need training in using the codes. Stages of sleep have been described also for infants older than 6 months.[233;234]

2.3.2.1.2 Foetal maturation

Obvious spontaneous foetal movements begin at a gestational age of 10 weeks and cycling of activity and rest periods can be detected from 28-32 weeks onwards. In preterm neonates the differentiation between AS and QS is not possible until 28 weeks when sleep is mostly active (with eye movements and irregular respiration). Quiet sleep does not become appreciable until approximately 36 weeks and eye movements associated with REM pattern appear around 37 weeks . Four types of respiratory activity have been described: regular, irregular, periodic and apnoea. Before 36 weeks periodic breathing and apnoea are common during sleep, and breathing becomes more regular and stable later.[122]

Table 2-3: Summary of observable criteria used to describe sleep, non-sleep and other states in normal full term newborn infants.

General state	***Specific State***	***Face***	***Body***	***Vocalization***	***Respiration***
Sleep (eyes closed)	Active	Smiles grimaces, frowns, bursts of sucking	Moves small digits or limb interspersed with slow body writhing with sudden jerks	Brief grunts, whimpers and cries	Irregular
	Quiet	Occasional mouth movements	None	Quiet	Regular
	Indeterminate	Mixed and changing	Mixed	Mixed	Mixed
Awake (eyes open)	Crying	Flushed and grimacing	Vigorous and diffuse	Crying	
	Active	Eyes moving	Gross	No crying	
	Quiet	In active, eyes bright, can follow slow moving object	Inactive	Quiet	
Other	Sleep onset and drowsiness	Eyes glassy, cannot follow slow moving object	non-specific	non-specific	

Summarised from descriptions published by Anders and colleagues.[123] Regular respiration is defined as varying less than 20 cycles per minute

2.3.2.1.3 Neurological examination of neonates

Two detailed monographs emphasise the importance of the state of sleep or wakefulness when making a neurological examination. Brazelton,[235] in 1973, developed a 6 point scale of wakefulness and Prechtl,[236] in 1977, described a 5 point scale. Brazelton's scale was developed from observations of term Caucasian infants who had had "good" Apgar scores and who had not been exposed to appreciable doses of maternal sedation or analgesia (Table 2-4). It was sufficiently detailed and reliable enough to demonstrate differences in behaviour between oriental and Caucasian infants and also between normal infants and those whose mothers were methadone addicts.

Table 2-4: Natural sleep or wakefulness states used in neonatal neurological testing.

Brazelton[235]	**Prechtl[236]**
• Deep sleep, regular breathing, eyes closed, no spontaneous activity • Light sleep, eyes closed; rapid eye movements, irregular respirations • Drowsy, eyes may be open or closed, eyelids fluttering • Alert, with bright look; seems to focus attention on source of stimulation • Eyes open; considerable motor activity, with thrusting movements of limbs • Crying; characterized by intense crying	• Eyes closed, regular respiration, no movements • Eyes closed, irregular respiration, small movement • Eyes open, no movements • Eyes open, gross movements • Crying (vocalization) • Other state – eg coma

The Neurologic and Adaptive Capacity Score (NACS) was a tool developed in 1982, to determine the effects of maternal drugs.[237] It assesses 20 items and can be completed in 60-90 seconds. Although it was originally thought to have high inter-rater reliability, subsequently, it has been criticised for its unreliability.[238-240] The Neonatal Intensive Care Unit Network Neurobehavioural Scale (NNNS) is a tool designed for a detailed and comprehensive assessment of 13 behaviours relating to neurological assessment in young infants.[241] It takes more than 30 minutes to perform and observers require training.

2.3.2.1.4 Arousal from natural sleep

Infants who are at risk from sudden infant death syndrome may be less able to respond or arouse to asphyxia and other stimuli during sleep. An influential study by McNamara and colleagues described spontaneous arousal as a consistent hierarchical pattern of changes in heart rate and respiratory pattern followed by a generalized startle response and finally a change in EEG.[242] Furthermore in provoked arousal, for example by tickling a foot, a withdrawal reflex response of that limb precedes autonomic, startle and EEG responses. These observations may be explained by a temporal activation of first the spinal reflex, then the brain stem, followed by sub-cortical and finally the cerebral cortex.

Other scales of arousal have been developed by researchers attempting to demonstrate a change in rousability relating to the risk of sudden infant death syndrome (SIDS) (see Table 2-5). In 1971 Schmidt and Birns[229] used the Behavioral Arousal Threshold (BAT) 6-point scale to record the response to cold stimulation of the skin. Because of wide variation, they could not show any reproducible response. In 1990 Trinder and colleagues adapted the BAT scale to create a 10-point scale. They were imprecise in their description of the scale but found that it was reliable between three observers.[231]

In 1992, the American Sleep Disorders Association recommended definitions of arousal but did not consider infants.[243] Since then, an international committee has published a statement of opinion specifically on infant arousal.[117] They considered that arousal tends to follow a hierarchy in which a stimulus causes spinal reflexes first, followed by autonomic activation and culminating in cortical (full) arousal.[242] This classification is summarised in Table 2-6. Autonomic arousal is defined as a

change in 2 out of 4 variables (heart rate, breathing pattern, facial expression, EMG). Cortical arousal has been defined by some investigators as a change in the raw EEG pattern to a high frequency and disorganized oscillation for at least one second.[117;242]

Table 2-5**:** Behavioral Arousal Threshold Scales

Behavioral Arousal Threshold (BAT) scale[229]	***Adapted BAT scale***[231]
1. No response, no change compared with pre-stimulus level 2. One jerky movement or a minimal increase of general activity. 3. A partial or full startle or a moderate increase in general activity. 4. A full startle and some additional evidence of awakening, or a large increase of general activity. 5. Awakening and crying, but returning to sleep within. 3 minutes. 6. Awakening and staying awake over a 3-minute period	0: No response 1-3: One jerky movement or a minimal increase in general activity 4-6: Partial startle or a moderate increase in general activity 7-9: Full startle, a large increase in general activity, or eyes open for less than 15 s 10: Awakening, as defined by eyes open and/or crying for over 15 s

Table 2-6: Classification of arousal

Summary of spinal, autonomic and cortical arousal definitions adapted from International Paediatric Work Group on Arousals.[117]

Arousal type	***Motor***	***Autonomic***	***Behaviour and EEG***
Spinal	Limb and trunk movements	None	None
Autonomic	None or as above	2 of the following: Heart rate: change in rate for 3 consecutive beats outside range of the steady baseline* Breathing pattern: either rate or amplitude (can be a single breath**) Facial expression: observed by direct observation or on video later Facial EMG: increase in amplitude of over 20%	None
Cortical	None or as above	None or as above	Eyes open EEG obvious change in power and frequency

*Baseline heart rate was considered "steady" provided it was (a) within the range 100-160/min, (b) the 2 SD was less than 20/min and (c) there was no obvious trend.

**Baseline breathing pattern was steady if (a) the inter-breath interval was no more than 1 sec, (b) the intervals varied by less than 10% and (c) amplitude varied by less than 20%.

2.3.2.2 Anaesthesia

The current recommended descriptions of depth of anaesthesia are those of the American Society of Anesthesiologists and are summarised in Table 2-7. They are helpful in infants provided the verbal stimulus is replaced with a suitable equivalent however they are too broad and lack the detail necessary to describe arousal or awakening.

Table 2-7: Definitions of states within "Continuum of Depth of Sedation"

Minimal sedation (anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Ventilatory and cardiovascular functions are unaffected.
Moderate sedation/analgesia (conscious sedation) Patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.
Deep sedation/analgesia Patients cannot be easily roused but respond purposefully following repeated or painful stimulation. The ability to maintain ventilatory function independently may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.
General anaesthesia Patients are not rousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired

(Abbreviated definitions published by American Society of Anesthesiologists)[244]

2.3.2.2.1 During induction

During the pioneer years of anaesthesia, the stages of anaesthesia during an induction (without any surgical stimulation) were described and regarded as levels or depth. Stages for ether[245;246] and chloroform[247] were widely accepted but detailed descriptions for other anaesthetic agents have not been published either because they do not exist or that they are more difficult to observe because the transition from light to deep levels of anaesthesia is too fast.[248] No definitions of depth have been described specifically for infants.[86;249]

2.3.2.2.2 During awakening

Observations during waking from anaesthesia may reflect pain and other effects of surgery and anaesthesia. Several scales have been developed to assess readiness for discharge from post anaesthesia recovery units and also to assist carers to manage return of adequate airway and breathing functions and to relieve pain and other causes of distress.[250-252] The Vancouver Sedative Recovery Scale concentrates on 12 neurological functions and their total score can range from 0 (anaesthetised) to a maximum of 22 (fully awake)) and has been used and said to be reliable in children as young as 6m.[253] It takes approximately 4 minutes to complete an assessment.[254] Consciousness is scored by the "response" function and is divided into 5 levels: (i) awake/alert, (ii) awake/drowsy, (iii) asleep/easily aroused, (iv) asleep/difficult to arouse and (v) asleep/unable to arouse.

In 2 recent studies[189;255] , testing LOC monitoring, the point of awakening was defined as the onset of purposeful movement, phonation, or eye-opening within 30 seconds of a stimulus.

2.3.2.3 Sedation

2.3.2.3.1 Medical procedures

The Observer's Assessment of Alertness/Sedation Scale (OAS/S) was developed to evaluate reversal of benzodiazepine sedation in adults.[228] It has been validated and is

reliable. It has been used to develop and calibrate the BIS and other monitors of conscious level. Observations of responsiveness, speech, facial expression and eye movements comprise the categories and the final score is a composite score. It is not applicable to infants who do not respond to speech. The Simple Pediatric Analog Sedation Score (PASS) is an analogue scale of 0-4 and uses face diagrams depicting facial expression, eye closure, and response to noise and ear rubbing.[256] Its validity or reliability is unknown.

The University of Michigan Sedation scale or UMSS (Table 2-8) was developed in 1990 for assessing sedation in children and infants for painless imaging; it aimed to be easier to use than any other scale but also relies on response to speech.[227]

Table 2-8: University of Michigan Sedation Scale (UMSS)

Score	Definition
O	Awake and alert.
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation
4	Unrousable

2.3.2.3.2 Intensive care

Many intensive care scales exist and have been reviewed by De Jonge et al.[257] There is some overlap with the consideration of coma and sedation but the scales have been developed with the intention of relieving distress and trying to achieve a desired conscious level or calmness. Marx developed a scale for children [258] that has subsequently been improved to form the COMFORT scale and this is widely used, and considered to be valid and reliable for both intensive care[259] and postoperative

pain.[260] It has 8 items including heart rate, blood pressure and ventilatory observations. The score ranges from 8 (coma) to 46 (awake and distressed), however the relative value of each of the dimensions in contributing to the overall score is not known. Other scales have been developed but none have published validation and reliability characteristics.

2.3.2.4 Coma

Several scales have been developed to identify levels of coma for the purpose of directing therapy and estimating prognosis, however none have been generally accepted worldwide. The GLASGOW COMA scale (GCS),[261] was developed to assess head injured patients and has been adapted for children who cannot speak.[262;263] Other common scales for children include the Adelaide[264], Jacobi[265] and Blantyre[266] scales, and also those described by authors Seshia,[267] Raimondi [268] and Morray.[269] For children younger than 2 years old a scale of facial grimacing has been devised.[270]

Most tools describe the response to a stimulus in terms of eye opening, motor and verbal responses. Three scales have been developed specifically for infants [268-270] and one for neonates which specifies the response to the auditory stimulus of a bell and eye response to light.[271] Reviewers of these scales have concluded that inter-observer variability was less in the simple than in the more detailed tools.[272-274]

2.3.2.5 Pain

Scales of pain related behaviour may be applicable to any cause of distress and therefore their properties could be applied to a scale of arousal. Thirty five scales have been extensively reviewed by Franck and Miaskowski[275] and include scales with acronyms such as CRIES, LIDS, CHEOPS, TIPP, POPS, FLACC, MIPS, RIPS, NAPI and COMFORT[260]. More continue to be developed including APH (aigue du nouveau-ne) and PIPP (premature infant pain profile).[276] The scales have three behavioural dimensions in common; facial expression, body movement and crying.

2.3.2.5.1 Facial expression

The characteristics of facial expression have been studied by Prkachin[277] and Rushforth and Levene.[278] They identified 2 common characteristics of movement of

the brow (lowering or bulging) and eye closing (or squeezing). A coding system has been developed by Grunau and Craig in 1990 called the Neonatal Facial Coding System (NFCS).[279] Of all the behavioural dimensions of pain, upper facial muscle action was found to differentiate best between heel prick from sham even in very preterm babies.[65]

2.3.2.5.2 Body Movement

An Infant Body Coding System (IBCS) has been developed by Craig et al in 1993 but its use has not clarified any specific body movements related to pain.[64]

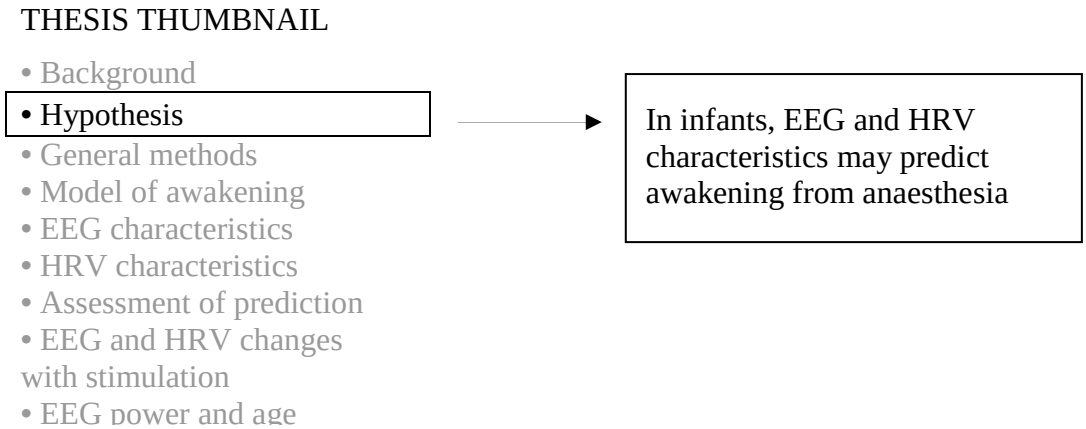
2.3.2.5.3 Crying

Analysis of crying sounds has revealed that crying in term neonates immediately after a painful procedure (circumcision for example) is more persistent than crying due to hunger[280]. Crying in preterm infants tends to be shorter, higher pitched and not as loud as in term babies.[281] However crying due to pain may be indistinguishable from crying due distress from non-painful causes.[282]

2.4 Summary of background

In infants, there are no accepted markers of adequate anaesthesia other than movement and the assumption that a specified end-tidal concentration of an inhaled anaesthetic causes unconsciousness. There are no validated tools or measures of consciousness to assess the rapid transition from anaesthesia to wakefulness. The EEG is different in infants compared to adults. There are no validated monitors of conscious level for infants and there are monitors of the effect of anaesthesia on the infant brain. There are few data on EEG and HRV characteristics during anaesthesia and awakening in infants. EEG and ECG monitoring are non-invasive and if they provide reliable and valid information on conscious level they may be useful in many clinical scenarios

3 Hypothesis and plan of investigation



3.1 Hypothesis

In infants, EEG and HRV characteristics may predict awakening from anaesthesia.

3.2 Plan of investigation

In brief, this investigation is under 2 main headings.

- Development of a clinical model
- Investigation and characterisation of EEG and HRV changes

3.2.1 Development of a clinical model

3.2.1.1 Assessment of stimuli

How should anaesthetised infants be stimulated? A response to a painful stimulus is influenced by the intensity of the stimulus and the effect of any analgesia. Using non painful stimuli to test arousal, is ethically more acceptable, commonly used in clinical practice and may be more relevant if effective analgesia can be assumed during

anaesthesia. Noise may reliably cause arousal from natural sleep (see section 2.3.2.1.4) but does it cause arousal from anaesthesia? Can a reliable model be developed in which an infant is not too deeply anaesthetised to be able to respond to noise or any other non-painful stimulus?

Arousal may or may not lead to full awakening. Is there a state, between anaesthesia (unresponsive) and wakefulness (fully responsive) in which the infant appears asleep yet can be roused (arousal responses = movement, autonomic or EEG changes) but not fully awakened? In other words, is there a *middle ground* between anaesthesia and wakefulness in infants? Can this *sedated* state be demonstrated reliably?

3.2.1.2 Determining which EEG channel to test

Processed EEG monitoring has been developed from recording of frontal channels. EMG interference may be greater in frontal channels and other channels may be more reliable, or may yield different and potentially useful information.

3.2.1.3 Defining awakening by consensus

There are no accepted criteria of awakening from anaesthesia in infants. The opinions of paediatric anaesthetists may help to provide a valid working definition of awakening that would be relevant to the rapidly changing scenario at the end of surgery.

3.2.2 Characterisation of EEG and HRV changes

Monitoring direct brain function using EEG may show changes before and during awakening. HRV may indicate changes in autonomic nervous activity affecting the cardiovascular system that may be a useful indirect measure of conscious level. Both of these are non invasive and could be developed into practical monitors in clinical anaesthesia.

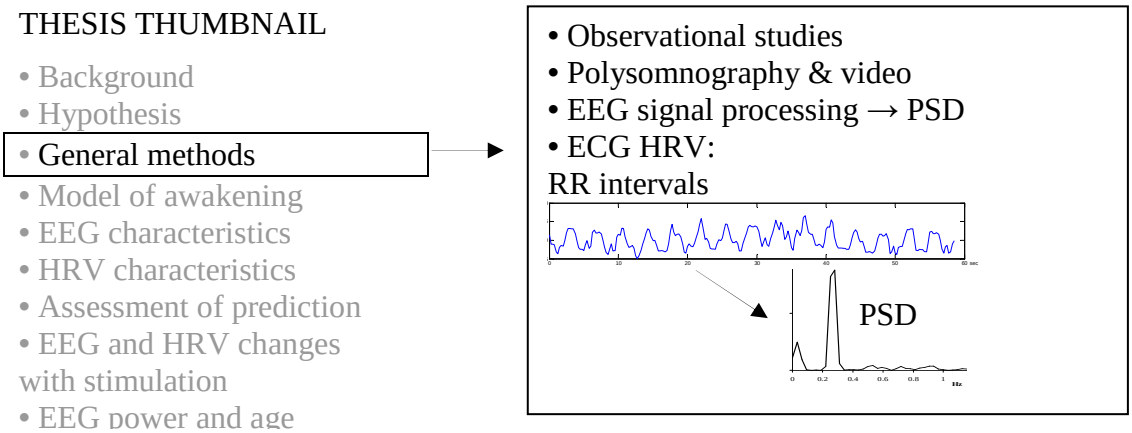
3.3 Practical constraints

There are obvious ethical constraints. In the absence of clear benefit, the risks of research overshadow any intervention such as altering the dose of anaesthesia.

Consequently it may only be reasonable, at least initially, to investigate EEG and HRV at the end of surgery during the transition from seemingly adequate anaesthesia until awakening.

In clinical anaesthesia there are many variables. Surgery causes a variable degree of pain and arousal, and the methods of analgesia will have a variable effect on relieving pain and may also affect conscious level. The choice of anaesthesia drugs used should be appropriate to the surgery and consequently will vary. Infants themselves may be abnormal and have diseases and syndromes that affect their response to anaesthesia. Consent for research may be refused by anxious parents and there are a limited number of infants who present for surgery who do not have an abnormal cerebral status. The type of any additional stimulus has to be acceptable to parents and unlikely to cause appreciable distress to infants.

4 Methods – general aspects and equipment



4.1 Subjects

Unless stated otherwise all projects involved with this thesis were registered with the Institute of Child Health and approved by the local ethical committee. Parents gave written informed consent for studies of infants during anaesthesia. Infants were defined as children aged less than 12 months old. Patients were included if they required anaesthesia involving tracheal intubation and excluded if they had any cerebral, cardiac or respiratory disorder or were receiving any medication likely to affect neurological function. All infants had normal behavioural development and hearing as judged by their parents. Post-menstrual age (PMA), body weight and relevant clinical details were recorded.

4.2 Anaesthesia technique

Anaesthesia technique was not altered by these studies and was chosen by individual anaesthetists. In all cases induction was by inhalation of sevoflurane. Maintenance was by either isoflurane or sevoflurane. Routine monitoring, which included pulse oximetry, ECG, respiratory gas analysis and non-invasive blood pressure, was applied as soon as possible. Tracheal intubation was achieved after muscle relaxation with atracurium. Gases were administered via either a Mapleson F (Jackson Rees

modification of the T-piece) or circle breathing systems. The inspired concentration of anaesthetic was adjusted to maintain end-tidal concentration considered compatible with an adequate depth of anaesthesia according to clinical judgment of the anaesthetist administering the anaesthetic.

Analgesia varied according to the type of surgery but was usually achieved with local anaesthesia using levobupivacaine either by skin infiltration or regional nerve block. Other potent analgesia included intravenous fentanyl or morphine. All infants received intravenous fluids in volumes guided by the clinical judgment of the anaesthetist who assessed heart rate, blood pressure and skin perfusion to ensure that infants were not hypovolaemic or dehydrated. Core temperature was recorded. Blood glucose was not estimated. At the end of surgery, before extubation, atracurium was not reversed with neostigmine because more than one hour had passed since the last dose; no anti-muscarinic drugs were used.

4.3 Study equipment

4.3.1 Electrodes

EEG signals were recorded from silver / silver chloride cup electrodes placed on the scalp. The skin was prepared with abrasive cleaning gel and skin contact was maintained with electrolyte paste. Electrodes were positioned according to international recommendations (10-20 system).[116] Electrodes and wires were held in place with an elasticised bandage or paper adhesive tape. Electrode impedance was kept below 5KΩ whenever possible. Three ECG electrodes were attached by self-adhesive gel and placed on the shoulders and left lateral aspect of the thorax.

4.3.2 Timing of events

Combined video and audio were used to record the time of events during awakening. The accuracy of the timing of video recording and playback was tested by recording the passage of time visible on a clock face and checking that this matched the video time. The clock face time was checked against the time on a personal computer which was assumed to be accurate. The synchronization of EEG/ECG and video recordings

were checked by videoing several event markers. Markers were made either by a push-button device or a brief manual interference of a non-essential recording channel.

4.3.3 Polysomnography

The Alice Respironics® integrated sleep polysomnography system collects synchronised video, audio, ECG, EEG, EMG and respiratory inductance signals. Two versions were used, Alice 4 and 5, to collect data for assessment of arousal to noise and other stimuli (see section 5.1.3.6). Respironics® software allowed real time viewing of all signals and could replay signals later. All signals were digitised internally and could be exported as numerical strings into other software for further analysis. Seven electrodes were applied (F3, F4, C3, C4, A1, A2 and a reference at the middle of the forehead) to record signals from 4 channels (F3A2, F4A1, C3A2, C4A1). EEG channel impedance was measured internally. Two respiratory inductance bands were applied and adjusted to ensure an obvious respiratory waveform; one at nipple level and the other close to the umbilicus. The respiratory signal was observed for changes to shape, oscillation and rate. Up to 3 EMG signals were recorded from standard neurophysiology skin electrodes applied to the leg, the chin and the forehead. Signals were observed for gross changes in amplitude and the leg EMG was used primarily as a movement detector. The video aimed to capture movements of the face; the rest of the body was covered to maintain body temperature.

4.3.3.1 Alice 4

The Alice 4 system internally digitised 2 EEG signals at 200 Hz (channels F3A2 and C4A1), and 2 at 100 Hz (F4A1 and C3A2). The processor was 8 bit and the limits of signal were -150 to +150 µV (signal resolution = approximately 1.2 µV). Signal output was in microvolts. Calibration was checked using an external signal generator. The synchronisation of the digital video with the Alice 4 monitors was found to be inaccurate and varied by up to 5 seconds. Nevertheless, using EMG and respiratory waveforms the timing of facial and body movements was possible.

4.3.3.2 Alice 5

The Alice 5 system internally digitised signals at 200 Hz using a 10 bit processor within an amplitude range of –300 to +300 µV (signal resolution = approximately 0.6 µV). Signal output was in integers ranging from 0 to 1024; these were converted to µVs by multiplication by 0.6 and subtracting 300. Calibration was checked using an external signal generator. The digital video of the Alice 5 system was shown to be synchronised with other signals. Integral ECG software had an automatic R wave recognition algorithm and calculated the time difference between each R wave to produce a sequence of RR intervals. The software was advertised as capable of estimating RR intervals to the nearest 0.2 millisecond yet ECG signals were digitized at 200 Hz allowing minimum R wave resolution of 5 milliseconds. Comparison of automatic RR intervals against "manual" estimates of RR intervals from the 200 Hz data showed that the R wave recognition may be inaccurate and misleading. Sampling frequency of 200 Hz is insufficient to determine RR interval with sufficient resolution to justify frequency domain analysis.

4.3.4 Grass-Telefactor

The Grass-Telefactor Twin (version 3.7.85.0) "AURA 10-20" is a multi-channel recording system designed for electrophysiological studies. Signals from recording electrodes are processed by an internal amplifier and analogue to digital converter connected to a control box both powered by an isolating transformer. The amplifier contained analogue signal filters set at 0.3 and 70 Hz (high and low pass filters respectively). Signals with a range of +2 to –2 millivolts were digitised at 400 Hz by a 16 bit processor providing a signal resolution of approximately 0.06 µV (precisely 0.06103515625 = 4000/ 2^{16}). Signal output was in microvolts. Grass-Telefactor software organises the data storage into files containing a maximum of 120 seconds. A text file is generated recording the lengths and start times of the data files. Signals could be viewed within Grass-Telefactor software and the view could be adjusted by altering filters and time resolution. Signal data stored in files were unfiltered. An internal calibration system provided a reference signal of +/- 400 µV.

All EEG channels were referenced to an electrode placed on the bridge of the nose; a ground electrode was placed on the forehead near the midline. An internal impedance check could be manually activated.

4.3.5 Video and audio recording

When using the Grass-Telefactor system events were recorded by an analogue cassette video camera (Sony Handycam®, DCR-HC27E/HC28E) which was digitised by Windows Movie Maker software for playback later on a personal computer. The time of the mark made on the EEG recording was checked with the video time and was always within 0.5 seconds.

4.4 Signal processing

4.4.1 Importing data into MATLAB

All signals were analysed by MATLAB program (version 7, with Signal Toolbox). Data from the Alice systems were identified while inspecting the recording and then selected manually for export into a *.csv* file that could be imported into MATLAB. For Grass-Telefactor data, after visual inspection using the Grass-Telefactor system, data were analysed directly from the data file; within each data file the start point could be identified automatically on the hexadecimal data sequence. The MATLAB program could either select an individual data file representing 2 minutes of data or select a series of files to analyse a sequence of data of up to 24 minutes.

4.4.2 Signal power estimation

The power spectrum density was estimated using bespoke Matlab “m” program files that incorporated the Matlab Discrete Fourier Transform algorithm. The Welch method of estimating power spectral density was used. The Welch method involves division of a sequence of data into segments. The PSD of each segment of data is calculated and the PSD for the whole sequence is the mean of the segment PSDs. Overlap the segments is permitted so that, for example, for a segment length of one

second in a sequence of 6 seconds, using an overlap of 0.5 will allow 11 window PSDs to be used to estimate the mean PSD for the 6 seconds. The segment PSD calculation is undertaken after the segment data has been multiplied by a "window" algorithm whose properties aim to reduce the effects on the power spectrum of the sudden changes at the beginning and end of the segment. Power within a frequency band, or frequency range, is the product of the frequency range and sum of the power densities within the frequency range.

4.4.3 EEG

The EEG was analysed in sequences or segments or "epochs" of length 6 seconds. The epoch length of 6 seconds was chosen to allow 10 epochs per minute.

4.4.3.1 Visual inspection of EEG

Digitised EEG signals were plotted to visually check for transients, periods of silence and signals that were out of the range of measurement. Epochs were not analysed if there was appreciable interference including:

- ECG interference with amplitude greater than twice the maximum EEG amplitude
- Transients, defined as an isolated feature, easily distinguished from background[283]
- K complexes, defined as single positive (upward) then negative voltage shifts of 200-300 µV lasting less than 1 second[283]
- Sleep spindles, defined as multiple spikes of 12-14 Hz with an amplitude of 90-100 µV lasting from 1-6 seconds[283]
- Eye-blinks, defined as steep positive change (takeoff is steep but curved) with slower recovery lasting less than 1 second [283]
- Accidentals, defined as single acute shifts lasting less than 1 second such as spikes (less than 200 µV) and sharp waves (less than 70 µV) [283]
- EMG high frequency "spiky" signals that obscure underlying EEG
- Non physiological artefacts; defined as sudden steep (almost vertical takeoff) changes in baseline greater than 70 µV lasting more than 1 second[283]

4.4.3.2 EEG power spectral analysis

Within each epoch the mean of the signal was subtracted from each data point in order to minimise any direct current component. A *Hanning* type window was used on each segment of length 1 second with an overlap of 0.5. The frequency resolution was 1 Hz (=1/window length). The frequency range is 50% of the sampling frequency (sampling frequency of 400 Hz gave a frequency range of 0-200 Hz). The following variables were calculated within the frequency domain for each time epoch: summated signal power within specified frequency bands, total power (TP) within a specified frequency range, median frequency (MF) and spectral edge frequency (SEF). MF and SEF are defined as the frequency below which there is 50% and 90% (respectively) of the total spectral power.

4.4.4 ECG and HRV

4.4.4.1 Visual inspection of ECG

Each ECG channel was processed with a low pass digital filter to remove frequencies higher than 40 Hz (Butterworth, M=8) and then plotted and inspected for obvious interference. The channel with the least interference and highest amplitude of R waves was selected for further processing.

4.4.4.2 HRV time domain

The selected ECG signals were processed to identify the time indices of R waves. R wave detection was performed by a modified Pan Tompkins algorithm.[284] Each beat was visually inspected and the indices of misidentified R waves were replaced by visually confirmed indices. Indices were analysed in both time and frequency domains. The calculated time domain variables were similar to those recommended and published in 1996 by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [211] and included:

- beat by beat RR interval (RR = NN = interval between normal beats)
- beat by beat heart rate (HR (60 divided by RR interval))
- difference between each successive adjacent pair of NN intervals (SDiffNN)

- square of the difference between each successive adjacent pair of NN intervals (SSDiffNN)

For each minute period the following were calculated:

- mean NN and standard deviation of NN (SDNN)
- mean HR and standard deviation of HR (SDHR)
- mean SSDiffNN (MSSD)
- square root of MSSD (RMSSD)
- the number of pairs of adjacent beats with an absolute difference more than 25 milliseconds (NN25)
- percentage of NN interval that differ by more than 25 milliseconds (pNN25).

A difference of 25 milliseconds was chosen rather than the recommended 50 milliseconds which is not appropriate to the shorter NN intervals of infants.[217] Graphical displays of time domain variability show heart rate rather than NN intervals for ease of clinical interpretation. Progression of change in heart rate was demonstrated by showing the change in mean heart rate for each epoch (calculated from RR intervals of successive beats within each epoch). Sampling frequency of 400 Hz enabled 2.5 millisecond resolution of RR intervals.

4.4.4.3 HRV frequency domain

Frequency domain analysis was performed on a waveform of RR intervals against time. This involved plotting beat by beat RR intervals against the time of the second beat of the interval, interpolation of this plot and resampling with a sampling frequency of 4 Hz. This generates a new waveform that has a maximum frequency of 4 Hz. A power spectrum analysis was performed using a window length of 32 seconds (or 128 data points) giving a frequency resolution of 0.03125 Hz and a range of 0 to 2 Hz. Typical plots of RR intervals together with their PSD is presented in Figure 4-1.

Band power was calculated (summated power densities within the frequency range * frequency range) in the following frequency ranges:

- low frequency (LF = 0.03 to 0.16 Hz),
- high frequency range (HF = 0.19 to 0.41Hz) and
- very high frequency (vHF = 0.42 to 1Hz).

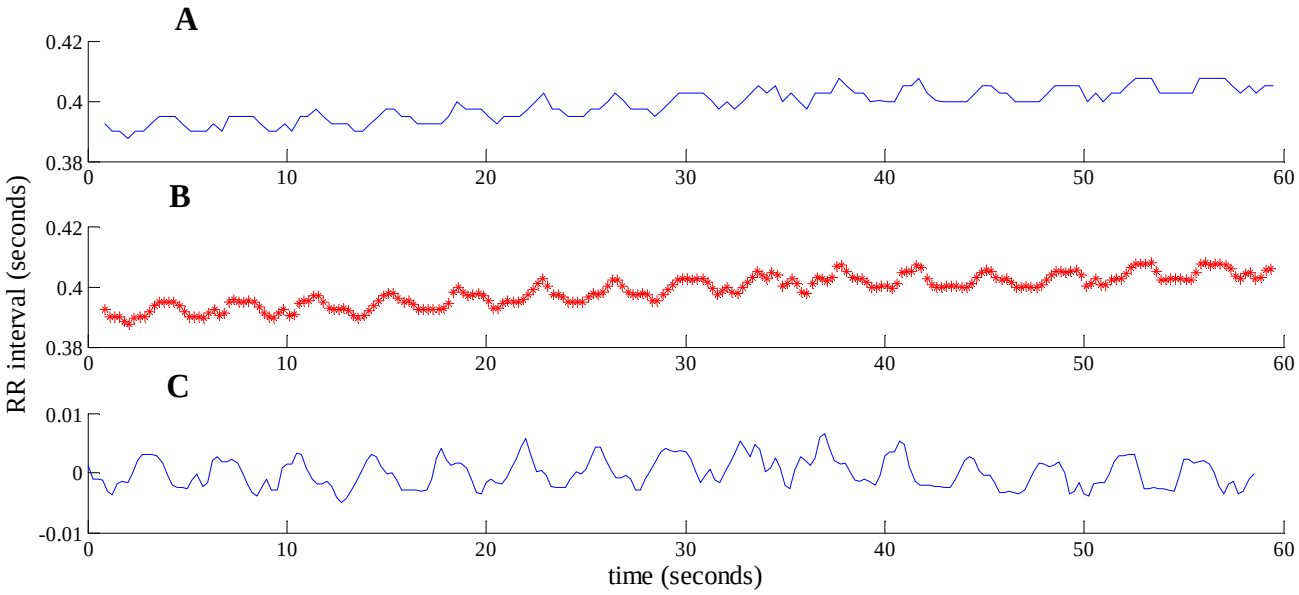
The HF range was chosen to capture the power due to the frequency of mechanical ventilation. The LF and VHF ranges were chosen to identify variation that was not related to mechanical ventilation.

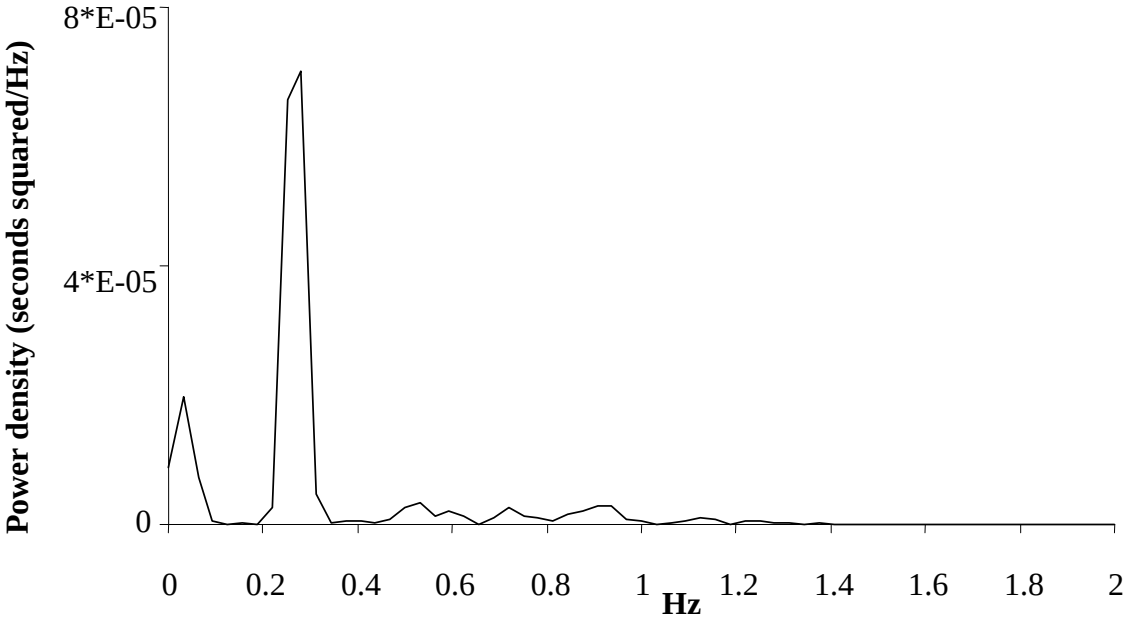
Figure 4-1: Typical plots of ECG RR intervals with their corresponding PSD

A: RR intervals plotted against time of the second R wave of the interval

B: Interpolated RR intervals (calculated using 'spline' function) plotted against time (resampled at 4 Hz)

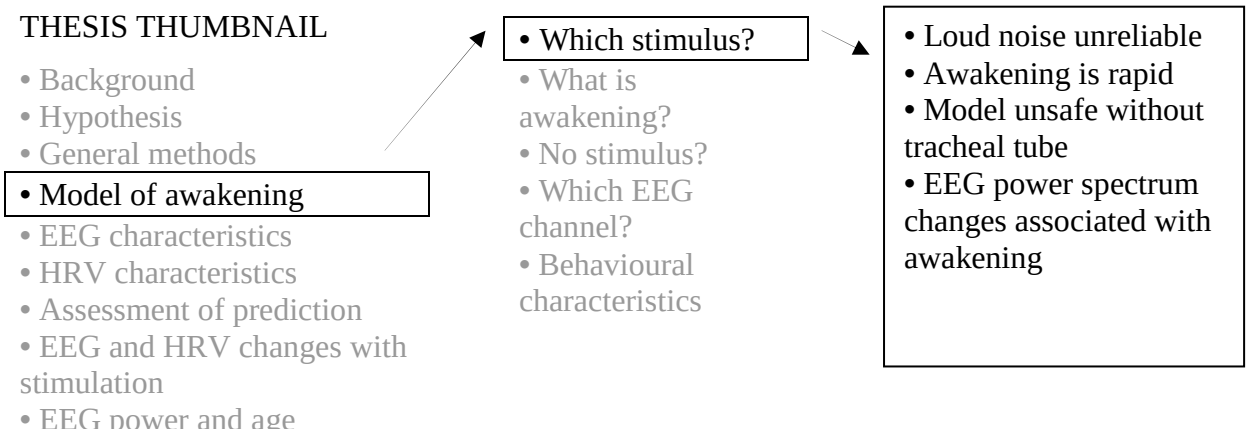
C: Interpolated RR intervals (adjusted for mean and trend) plotted against time.





5 Development of the model of awakening from anaesthesia

5.1 Assessment of arousal and stimuli in non-intubated infants



5.1.1 Introduction and aims

Is there a state, between anaesthesia and wakefulness in which the infant appears asleep but cannot be not fully awakened? Is there a demonstrable *middle ground* (perhaps a sedated state) between anaesthesia and wakefulness in infants? Such a sedated state could be present in infants who are receiving low doses of anaesthesia and in those whose tracheas are not intubated.

What stimuli should be used to test arousal from such a state? At the end of surgery while anaesthesia levels are reducing, awakening should occur when the hypnotic effects of anaesthesia no longer oppose stimuli. If there are no stimuli, either internal (e.g. pain) or external (e.g. pharyngeal suction) then awakening may be delayed. It is common clinical practice to use mild non-painful stimuli to provoke awakening.

In verbal children, calling their name is used but in infants a reliable auditory stimulus has not been described. During natural sleep *pink* noise (noise power is inversely

proportional to frequency) causes autonomic arousal in most infants[118;231] and if this occurred reliably during recovery from anaesthesia it may be useful as a marker of depth. The noise of MRI scanning is another potentially useful stimulus. It disturbs the sleep of infants and prevents them staying immobile for imaging; anaesthesia or sedation is often required that must be deep enough to prevent a response to noise.[285]

Shallow depth of anaesthesia may not be possible if the trachea is intubated because the tube itself may be uncomfortable and cause arousal instead of the noise. Noise, therefore, may only be useful in non-intubated infants. The scenario of non-intubated infants is relevant during MRI scanning.[79;80;286]

5.1.2 Objectives

- to determine the reliability of loud noise as a stimulus to rouse an infant from anaesthesia
- to assess the feasibility of using a model of awakening from anaesthesia in which the infant is breathing spontaneously without a tracheal tube
- to examine responses (including EEG changes) associated with arousal or awakening

5.1.3 Methods

5.1.3.1 Subjects

Two groups of sleeping infants were studied. Infants recovering from anaesthesia were the main study group. A smaller group of infants sleeping naturally were studied to test the arousal effect of noise.

5.1.3.2 Noise provocation and other stimuli

Noise provocations were mixed frequency sounds of 85 dB presented for 3 seconds via speakers placed 10 cm from the ears. Three seconds was chosen to enable repeat noise testing (approximate interval of 60 seconds). Noise was played only when there

had been at least 60 seconds of both sleep and steady breathing (as judged by observation of the respiratory waveform).

The first 5 infants tested during anaesthesia had *pink noise* and the remainder had a pulsatile *MRI scanner* noise. Other stimuli were used if noise provocation was considered unsuccessful. These included insertion of an oral airway into the mouth or gently squeezing the nose.

5.1.3.3 Anaesthesia

Anaesthesia was induced with sevoflurane and maintained with isoflurane in oxygen and air. After surgery ended infants were moved to a quiet room (the anaesthetic room) for observation and monitoring. Extubation was delayed for approximately 5 minutes until extra monitoring (described below) was applied. Extubation was carried out under isoflurane anaesthesia and when spontaneous breathing was judged to be adequate. Sleeping infants were placed in the supine position and their airway was usually self-maintained; an oropharyngeal airway was used if necessary. Oxygen was administered via a simple tube positioned close to the face. Tidal gas was sampled from a soft catheter placed either in a patent nostril or in the oropharyngeal airway. The room had standard lighting and was quiet except for the sound of a pulse oximeter.

After extubation, arousal was expected at a variable time either spontaneously or in response to a provocation. Infants were expected to be in one of three categories:

- Early recovery. Arousal or awakening would be unprovoked within 3 minutes of extubation.
- Expected recovery. The infant would be asleep initially but arousal and awakening would occur within 15 minutes of extubation, either spontaneously or in response to provocation with noise.
- Delayed recovery. The infant would remain asleep for longer than 15 minutes. There would be no arousal, either spontaneous or provoked by noise. After 15 minutes, arousal and awakening would be provoked by the gentle stimulation of the mouth or nose.

5.1.3.4 Natural sleep

Infants were studied either before or at least 24h after surgery, and were observed and monitored after feeding during quiet sleep. None had received any medication other than paracetamol for the previous 24h. Quiet sleep was observed for at least 10 minutes before any noise provocation. Infants were considered to be asleep if, for a 30 second period, they had a steady heart rate and breathing pattern, sustained eye closure, were quiet and had no gross facial, trunk or limb movements.

5.1.3.5 Definition of arousal response

Responses to noise were assessed during anaesthesia and natural sleep. Arousal was defined and categorized according to the system published by the International Paediatric Work Group on Arousals[117] except that EEG changes were not included. EEG changes were considered separately after signal processing (see below). Arousals were considered provoked if they occurred within 3 seconds of the stimulus and were recorded as sustained if they lasted more than 15 seconds. Awakening was defined as 2 out of the following 4 behaviours provided they occurred continuously for at least 30 seconds; eyes open, grimacing, crying, or gross motor activity.

5.1.3.6 Monitoring

The Alice 4 system was used for the first 10 infants and the Alice 5 for the remainder.

5.1.3.7 EEG signal processing and comparisons

Powers within both narrow and wide frequency bands were calculated with a frequency resolution of 1 Hz.

5.1.3.8 Signal comparisons

EMG interference may have influenced the power analysis despite exclusion of visually obvious contaminated epochs. Assuming that EMG interference was more likely to have occurred in frontal rather than central channels, the means and distributions of power in the frontal (F3A2, F4A1) and central (C3A2, C4A1) channels were compared first.

Arousal responses to noise were assessed during anaesthesia and natural sleep.

In infants waking from anaesthesia, processed EEG data were compared during:

- 60 seconds of steady state sleep versus 60 seconds of awakening (or maximal arousal). The sleep data was sampled early in the recording and the awakening was generally at the end of the recording.
- 60 seconds before and after autonomic arousal
- 60 seconds before and after awakening

5.1.4 Results

5.1.4.1 Description of infants

Demographic details are presented in Table 5-1. Anaesthesia was studied in 15 infants and natural sleep in 5. Every infant had a period of sleep and arousal.

5.1.4.2 Technical issues

The change in respiratory waveform was a good indicator of body movement and always coincided with other features of autonomic arousal and with awakening. Heart rate changes were less easy to detect by observation. The timing of EMG signals was compared with video recording of movement and was shown to coincide with movement in general. Visual inspection of EEG signals showed that there were frequent ECG, EMG, and non-physiological interference. These were most likely due to poor electrode contact and variable impedance. Approximately 60% of *awake* epochs (compared with 18% of *anaesthesia* epochs) were excluded from analysis. Transients or eye blinks were not seen except for one K complex. Aproximately10% of all epochs were excluded because of ECG interference. ECG interference produces spiky waveform that should produce high frequency interference. In a small sample, the ECG waveform of different heart rates was tested by PSD and power within broad frequency bands did not show a gross change.

Table 5-1: Demographic details of infants tested with noise and other stimuli

Infants are grouped by sleep type and in order of ascending age.

Patient ID	Sleep type	PMA (w)	Weight (kg)	Operation	Alice
10	anaesthesia	41	4	amputation foot	4
15	anaesthesia	41	3.6	anoplasty	5
13	anaesthesia	42	3.5	lensectomy	5
9	anaesthesia	42	4	inguinal hernia repair	4
18	anaesthesia	42	4.1	lensectomy	5
6	anaesthesia	43	5.2	anoplasty	4
8	anaesthesia	44	3	inguinal hernia repair	4
11	anaesthesia	45	4.7	arm amputation	5
19	anaesthesia	46	4.1	closure of ileostomy	5
7	anaesthesia	48	4.4	gastrostomy	4
14	anaesthesia	52	5.6	cleft lip repair	5
2	anaesthesia	56	5.6	anoplasty	4
16	anaesthesia	56	5.7	anoplasty	5
20	anaesthesia	58	7.6	closure of ileostomy	5
5	anaesthesia	70	6.7	anoplasty	4
4	sleep	39	3.4	urethral valves	4
17	sleep	41	2.5	Awaiting repair of tracheo-oesophageal fistula	5
1	sleep	42	2.9	Repaired gastroschisis	4
3	sleep	42	3	Repaired bladder extrophy repair	4
12	sleep	45	4.7	36h after arm amputation	5

5.1.4.3 Behavioural response to noise

5.1.4.3.1 During recovery from anaesthesia

Of 15 anaesthetised infants 4 had early spontaneous recovery and 9 had expected recovery. Of the 9 infants who recovered expectedly 8 were tested with noise and only 4 of these had any obvious evidence of autonomic arousal. In one infant oral stimulation was used and it caused autonomic arousal. Two infants had delayed recovery and arousal was provoked by oral or nasal stimulation. Out of 15 infants 3 had oxygen saturations below 90% after removal of the tracheal tube due to either apnoea or laryngospasm. No intervention was required other than oxygen delivered by face mask.

5.1.4.3.2 During natural sleep

Noise caused obvious autonomic arousal in 4 out of 5 infants. In those who did rouse there was evidence of habituation of response. Repeated noise stimuli became less effective (autonomic arousal occurred with approximately 30 to 40% of repeated noise stimuli).

5.1.4.4 EEG changes

5.1.4.4.1 Comparison of power in frontal and central channels

Figure 5-1 shows the mean power in frequency bands of frontal and central channels during both sleep and awake states. The total power in central channels was statistically higher than in the frontal channels. Power with frequencies higher than 30 Hz were almost zero during anaesthesia and this demonstrates absent EMG activity.

5.1.4.4.2 Anaesthesia versus awake

Continuous EEG signals were satisfactory in 10 anaesthetised infants. There were no consistent patterns of change in TP, MF and SEF between anaesthesia and wakefulness: TP increased in 7, MF increased in 3 and decreased in 6, SEF increased in 4 infants and decreased in 5.

Table 5-2: Mean log transformed EEG variables during anaesthesia and awakening

TP = total power, MF = median frequency, SEF = spectral edge frequency

Variable	**Anaesthesia**	**Awake**	**t test P value**
TP	2.65	3.28	<0.01
MF	.22	.27	0.28
SEF	.74	.82	0.012
Band power			
1-4 Hz	2.65	3.28	<0.01
5-8 Hz	2.52	3.22	<0.01
9-13 Hz	1.49	1.89	0.2
14-20 Hz	1.51	1.55	0.9
21-30 Hz	1.57	1.53	<0.01

The raw variables were not normally distributed but their log10 values were normally distributed. Table 5-2 compares the mean log10 transformed variables by unpaired t tests: all variables increased after awakening except for log10 power in bands 9 to 13 Hz and 14 to 20 Hz. Powers in frequency bands below 6 Hz were much higher than in higher frequency bands and were excluded from further analysis. Figure 5-2 shows the distribution of mean log10 power in each single Hz during anaesthesia and wakefulness. Mean power was consistently higher during wakefulness than anaesthesia in frequency bands higher than 20 Hz.

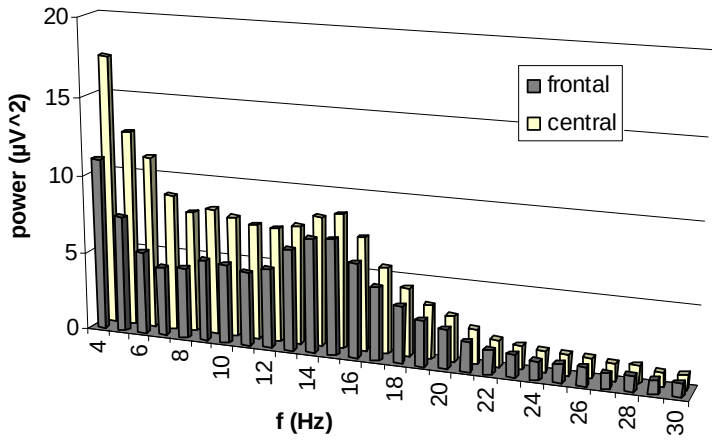
The percentage change in mean power (all channels and all epochs) from sleep to wakefulness was calculated in each frequency band for each infant. Figure 5-3 shows that there was a consistent pattern in infants over 50 weeks PMA. In these infants

power in frequencies of approximately 10 to12 Hz decreased and power in the highest frequency bands increased. Figure 5-4 shows a consistent change in the ratio of log power from sleep to wake states in each infant. Irrespective of age, a ratio of the power in high and low frequency bands may differentiate between sleep and wake states.

Figure 5-1: Comparison of mean raw EEG power in frontal and central channels

Bars represent mean raw power of all epochs in 10 infants in each EEG single frequency band ranging from 4 to 30 Hz

A: during 1 minute of anaesthesia



B: during 1 minute of wakefulness

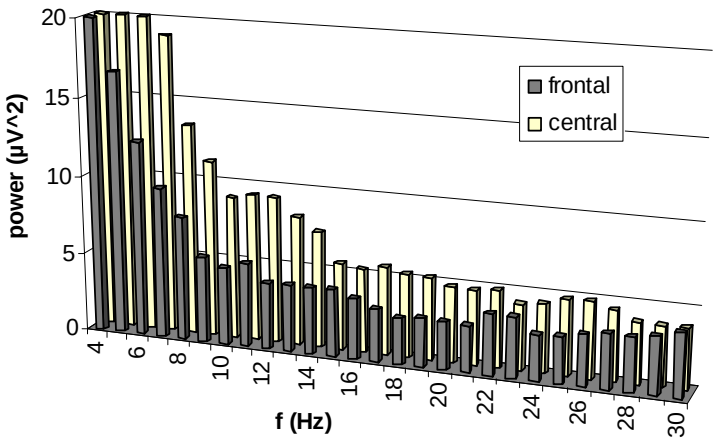


Figure 5-2: Comparison of EEG power during anaesthesia and wakefulness

Bars represent mean log10 power (of all channels and all epochs in 10 infants).

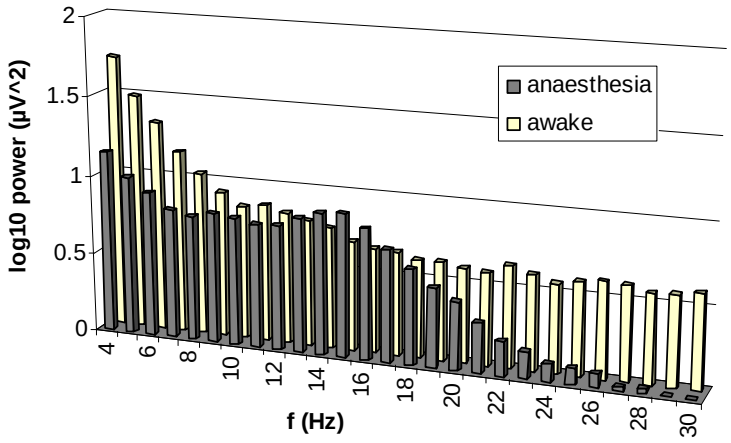


Figure 5-3: Age related change in EEG log 10 power from anaesthesia to wakefulness

Each set of bars represents the change in power spectrum for a single infant. Each bar represents % change in mean log10 power in single frequency band (range 6 to 30 Hz).

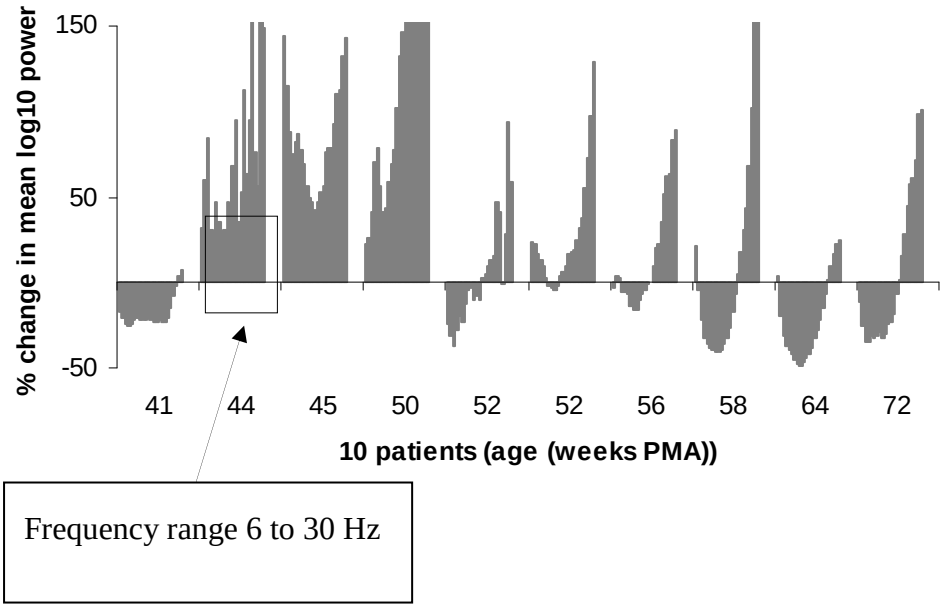
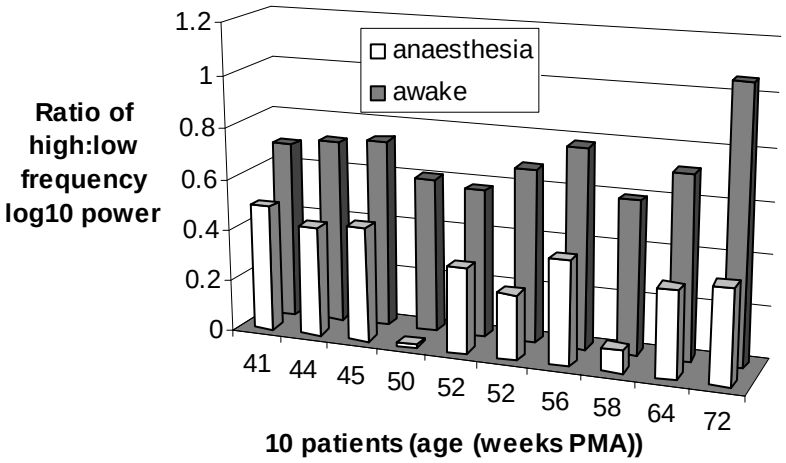


Figure 5-4: Ratio of the mean log10 EEG power in 30 and 11 Hz frequency bands in sleep and wake states in each infant



5.1.4.4.3 Provoked autonomic arousal from anaesthesia

Four infants had good examples of provoked autonomic arousal in which they were asleep before arousal and then settled within a few seconds. Neither visual inspection nor power spectrum analysis showed an obvious change in EEG over these brief periods. Five infants had good examples of provoked awakening from sleep. Figure 5-5 shows spectrum of mean EEG power in each power band for each child during one minute of sleep, just before awakening, just after awakening and when fully awake. The bar graphs show there is an increase in EEG power in high frequency bands except in patient 16. Nevertheless the ratio of power in higher over lower frequencies always increased (see Figure 5-6).

Figure 5-5: Mean EEG power during anaesthesia and awakening in 5 infants

Bars represent mean raw EEG power in single frequency bands for each child during one minute. The awake EEG of patient 18 was heavily contaminated with non-physiological interference.

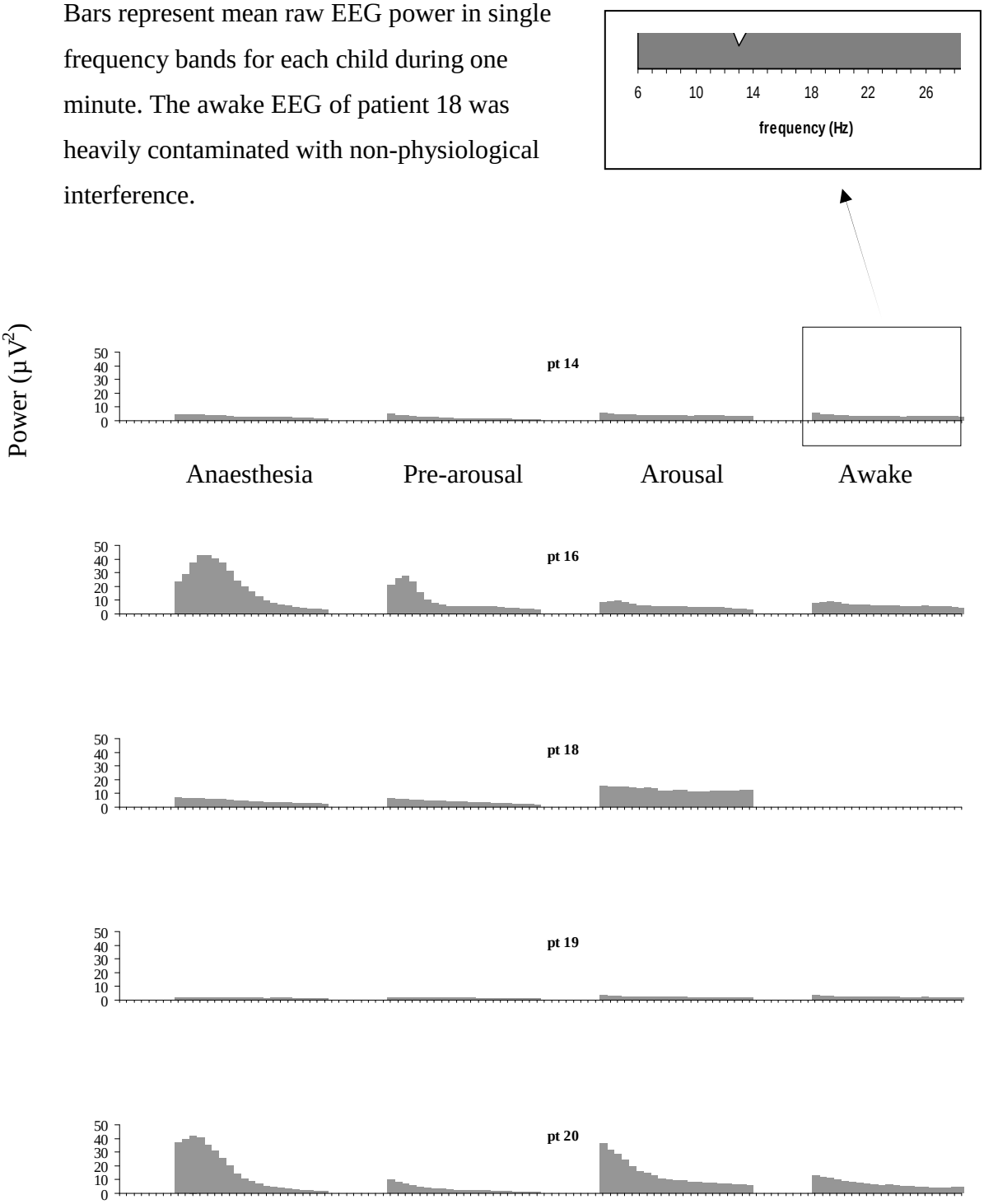
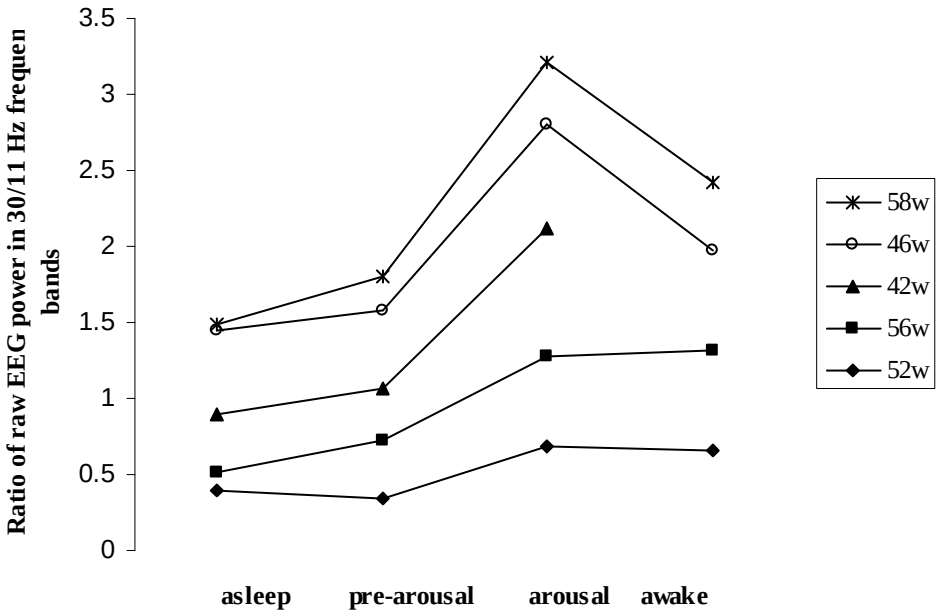


Figure 5-6: Ratio of raw EEG power in 30 to 11 Hz during recovery from isoflurane anaesthesia in 5 infants.

Each point represents ratio of mean raw power (in 4 EEG channels over one minute) in 5 infants.



5.1.5 Discussion

These data show that noise can provoke arousal during natural sleep although arousals were reduced after repeated noise stimuli. During anaesthesia noise was not a reliable stimulus of arousal or awakening. Arousal patterns (spontaneous and provoked) from anaesthesia were mixed, with some infants rousing quickly and others slowly. When autonomic arousal occurred it was unusual for the infant to return to sleep again; i.e. autonomic arousal was not clearly separated from full arousal or awakening. This supports the observation that awakening in infants is “all or none” and that the *middle ground* or sedated state cannot be reliably demonstrated in this scenario.

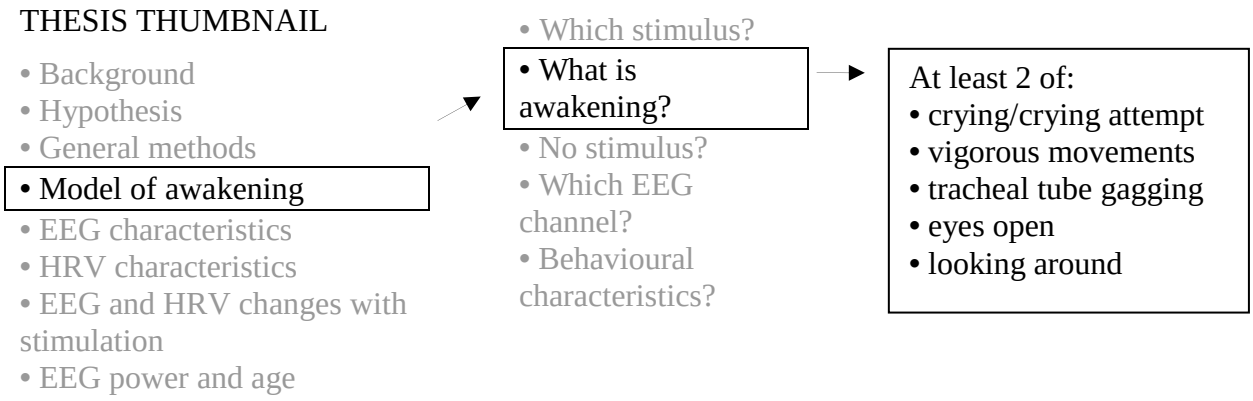
EMG interference could have introduced a high frequency component into the EEG and if so, the frontal channels should receive more interference than the central. No appreciable differences, however, were found between power spectra of the channels. This suggests that appreciable EMG interference was excluded or not present. The mean power in all frequency bands was higher in central channels than in frontal. This difference was greatest in the lowest frequency bands.

The comparison of the EEG power spectra of anesthetised babies versus spectra in awake babies showed that in infants over 50 weeks PMA (n=6) there was a similar pattern of change. There was a general increase in power over 20 Hz but that the power in frequencies close to 10 Hz decreased. In infants under 50 weeks PMA (n=4) the EEG pattern was less constant but power in all frequency bands tended to increase upon awakening. Irrespective of age, the ratio of high frequency power to low frequency power always increased with awakening.

5.1.6 Conclusions

- Loud noise is not a reliable stimulus to rouse an infant from anaesthesia
- A sedated state could not be reliably demonstrated.
- The model of awakening from anaesthesia in which the infant is breathing spontaneously without a tracheal tube is associated with airway and breathing problems.
- There may be age related EEG power spectrum changes associated with awakening.

5.2 Defining awakening by consensus



5.2.1 Introduction and aims

In a review of the literature no definitions or criteria of awakening were found that were specifically developed for anaesthetised infants. Scales or criteria have been developed for children awakening from anaesthesia and some have been used in infants. No scale has been developed or applied to the study of anaesthetised neonates.

An observational tool, in which awakening (involving both provocation stimulus and the response to it) could be developed by discussion and agreement between experts. Consultant paediatric anaesthetists are experienced in assessing whether their patients are awake or not and should have important opinions about this subject. In a small pilot survey of colleagues however 2 possible obstacles to obtaining consensus were identified. First, some anaesthetists were confused about the meaning of *arousal;* they reasoned that arousal was related to the ability of the infant to maintain vital reflexes rather than any relation to conscious level. However the objective was to ask questions about conscious level and therefore instead of *arousal* the questions used the word *awakening* to direct the discussion to conscious level rather than vital reflexes. Second, the term *infant* covers a wide range of age and development and

therefore the age range of *neonate* was chosen as this age range was least well served by any existing scales.

5.2.2 Objective

The objective of this survey was to seek answers to three main questions:

- Is it possible to define awakening from anaesthesia in neonates?
- What are the observable phenomena that can be used to describe awakening from anaesthesia in neonates?
- What stimulus should be used to test rousability in sleeping neonates at the end of anaesthesia?

5.2.3 Methods

This survey was registered with the Institute of Child Health in London and did not require consideration by an ethics committee. A modified Delphi technique[287-289] employed a series of questionnaires based on the questions above. “Neonate” was defined as an infant less than 28 days old and born full term. All consultant anaesthetists were invited to participate who were employed in specialist paediatric hospitals in Great Britain and Ireland where neonates are anaesthetised. The lead clinician of the each anaesthetic department was telephoned and asked to distribute to all their colleagues, by internal email, an invitation to take part. Willing participants replied to the authors by email. All questionnaires and communications were by email. Questionnaires were piloted within a small group of colleagues before beginning this study.

Table 5-3: Awakening consensus questions

Please describe your level of agreement with the following statement: "In neonates, it is possible to describe observable phenomena that can be used to define awakening from anaesthesia"
List reasons why you think that it may not be possible to describe observable phenomena that can be used to define awakening from anaesthesia in neonates
In neonates, what observations do you consider could be useful as indicators of awakening after anaesthesia?
If a neonate looks asleep, what stimulus would you use to test rousability after anaesthesia?

The series of questionnaires were as follows. The initial questionnaire asked one specific question and several other broad open questions (see Table 5-3) that enabled a list of issues for further discussion. In the second questionnaire respondents' first answers were used to form a list of statements; minor editing was used to aid clarity. Respondents were asked to describe their agreement to these using a 5-point Likert scale[290]; they had to choose one of *strongly disagree*, *disagree*, *neither agree nor disagree*, *agree* and *strongly agree*. In the third questionnaire individuals were given a summary of the opinion of the whole group (as percentage of respondents agreeing with the various statements) and were invited to reconsider their original answers. Opinion could be recorded in free-text boxes. Questionnaires were planned until consensus was achieved or when a low response rate made further rounds impractical. Anonymity in feedback prevented undue dominance of any particular participant.

In the final summary, and analysis, the *strongly disagree* and *disagree* were grouped together as "disagreement" and *agree* and *strongly agree* were grouped together as "agreement". The percentage of respondents giving the same answer was calculated from the total number who completed the 3rd questionnaire. Consensus was defined as 80%, or more, of respondents giving the same answer.

5.2.4 Results

Out of an estimated 275 potential participants 31 (11%) responded to the first questionnaire, 30 to the second and 29 to the third.

In answer to the specific question ‘in neonates is it possible to describe observable phenomena that can be used to define awakening from anaesthesia?’ only 2 respondents changed their answer in the second round and so this question was not asked again in the third round. At the second round, 25 (83.3%) agreed that it was possible, 2 (6.7%) neither agreed nor disagreed and 3 (10.0%) disagreed. Of those who agreed, 2 (6.7%) strongly agreed. No participants strongly disagreed.

When asked why it “may not be possible to describe observable phenomena” consensus was reached on three statements: “apnoeas may occur when neonates are awake” (27 (93.1%)), “their eyes may not open” (24 (82.8%) and “awakening is a continuous process” (24 (82.8%)). More than half of participants agreed with the following statements: “airway problems can occur even if the baby appears awake”; “communication is not possible”; “there is no response to verbal stimuli”; “opiates reduce responsiveness and make assessment difficult”; “neonates normally sleep for long periods”; “we do not know the variation in awakening in neonates” and “phenomena are likely to be similar to awakening from natural sleep”.

There was unanimous agreement that crying could be a useful indicator of awakening. Consensus was reached on 5 other criteria and also that a combination of criteria must be used (see Table 5-4). There was majority agreement on another 8 criteria. Consensus was reached (more than 23 out of 29) on three interventions used to test rousability after anaesthesia: “removal of skin adhesive tape (for tracheal tube, surgical drapes or diathermy plate” (25 (86.2%)); “light touch (e.g. stroking head, tickling feet or other part, gentle shaking) (24 (82.3%))”; “pharyngeal suction” (24 (82.8%)). There was majority agreement with “manipulation of tracheal tube” (18 (62.1%)). Two respondents felt that stimuli to test rousability may be inappropriate because “if stimulation is needed the neonate isn’t awake enough” and “routine stimuli can give some information about awakening but other stimuli shouldn’t be used to test awakening”. There was no consensus about what was the most extreme

intervention appropriate to test awakening; however the majority agreed with the use of “removal of tape for tracheal tube, drapes or diathermy plate” (16(55.2%)).

Table 5-4: Agreement to criteria of awakening

Percentage agreement (out of 29, and in decreasing order of magnitude) on criteria that could be used for determining awakening from anaesthesia in neonates (SD/D – strongly disagree or disagree, NN – neither agree nor disagree, A/SA – agree or strongly agree, TT – tracheal tube). * = one respondent did not answer.

Criteria	**SD/D**	**NN**	**A/SA**
Consensus achieved (%):			
Crying	0.0	0.0	100.0
Vigorous movements	3.4	0.0	96.6
Gagging on tube/obvious attempts to spit out the ETT	6.9	0.0	93.1
Attempting to cry	0.0	6.9	93.1
Looking around	3.4	3.4	93.1
Eyes open	3.4	6.9	89.7
Must be a combination of factors	3.4	3.4	89.7*
Majority agreement (%):			
Purposeful movements	10.3	13.8	75.9
Eyes screwed up or grimacing	13.8	17.2	69
Same behaviour as was observed before the anaesthetic	3.4	24.1	69.0*
Normal movement for that baby	6.9	27.6	65.5
Different signs correspond to different levels of consciousness	3.4	31.0	65.5
Increasing amounts of eye opening	3.4	31.0	62.1*
Localisation to a stimulus	20.7	20.7	58.6
Opening mouth	17.2	31.0	51.7
No majority agreement (%):			
Sucking reflex	10.3	41.4	48.3
Movement in response to pain	20.7	31.0	48.3
Increased tone	24.1	31.0	44.8
Varied movements	17.2	41.4	41.4
Sustained/regular or ‘normal’ respiration	31.0	27.6	41.4

5.2.5 Discussion

In this sample of anaesthetists, over 80% thought that it was possible to define observable characteristics of awakening from anaesthesia in neonates. Consensus was achieved for 6 behaviours. It was considered reasonable, without seeking their approval, to simplify these 6 to 5 because crying and attempting to cry are similar. Therefore the working criteria of awakening in a neonate or young infants for this thesis the combination of at least 2 of:

- crying or attempting to cry
- vigorous limb movements
- gagging on a tracheal tube
- eyes open
- looking around

Eyes open, alone, may not be enough to define awakening and therefore looking around is an additional criterion.

The range of agreement suggests that the criteria might be ranked in importance but this should not infer any particular hierarchy of criteria. For example it may not be true that a crying neonate is any more, or less, awake than one who is not crying but whose eyes are open. However some respondents thought that awakening is a continuous process and this suggests that a scoring system might be possible. The survey focused on neonates and thus its findings may not be applicable to preterm infants (if they cannot move or cry), nor to older infants (who may respond to the spoken word).

There was less agreement about testing rousability. Of the three interventions suggested (removal adhesive tape, light touch and oral suction) only light touch seems reasonable to use repeatedly. The others could be used but only if they were necessary for clinical reasons. One respondent recommended that rousability should be tested by progressively more uncomfortable stimuli. Skin stimulation is the least unpleasant of the suggest stimuli.

The Delphi method has been used widely in anaesthesia and surgery[291-294]. The questionnaires were structured to avoid bias; the first asked open questions and the second asked for opinions about reasons for not only what characterises awakening but also why awakening might not be characterised. By this approach opinion was challenged rather than lead. Nevertheless only 2 out of 31 original respondents changed their mind. Some respondents were slow to respond to the third questionnaire and further rounds of questions were considered unlikely to change opinions and might induce sample fatigue.[295] Although some researchers have defined consensus as 51% agreement,[295] 80%[296] was used to increase confidence that the chosen descriptors of awakening would be accepted.

This survey has several limitations. Although the Delphi technique is based on the principle that the aggregate opinion of a group will provide superior judgement to individuals from that group,[292;295] existence of consensus does not mean that the correct answer has been reached.[288] Answers were not based upon consideration of evidence and it is difficult to test the validity of the results unless another standard is used. Even expert opinions on this subject are subjective and vary, and it is possible that a different sample of anaesthetists could have different opinions or that the same group could change their conclusion in the future. Amongst colleagues several would not readily distinguish between awakening as a concept of conscious level (which is difficult to define) and the return of airway reflexes (that is easy to observe and could be considered to be more relevant to safety). For some anaesthetists therefore, assessing consciousness in neonates may have a low priority. Yet opinion can change, for example there has been a major change in opinion about the need for analgesia in neonates.[297;298] Anaesthetists are not the only professional group who have expertise on this subject and other surveys could ask for opinions of recovery and intensive care staff; neurophysiologists also have a wealth of experience and have coded neonatal behavioural for EEG studies. Nevertheless, anaesthetists do observe awakening at the crucial period of anaesthesia and should have a valuable insight. Even though the sample size was small in comparison with the number of invited anaesthetists it is possible that these willing respondents are representative of their non-participating colleagues.[299] Future surveys of different anaesthetists may be justified. Further

research may be able validate the conclusions by evidence from physiological measurements such as electroencephalography.

5.2.6 Conclusions

Anaesthetists responding to this survey have agreed that awakening in neonates after anaesthesia is a combination of at least 2 of 6 behaviours and these could reasonably be reduced to 5. For the purposes of this thesis the working criteria of awakening in a neonate or infant is combination of at least 2 of:

- crying or attempting to cry
- vigorous limb movements
- gagging on a tracheal tube
- eyes open
- looking around

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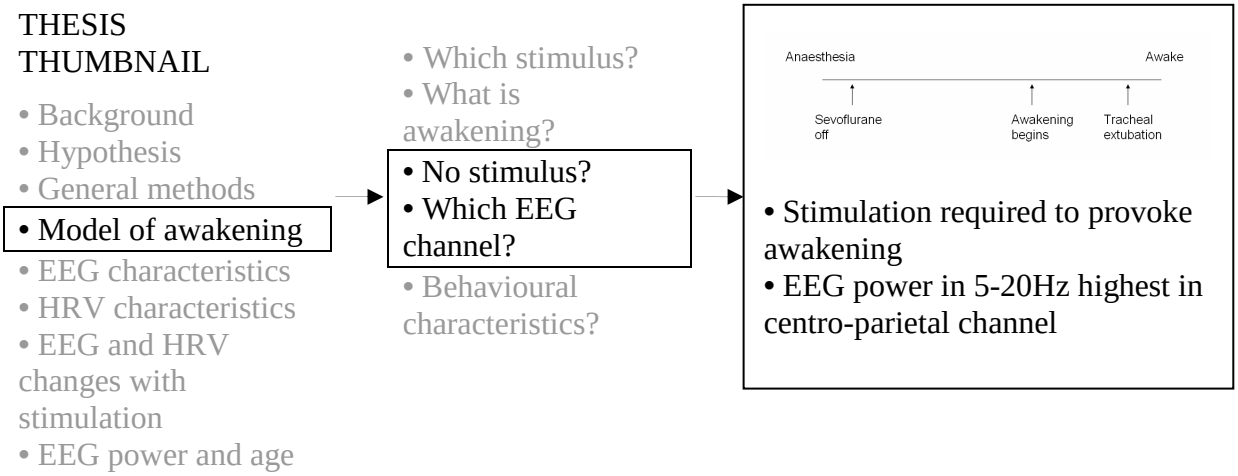
5.3 Assessment of awakening in unstimulated intubated infants



5.3.1 Introduction and aims

The change, shown in the previous section, in EEG power spectrum during awakening from anaesthesia may be more clearly characterized by processing a longer continuous signal. Events continuously recorded and timed by video starting from steady state anaesthesia until awakening, may relate to EEG changes. The safest possible model of anaesthesia is that of an intubated mechanically ventilated infant. The problem of what stimulation should be used, and when (or at what depth), remains troublesome but could be ignored for the present if the infant was left unstimulated. Awakening could then be considered to be unprovoked, or at least not provoked by any obvious external stimulus (excepting the stimuli of the tracheal tube and surgical pain).

Internal stimuli, probably from pain may be assumed to be variable and are reduced, also to a variable degree, by analgesia. As inhalational anaesthesia is washed-out, and its effects are diminishing, internal stimuli are likely to cause awakening at some stage. If, despite adequate time for anaesthesia levels to decrease, arousal has not occurred, it is standard practice to provoke arousal and awakening because of clinical time constraints.

Many EEG channels could be monitored but the application of many electrodes can be time consuming. The minimum number of electrodes should be used however there are few published data to indicate which electrodes are most useful. The frontal channels are used for commercial LOC monitors because the forehead usually is accessible and hairless. Nevertheless the frontal channels may often be contaminated by EMG. The signals over the scalp may be different and should be investigated.

5.3.2 Objectives

- To further investigate the characteristics of EEG changes during awakening from anaesthesia
- To determine which EEG channels may be most useful to detect changes during awakening

5.3.3 Methods

5.3.3.1 Subjects

Anaesthetised infants were studied after surgery was complete.

5.3.3.2 Anaesthesia

Anaesthesia was induced by sevoflurane and maintained by either sevoflurane or isoflurane. All infants were mechanically ventilated via a tracheal tube. Anaesthesia management was not altered by this study. After surgery had been completed anaesthesia was maintained while dressings were applied. During this steady state, in which the infants were undisturbed, EEG and ECG recordings were taken for at least one minute. Anaesthesia administration then stopped and fresh gas flows were increased to at least 8 litres per minute. Mechanical ventilation was unchanged. Observations were made and recordings taken during the washout of inhalational anaesthesia until a predefined time or event.

5.3.3.3 Study monitoring

The Grass-Telefactor “AURA 10-20” was used to monitor EEG, EMG and ECG (study monitoring). Electrodes were applied before surgery and included the

following sites: midline central (Cz), midline frontal (Fz), midline occipital (Oz), over the temporal region above the left ear (T7), either side of the midline between the central and parietal sites (CP3 and CP4), an over the right masseter for EMG.

5.3.3.4 Recordings

When surgery was completed the study monitoring was connected to the recording devices and, after at least one minute recording, delivery of anaesthetic vapour was stopped. A video recorded the events during awakening. At the end of surgery EEG monitoring was connected and the anaesthesia was turned off. Infants were allowed to awaken undisturbed for at least 5 minutes until the anaesthetist considered that the concentration of end-tidal anaesthetic was compatible with awakening; stimulation at that stage included suction of the pharynx and removal of adhesive tapes from the face.

5.3.3.5 Signal processing and analysis

All signals were visually inspected and epochs were identified that had appreciable interference or non-EEG signals as defined in section 4.4.3.1. These epochs were excluded from further analysis. Data files were imported into MATLAB software and power within single frequency bands were estimated for each epoch using the Welch method (epoch = 6 seconds, Hanning window, window length 1 second, overlap 0.5).). A sequence of data (lasting several minutes) representing the progression of EEG from anaesthesia until awakening was processed to create a 3 dimensional plot of power spectrum against time (x, y and z axes representing frequency, power and time respectively). The plot of each of the 6 channels was observed for obvious characteristics. Data from each plot representing anaesthesia were used to describe and compare the 6 EEG channels in terms of:

- Changes in power spectrum during awakening
- Mean power in frequency range of 5-20 Hz during anaesthesia
- Epochs with EMG interference were identified by
- visual identification.
- power more than 50 μV^2 in frequency band 30 to 45Hz

5.3.4 Results

5.3.4.1 Description of infants

10 infants were studied and their demographic and anaesthesia details are presented in Table 5-5. There was an error with both video and EEG recording of infant 1. In the following tables data are presented in order of increasing infant age. In 5 infants awakening was spontaneous and occurred within 5 minutes after anaesthesia had been turned off. In 4 infants first movement began 5 minutes or more after anaesthesia had been turned off and in these infants awakening was provoked by pharyngeal suction.

Table 5-5: Demographic details of unstimulated anaesthetised infants

ID	PMA	gestation	wt	anaesthesia	operation	analgesia
8	44	40	4	Sevoflurane	Pyloromyotomy	Fentanyl
9	46	41	5.9	Sevoflurane	Duhamel	Fentanyl & caudal
6	50	38	4.6	Isoflurane	Cleft lip repair	Fentanyl
5	51	38	4.6	Isoflurane	Cleft lip repair	Fentanyl
10	52	40	4.6	Sevoflurane	Pyloromyotomy	Fentanyl
7	56	42	5.9	Sevoflurane	Anoplasty	Caudal LA
4	61	40	7.4	Isoflurane	Excision skin lesion	Fentanyl
3	69	40	9.8	Sevoflurane	Pancreatectomy	Morphine
2	90	40	12.7	Sevoflurane	Cleft lip repair	Fentanyl

5.3.4.2 Changes in power spectrum during awakening

The majority of the power of the EEG lies within the frequencies less than 5 Hz. On visual inspection of the time progression of power spectra changes, infants could be separated into 2 groups according to the spectra during anaesthesia. Infants either had

or did not have appreciable power in frequency bands higher than 4 Hz. In those who had appreciable power frequencies over 4 Hz there tended to be 3 obvious periods in the progression of the power spectrum. The 3 periods were:

- During anaesthesia there was a prominent oscillation at approximately 8-12 Hz which decreased as sevoflurane washed out.
- Before the first movement, that usually preceded awakening, this oscillation disappeared.
- With movement and awakening there was a general increase in power across all frequency bands but especially in the frequency bands less than 4 Hz.

A typical power spectrum progression is presented in Figure 5-7. There were 4 infants with this pattern and all were over 52 weeks PMA.

In infants who did not have appreciable power in frequencies higher than 4 Hz, the power in low frequencies increased during movement. Infants in this group were younger than 52 weeks PMA and a typical power spectrum progression is presented in Figure 5-8. There was one exception in this group who was 62 weeks old (PMA); this infant had an oscillation pattern of low power.

Figure 5-7: Typical EEG power spectrum progression in an infant older than 52 weeks PMA

Power units are μV^2.

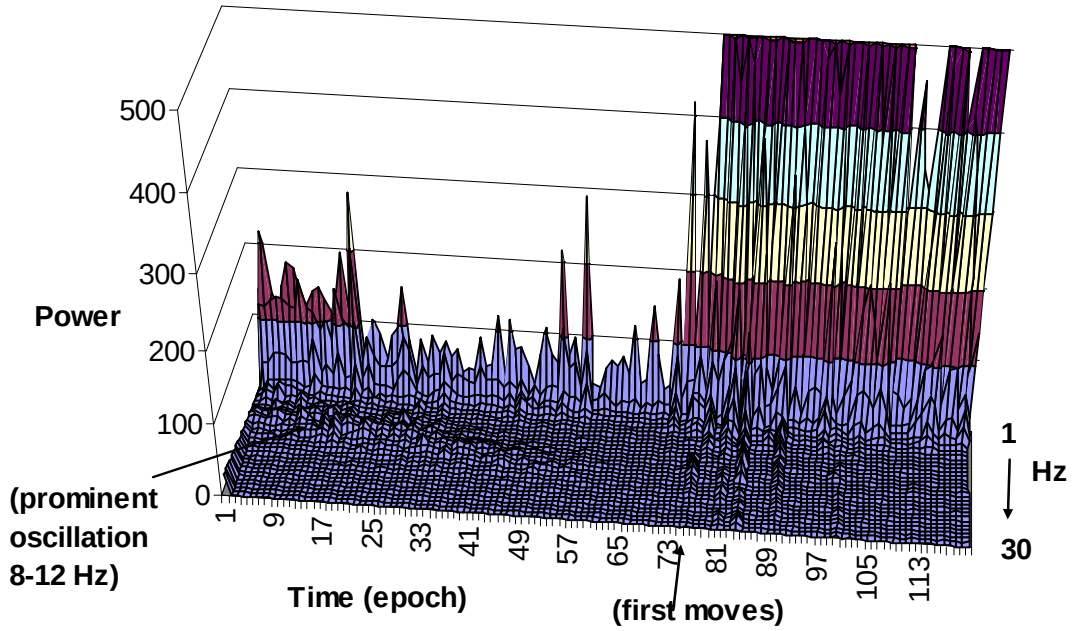
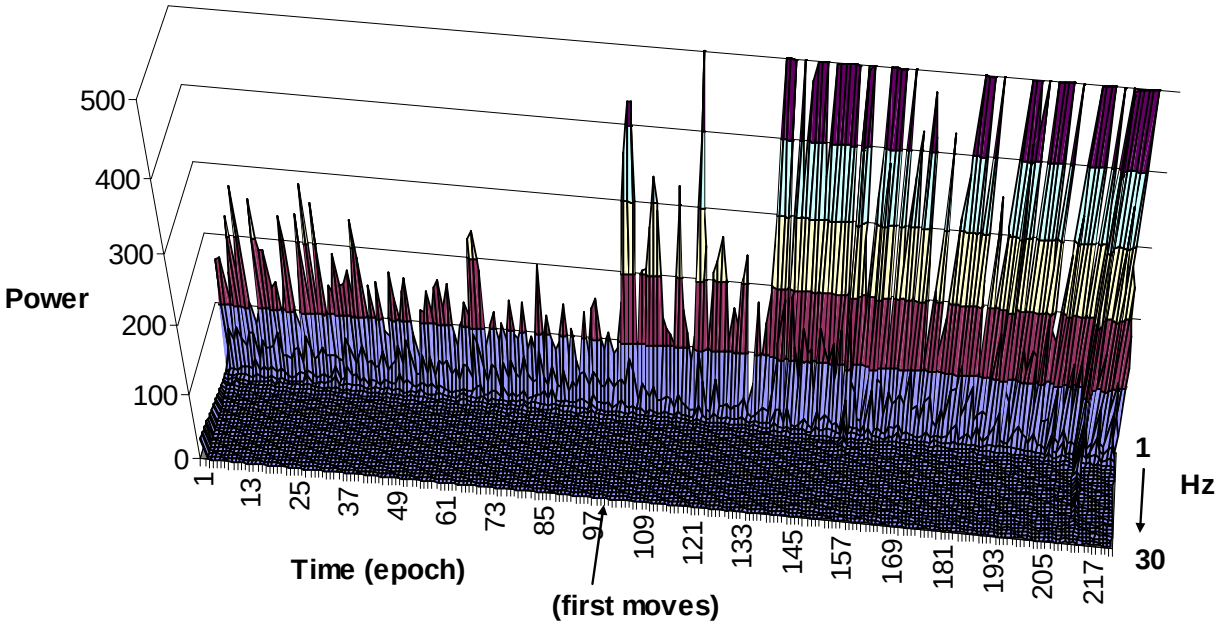


Figure 5-8: Typical EEG power spectrum progression in an infant younger than 52 weeks PMA



5.3.4.3 Assessment of EEG channels

5.3.4.3.1 Signal size

Summated power within the frequency band 5 to 20 Hz was used to assess the size of signal in each channel. Table 5-6 shows the mean power over 10 epochs (one minute) during steady state undisturbed anaesthesia after surgery had been completed. Mean power was highest in the frontal channel and lowest in the occipital.

5.3.4.3.2 EMG interference

EMG interference was uncommon and intermittent during anaesthesia. Table 5-7 shows that there was wide variation in the number of excluded epochs. Patient ID 7 had the most EMG interference and this was found in the frontal channel. After calculation of power spectra few epochs were identified with power greater than 50 μV^2 in frequency band 30 to 45Hz. Almost all of these matched the visual identification of EMG interference.

Table 5-6: Mean EEG band power (5-20Hz) during one minute of anaesthesia

Infants are in order of increasing age. x = channel not recorded. Power units are μV^2.

Infants	**EEG channel**					
ID	**Cz**	**Oz**	**Fz**	**CP3**	**CP4**	**T7**
8	29.3	8.4	6.8	15.6	14.7	17
9	14.7	6.2	18.8	12.9	10.9	9.9
6	55.6	82	10.4	50	41.1	34.4
5	351	50.9	169.9	103.4	56.9	39.4
10	459	34.3	90	158	129.7	54.2
7	108.5	40.4	108	135.9	127	61
4	79.9	45.9	61.6	118.4	114	x
3	156.5	x	60.9	172	139	x
2	1064	367.8	1915	1048	918	664
mean	257.6	79.5	271.3	201.6	172.4	110.0

Table 5-7: Visual identification of EMG interference according to EEG channel

Number of epochs during anaesthesia (before first movement) with EMG interference identified by visual inspection of the recording

Infants		**EEG channel**					
ID	**Total number of epochs**	**Cz**	**Oz**	**Fz**	**CP3**	**CP4**	**T7**
8	**127**	1	1	1	1	1	1
9	**100**			9			
6	**63**		8			8	
5	**10**						
10	**76**	4	3	3	4	4	
7	**79**	5		28	4		
4	**80**						
3	**100**		x			4	x
2	**129**	8	7	7	9	9	9
total		18	19	48	18	26	10

Blank cells = 0%. x = channel not recorded.

Table 5-8: High power high frequency interference according to EEG channel

Number of epochs during anaesthesia (before first movement) with EMG interference defined by summated power >50 μV^2 within frequency band 30-45Hz.

Infants		**EEG channel**					
ID	**Total number of epochs**	**Cz**	**Oz**	**Fz**	**CP3**	**CP4**	**T7**
8	**127**						
9	**100**			1			
6	**63**						
5	**10**						
10	**76**	1		1	1		
7	**79**			1			
4	**80**						
3	**100**		x			1	x
2	**129**	8	4	4	12	4	6
Total		9	4	7	13	5	6

Blank cells = 0%. x = channel not recorded.

5.3.5 Discussion

These data suggest that EEG characteristics of awakening of infants depend upon their age. In this small number of infants, those older than 52 weeks PMA had appreciable power within the frequency band 5-20Hz during anaesthesia and it decreased as sevoflurane and isoflurane levels decreased. There are insufficient data to compare, in statistical terms, the recordings from all channels. Within the limitations of this pilot however, some channels provided better data than others. Before infants first moved, interference from EMG activity was uncommon and was least in the occipital and temporal channels. Nevertheless, in occipital and temporal channels the power within the frequency band 5-20 Hz was least. If the EEG signal in

this frequency band is important, these two channels did not add more information than the other channels.

Other authors have used central and frontal EEG channels possibly because these are more convenient than others (occipital electrodes are awkward for patients lying supine; hair hinders the adhesion of parietal electrodes). No data has been published to support the preference of central and frontal channels over other channels in terms of signal properties.

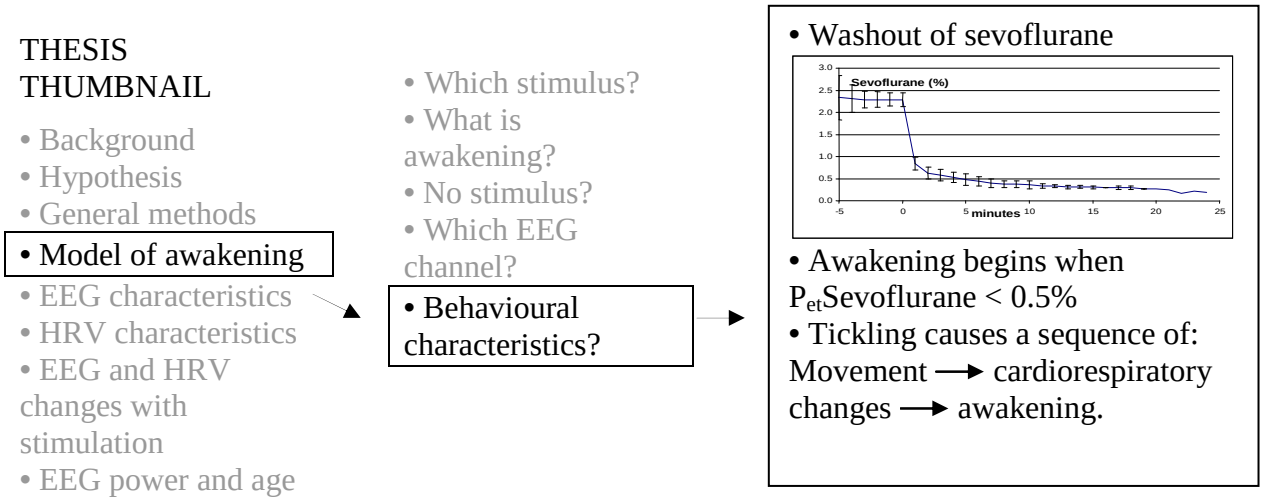
Unstimulated infants may take a long time to awaken spontaneously; too long to be reasonable in the clinical scenario. Neither the stimuli of surgical pain nor the presence of a tracheal tube reliably stimulate awakening. Suctioning the pharynx or moving the tracheal tube caused coughing and awakening and this may be because tracheal tube is not stimulating until it is moved within the trachea.

Rather than use painful stimuli, it seems reasonable to stimulate the infants with non-painful stimuli to test whether or not they can be roused. For this reason this pilot was curtailed in favour of a developing a model of stimulation in intubated infants.

5.3.6 Conclusions

- High power and a prominent frequency within the range of 5-20Hz is a feature of the EEG in anaesthetised infants older than 52 w PMA.
    - One minute before movement or awakening power within 5-20Hz decreases.
        - Younger infants do not have this feature.
        - It is most obvious in frontal, central and centro-parietal channels.
- Unstimulated infants may take too long to awaken spontaneously
    - A stimulus should be applied to intubated infants to test the sequence of behavioural changes that may be predicted by changes in EEG and HRV.

5.4 Assessment of awakening in stimulated intubated infants



5.4.1 Introduction and aims

When anaesthesia ceases an infant may not wake unless stimulated. What stimulus should be used? A stimulus causes arousal or awakening when it breaks through the sedative effect of the anaesthetic. Since the sedative effect is dependent upon anaesthesia dose (or concentration at the effect site), arousal from a defined stimulus should occur at a threshold dose. The stimulus will need to be repeated in order to identify the threshold.

A painful stimulus cannot be justified during recovery from anaesthesia because it could cause unnecessary distress. Even if a painful stimulus was justified, such as suction of the pharynx, it could only be applied once, and only if clinically necessary. Furthermore, the ideal stimulus should cause a gradual awakening and not a sudden and potentially distressing return to full consciousness.

Which painless stimulus should be used? In section 5.1 noise was not found to be a sufficiently reliable stimulus of arousal during anaesthesia, but gentle stimulation of the mouth or nose caused awakening infants who did not rouse to noise. In the survey of opinions over 80% of the sample of anaesthetists considered that skin stimulation was a practical stimulus to use to test whether an infant was rousable. This section

determines whether skin stimulation is useful to provoke gradual arousal and awakening from anaesthesia.

5.4.2 Objectives

- To determine the reliability of skin stimulation in causing gradual arousal or awakening
- To observe the timing of behavioural changes during awakening provoked by skin stimulation

5.4.3 Methods

5.4.3.1 Subjects

Infants undergoing anaesthesia for painful surgery were recruited according to the criteria described in section 4.1.

5.4.3.2 Anaesthesia

No premedication, either sedative or antimuscarinic, was used. Anaesthesia was both induced and maintained by sevoflurane in oxygenated air (inspired oxygen concentration 40-50%). Routine monitoring included pulse oximetry, ECG, respiratory gas analysis and non-invasive blood pressure and was applied as soon as possible. In intravenous cannula was inserted in a hand or a foot after anaesthesia had been induced. All infants had a tracheal tube inserted after muscle relaxation with atracurium (0.5-0.8 mg/kg). Ventilation thereafter was controlled to maintain end-tidal concentration between 3.5 and 5.5 kPa. The inspired concentration of sevoflurane was adjusted to maintain end-tidal concentration considered to be compatible with an adequate depth of anaesthesia according to the clinical judgment of the anaesthetist. Analgesia, including opioids, were appropriate to the surgery and were administered after induction and after initial EEG and HRV recordings were made. After surgery the inspired concentration of sevoflurane remained unchanged from that used during surgery for at least one minute. Sevoflurane administration was then stopped and the flow of fresh gas was increased to at least 8 l/min. Mechanical

ventilation was unchanged. Observations were made and recordings taken during the washout of sevoflurane until a predefined time or event.

5.4.3.3 Painless skin stimulation

From ceasing sevoflurane until awakening, awakening was provoked by two types of stimuli. The sole of the foot was continuously stroked with a 20g Abbocath intravenous catheter. Stroking the foot was considered to be a “tickle” and irritating but not painful or likely to cause distress. If the infant had had a caudal extradural local anaesthetic block, a hand was tickled instead. In addition, once each minute, a standard blood pressure measurement caused stimulation by its cuff inflation. The cuff, placed on the arm, is automatically inflated to a maximum pressure of approximately100mmHg. Each inflation lasts approximately 30 to 40 seconds. Ambient noise was unrestricted normal for an operating theatre environment (no load noises).

5.4.3.4 Observations

Video recording provided a visual record and timing of all movements including change in respiratory pattern. Times of the following events were recorded:

- Sevoflurane turned off (SO)
- First movement of a limb (M1)
- Awakening began (AB)
- Full awakening (AW)
- Trachea extubated

Awakening was defined as least 2 of the criteria described in section 5.2.6. Beginning of awakening was defined as one of the criteria described in section 5.2.6. The end-tidal sevoflurane concentration (P_{et}Sevoflurane) was recorded at least every minute between 5 minutes before SO until extubation of the trachea. EEG and ECG were recorded using the Grass Telefactor system described in section 4.3.4 and data from these are presented in the following chapters. The timings of the events are presented in decimal minutes (e.g. 6.2 decimal minutes = 6 minutes and 2 epochs (1 epochs = 6 seconds)).

5.4.4 Results

5.4.4.1 Demographic details

Parents of 35 infants were approached and twenty consented to have their infants studied. Their details are presented in Table 5-9. Age ranged from 39 to 77 weeks PMA. Only one infant had been born preterm (32 weeks gestation).

5.4.4.2 Reliability of skin stimulation

All infants except one moved the same limb that was being tickled before any other movement or a change in heart rate. In the exceptional infant there was a generalized motor response that led to beginning of awakening within the following epoch. From visual observations made at the time of the recording, blood pressure cuff inflation did not appear to have a time relationship to awakening.

Table 5-9: Demographic details of infants arranged in age order

PMA (gestation)	**ID**	**Wt (Kg)**	**G**	**Operation**	**Analgesia**
39 (38)	28	2.52	F	closure of gastroschisis	Morphine
43 (32)	18	3.9	M	lap inguinal hernia repair	Fentanyl
45 (40)	25	3.9	M	lap pyloromyotomy	Fentanyl
46 (40)	22	4.8	F	excision of sacral tumour	Fentanyl & morphine
47 (40)	27	4.8	M	lap pyloromyotomy	Fentanyl
50 (40)	26	4	M	lap inguinal hernia repair	Fentanyl
51 (40)	20	5.2	F	cleft lip repair	Fentanyl & morphine
51 (40)	24	4.6	M	cleft lip repair	Fentanyl
51 (40)	23	6.2	F	fashioning of rectum	Morphine & caudal
52 (40)	14	4.5	F	cleft lip repair	Morphine
53 (38)	19	5.7	F	cleft lip repair	Fentanyl
53 (38)	31	5.3	M	cleft lip repair	Fentanyl
53 (40)	29	6.56	M	cleft lip repair	Fentanyl
63 (40)	11	7	M	cleft palate repair	Fentanyl
65 (36)	12	7.6	M	closure of colostomy	Morphine
68 (40)	21	8.4	M	closure of colostomy	Fentanyl & morphine
69 (40)	30	7.3	M	cleft palate repair	Fentanyl
73 (40)	32	8	M	renal pyeloplasty	Fentanyl
77 (40)	13	7.8	M	closure of ileostomy	Morphine & caudal
77 (40)	15	5.4	F	lens capsulotomy	Fentanyl

PMA and gestation are in weeks. G = gender. All opioids were administered intravenously.

5.4.4.3 Summary of sequence of events during recovery

The times of events during recovery are represented in Table 5-10. A video was not recorded from one infant and written recording of times was made contemporaneously. There was a wide variation in awakening times however all infants continued to remain asleep after SO for at least 5 minutes. Movement was always the first event. Four infants moved almost immediately on being tickled but then took 7.5, 8.2, 10 and 14.5 minutes to the beginning of awakening. None of the infants had a rapid transition between M1 and AW, but 6 infants took less than one minute between AB and AW. The shortest time between SO and AW was 62 epochs (6.2 decimal minutes), and the longest was 363 epochs. Figure 5-9 shows the variation in the length of time taken to reach AB and AW criteria and that these times may have been inversely related to age in infants younger than 55 w PMA (i.e. the youngest infants took the longest to begin awakening).

5.4.4.4 Washout of sevoflurane

The P_{et}Sevoflurane during the events during recovery are presented in Table 5-11. During the last stages of surgery until SO the mean P_{et}Sevoflurane was 2.3% (range 1.5 to 3.5%). Figure 5-10 shows the decrease of sevoflurane during washout. By 5 minutes after SO the mean P_{et}Sevoflurane was 0.5%. By 7 minutes the mean + SD P_{et}Sevoflurane was 0.5%. At AB mean P_{et}Sevoflurane was 0.3% (range 0.1 to 0.6%).

5.4.5 Discussion

Tickling the feet (or hands) of an infant in whom sevoflurane is being washed out appears to cause a similar sequence of arousal behaviours to that described in natural sleep studies. [242] This sequence is almost always gradual so that there is a motor response to tickling before any other behavioural, cardiac or respiratory change. There was always at least one minute between the first movement and the beginning of awakening. The washout of sevoflurane was measured and by 7 minutes after sevoflurane had been turned off the mean +SD P_{et}Sevoflurane was 0.5%. The P_{et}Sevoflurane was greater than 0.5% at awakening in one infant only. The EEG and HRV characteristics under these conditions may now be investigated.

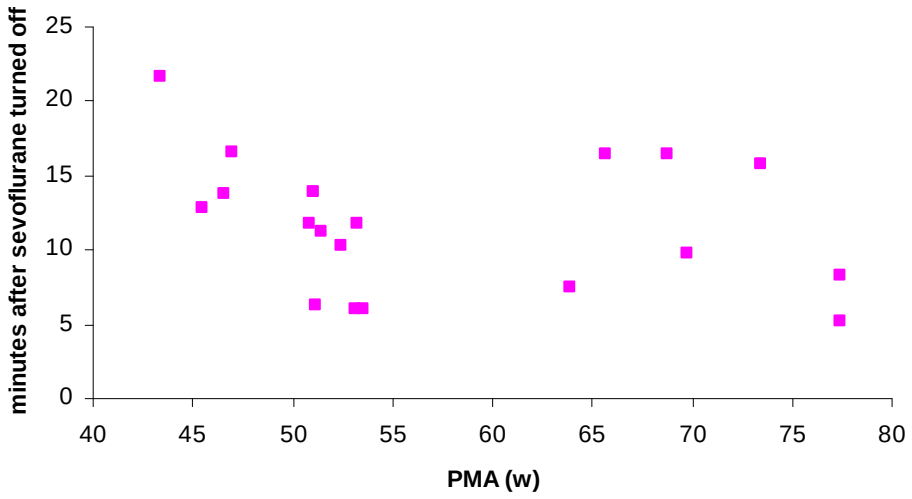
Table 5-10: Event times after turning sevoflurane off.

PMA (weeks)	**Movement began**	**Awakening began**	**Awakening criteria met**	**Trachea extubated**
39	20.4	29.2	36.3	35.2
43	16.6	21.6	29.4	27.2
45	6.0	12.8	15.4	15.3
46	6.1	13.7	29.7	32.9
47	11.2	16.6	18.2	17.4
50	1.9	11.7	19.3	17.3
51	0.0	13.9	14.5	18.5
51	3.8	6.3	8.5	9.4
51	10.0	11.2	11.6	12.9
52	0.3	10.3	10.9	12.8
53	5.5	6.0	6.2	8.4
53	0.4	11.8	16.8	17.1
53	4.0	6.0	6.6	7.3
63	X	7.5	8.3	10.0
65	11.8	16.4	16.4	16.9
68	11.8	16.4	19.1	19.3
69	4.6	9.7	11.4	11.2
73	11.9	15.8	15.8	16.3
77	2.3	5.2	15.0	X
77	0.0	8.2	8.8	8.9
mean	6.8	12.5	15.9	16.5
median	5.5	11.8	15.2	16.3
SD	5.9	5.9	8.0	7.8

All times are in decimal minutes. X = missing data.

Figure 5-9: Relationship between age and timing of events during awakening from anaesthesia

A: Scatter plot of time of beginning of awakening versus age



B: Cumulative bar chart of time of events

Length of each bar represents time of awakening after sevoflurane was turned off

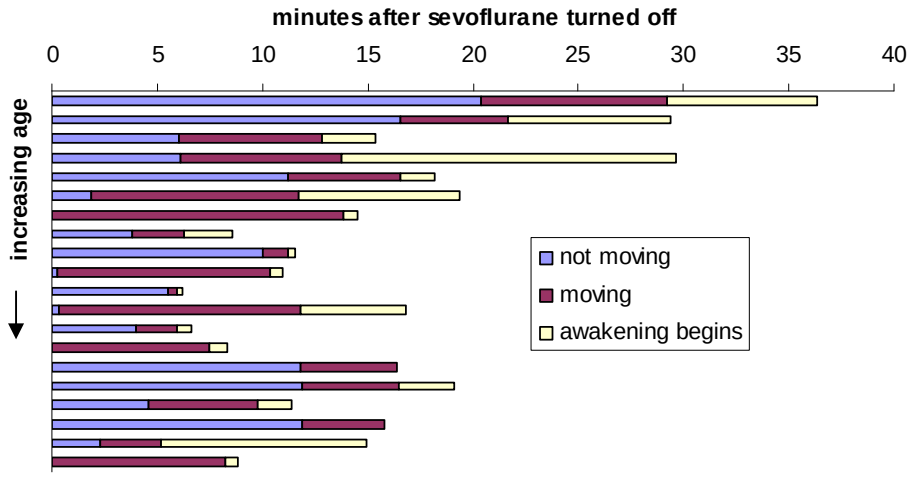
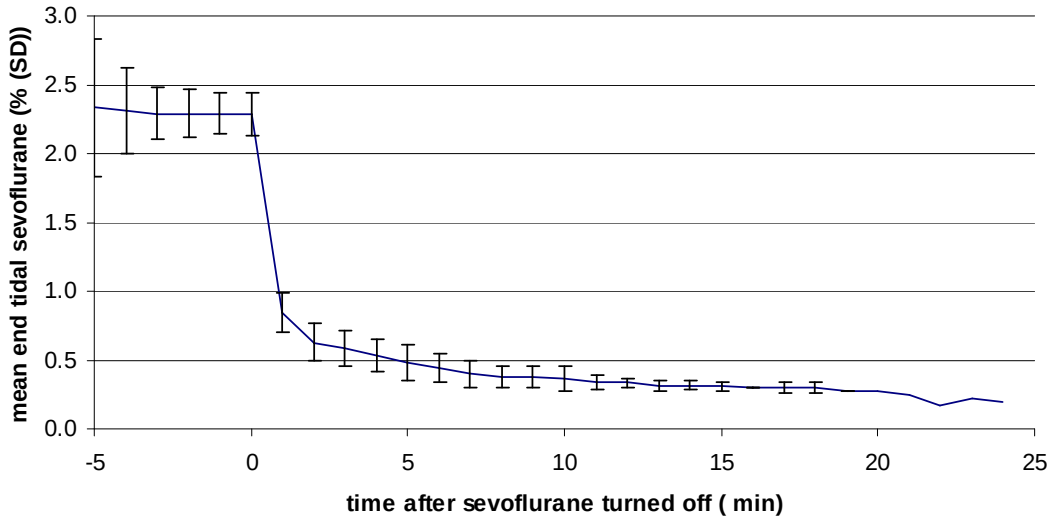


Table 5-11: End-tidal concentrations of sevoflurane

Pt ID	**PMA (weeks)**	**Before sevoflurane turned off**	**Before awakening began**
28	39	1.9	0.25
18	43	3	0.15
25	45	2.15	0.25
22	46	2	0.1
27	47	1.5	0.2
26	50	2.2	0.4
20	51	2.05	0.2
24	51	2	0.2
23	51	2.3	0.25
14	52	2.1	0.35
19	53	3.1	0.45
31	53	1.95	0.15
29	53	1.8	0.25
11	63	2.95	0.6
12	65	2.8	0.2
21	68	1.7	0.3
30	69	2.3	0.25
32	73	2.55	0.2
13	77	3.5	0.3
15	77	2.1	0.2
	mean	**2.3**	**0.3**
	median	**2.1**	**0.3**
	SD	**0.5**	**0.1**
	max	**3.5**	**0.6**
	min	**1.5**	**0.1**

Figure 5-10: Washout of sevoflurane

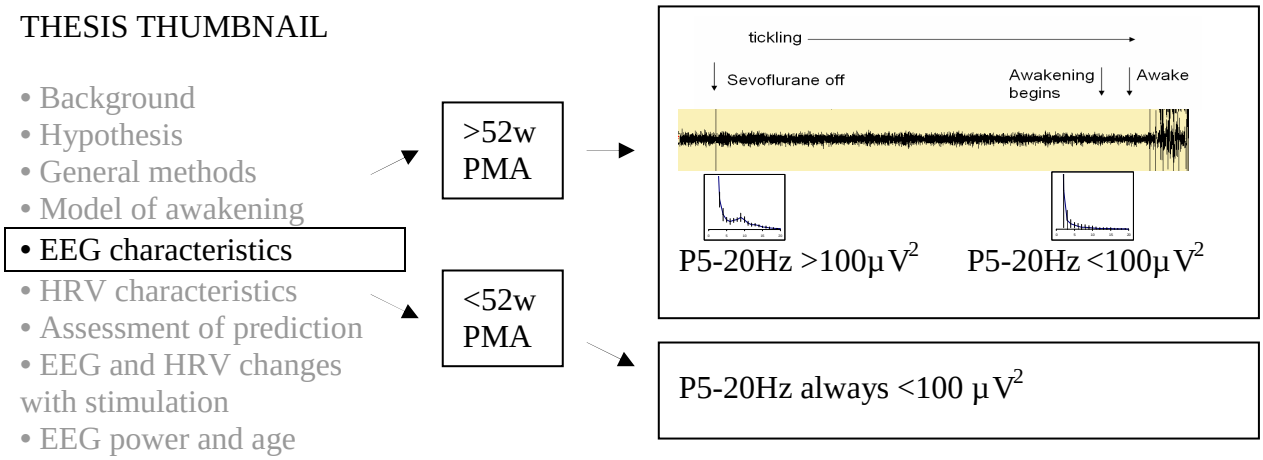
Mean (of all infants) end tidal sevoflurane before and after sevoflurane was turned off. Vertical bars represent SD.



5.4.6 Conclusions

- In an intubated infant, in which sevoflurane is being washed out, tickling the feet produces a progression of responses, beginning with movement, then cardiorespiratory changes and culminating in awakening.
- Awakening did not begin until P_{et}Sevoflurane was approximately 0.5%

6 Characterisation of EEG changes



6.1 Introduction and aims

Stimulation to provoke arousal and awakening can be achieved by tickling the feet or hands to produce a steady increase in behavioural response culminating in arousal and awakening. Behavioural criteria of awakening, established by a consensus method in section 5.1, could be used identify the times at which both awakening begins and is achieved. The characteristics and changes in EEG and ECG HRV during awakening can therefore be studied.

In the previous chapter, in section 5.3, a characteristic of the EEG during awakening was identified, in which infants over 52 weeks PMA had appreciable power in the frequency range of 5-20 Hz during anaesthesia and that this power diminished to a low level at least one minute before arousal and awakening. In some of these infants there was a prominent frequency between 5 and 20 Hz during anaesthesia (a frequency that had more power in it than other adjacent frequencies). The main aims of this section are to confirm that these findings, described previously in unstimulated infants, are present also in infants in whom awakening was provoked by skin stimulation.

These findings, if consistent, may be associated with several factors including the combination of anaesthesia drugs themselves and the effects of stimulation of the nervous system by surgery. EEG data in anaesthetised infants before surgery and analgesia could be used for comparison. This can be readily achieved after induction of anaesthesia and before surgery because at that time, apart from tracheal intubation and venepuncture, there is no apparent painful stimulation.

Once changes in the EEG, associated or coinciding with awakening, have occurred can they be reversed by re-establishing anaesthesia? If so, such a finding would support the association between the EEG change and level of anaesthesia rather than the explanation that EEG change is related to purely time or circumstance. This was reviewed by the ethical committee who decided that re-establishing anaesthesia for 10 minutes did not add risk. It was acknowledged that re-establishing anaesthesia was occasionally necessary for clinical reasons.

This chapter investigates EEG changes and Chapter 7 reports the HRV changes. Except for details of signal processing, the methods in both chapters are the same.

6.2 Objectives

- To determine EEG characteristics during awakening from anaesthesia after surgery.
- To compare EEG characteristics during awakening after surgery with those during anaesthesia before surgery.
- To determine if EEG characteristics of awakening can be reversed when anaesthesia is re-established.

6.3 Methods

6.3.1 Subjects

The subjects were those described in section 5.4.4.1.

6.3.2 Anaesthesia

Anaesthesia methods are presented in section 5.4.3.2. In addition, and towards the end of recruitment of this study, parents were asked to consent to allow a minor change in anaesthesia management. This change was that as soon as awakening began, the sevoflurane would be restored to the same level used during surgery for a period of 10 minutes in order to observe if the EEG characteristics of awakening could be reversed.

6.3.3 Recordings before surgery

Study monitoring was applied after tracheal intubation when the cardiovascular and respiratory states were considered to be stable and not requiring intervention. Recording from the study monitoring began when the infant had been anaesthetised (P_{et}Sevoflurane > 2%) for at least 10 minutes. Two minutes of recordings were at least 3 minutes after tracheal intubation. The respiratory rate and P_{et}Sevoflurane were recorded.

6.3.4 Recordings after surgery

The process described in section 5.4.3.3 was followed. After surgery had been completed, and before anaesthesia was reduced, study monitoring recordings were restarted. Study monitoring continued until both the tracheal tube was removed and for at least one minute after the infant had met the criteria for being awake. Using these times defined in the previous chapter, the following sequences of digital EEG and ECG data were created for further processing.

- 60 seconds before sevoflurane turned off (bSO)
- 60 seconds before awakening began (bAB)
- From sevoflurane turned off (SO) until awakening began (AB)

If consent was given, as awakening began, sevoflurane was re-established by maintaining expired concentration of 2% for 10 minutes. Thereafter sevoflurane was discontinued and anaesthesia was managed according to clinical need.

6.3.5 Study monitoring and recordings

The Grass-Telefactor "AURA 10-20" was used to monitor EEG (study monitoring – see section 4.3.4). Four channels were recorded from the following electrodes: 2 frontal (F3 and F4) and 2 electrodes between the central and parietal sites (CP3 and CP4). These data were visually inspected within the display facility of the Grass Telefactor software for obvious interference and artefacts. One frontal and one centro-parietal channel were chosen that had the least interference or lowest impedance. Signal processing has been described in section 4.4.

6.3.6 EEG - visual inspection

Plots of the signal in each epoch were created. Epochs were excluded if, on visual inspection, they had appreciable interference or non-EEG signals as defined in section 4.4.3.1. The number of excluded epochs (and the reason for exclusion) was recorded. The visual appearance of each signal was described in terms of the presence of the following oscillatory and other potentially important features.

6.3.6.1 Oscillatory features

Oscillations were described by simple estimates of amplitude, frequency, continuity and duration (adapted from those used by Zampi and colleagues[126]).

- Amplitude
- LV (low-voltage) <50 µV
- HV (high-voltage) >50 µV
- Frequency
- Slow <3Hz
- Fast > 7Hz
- Continuity
- Signals were continuous if they lasted at least one epoch
- Duration
- Number of epochs

6.3.6.2 Other potentially important features

EEG transients and non-EEG signals were noted as described in section 4.4.3.1. Epochs with these features were excluded from signal processing and analysis.

6.3.6.3 Signal processing and analysis

The remaining data were processed by a Matlab program to create a matrix of powers within single frequency bands. Power was estimated for each epoch using the Welch method (epoch = 6 seconds, Hanning window, window length 1 second, overlap 0.5).

6.3.6.4 Frequency resolution

Initially, the power spectrum was calculated for epochs of 6 seconds using a window length of one second. This enabled a visual display of the progression of spectra every 6 seconds and a frequency resolution within each spectrum of one Hz. In such a display frequencies of less than 0.5 Hz are represented in the zero Hz band and may be mistaken for a direct current component. In order to inspect the power in the low frequencies the power spectrum was estimated for one minute (rather than 6 seconds) using a 5 second window enabling a frequency resolution of 0.2 Hz; any power in the zero Hz band (the direct component) would therefore represent power in frequencies less than 0.1Hz.

To summarise, two estimates of power density spectrum were used.

1. Frequency resolution one Hz ($F_{res}1Hz$)

- range 1-70 Hz
- epoch length 6 seconds
- window length one second

2. Frequency resolution 0.2 Hz ($F_{res}0.2$ Hz)

- range 1-20 Hz
- period length 60 seconds
- window length 5 seconds

6.3.6.5 Power spectrum array

Three dimensional plots (arrays) of power spectrum density (F_{res}1 Hz) against time with axes representing frequency, power density and time were created for visual inspection.

6.3.6.6 Frequency bands

Data (F_{res}1Hz) were further analysed to calculate total power within the following frequency bands: 1-28, 1, 2-4, 5-8, 9-12, 13-16, 17-20, 21-24, 25-28 and 5-20Hz (P5-20Hz). The mean powers for a specified 10 epoch period were calculated. The mean, median and SD of the mean band power for all infants were then calculated. The mean band powers at bSO were compared with that at bAB. Graphs were plotted to show the change within these power bands over time. Further comparisons were made between band powers at specific times chosen after consideration of change in band power over time.

6.3.6.7 Prominent frequencies

The following were calculated using F_{res}1 Hz for each epoch from the beginning of bSO until AB.

- prominent frequency (defined as the single frequency band with the highest power within a specified frequency range)
- power of prominent frequency
- background power (defined as the mean power within the surrounding frequencies (not including the power of the prominent frequency)).
- ratio of the prominent frequency power to the background power

These variables were calculated for each infant to represent the EEG characteristics during bSO and during the period SO until AB to show the progression of the prominent frequency.

6.3.7 Data analysis and statistical methods

Mean band power during bSO in frontal and centro-parietal channels were compared first by estimating the difference in total power (frequency range 1-28Hz) and then by

the difference between smaller constituent band powers. The differences between mean band power at (1) bSO and bAB, and (2) before surgery and bSO were compared similarly. Histograms and Normal plots were examined to check that data was normally distributed and to check for outliers. Parametric statistical tests were used if the mean, median and SD were similar. Data was log10 transformed if necessary. Differences between means were supported by 95% confidence intervals.

Where differences between bSO and bAB were appreciable for any variable, the variable was calculated for each epoch from bSO until end of recording and plotted to identify any trend of change over the time. Initially descriptive statistics and plots of all patients were grouped together. If there were wide ranges or obvious differences, groups of infants were identified and described separately. Logistic regression was used on selected variables to test and measure the association between variables. Regression (with confidence intervals) was used to measure the trend over time. The time taken to achieve a chosen critical level of a variable was estimated.

In previous work in this project, the power within the frequency band 5-20Hz (P5-20Hz) was appreciable in infants older than 52 weeks PMA and this power decreased as sevoflurane was washed out and before awakening began. If this feature is robust enough to be considered as a warning sign of impending awakening, the P5-20Hz would need to change by at least 1.5 SDs from the baseline mean value. In order to determine this change, 10 infants would need to be studied to have a 90% power of determining the difference at 5% level of significance if such a change truly occurs. The estimation of the number of infants needed to find a change of 1 or 2 SDs (with the same power and significance) is 22 and 6 respectively.

6.4 Results

6.4.1 Recruitment

Twenty infants were recruited to have awakening studied; 10 were older and 10 were younger than 52 weeks PMA. Parents from 3 infants were approached and asked to consider allowing a minor change in anaesthesia management. All refused, but agreed

to consent for the EEG characteristics to be recorded during awakening. These infants are included in the 20 described above.

6.4.2 Visual appearance of unprocessed signals

6.4.2.1 General comments

In each infant, the amplitudes of the pre-awakening signals were obviously higher in the centro-parietal channels than in the frontal channels and therefore the visual characteristics of only the centro-parietal signals are described. This is supported by the comparisons of signal power (shown below in section 6.4.3.2). The signal from each patient usually had two easily distinguishable periods:

- almost artefact free EEG activity before awakening began, and
- artefact ridden activity associated with movement during awakening.

The change from one period to the other was often abrupt and related to the beginning of awakening. The identification of the beginning of awakening was dependent upon whether the behavioural changes themselves were obvious and upon observer error and consequently appreciable error was possible. The timing of the beginning of awakening was much easier to see from the GTF display but, for the purposes of analysis the beginning of awakening was identified according to the epoch in which it was first identified. For these reasons the timing of awakening may be no more precise than +/- one epoch (6 seconds).

6.4.2.2 Before awakening began

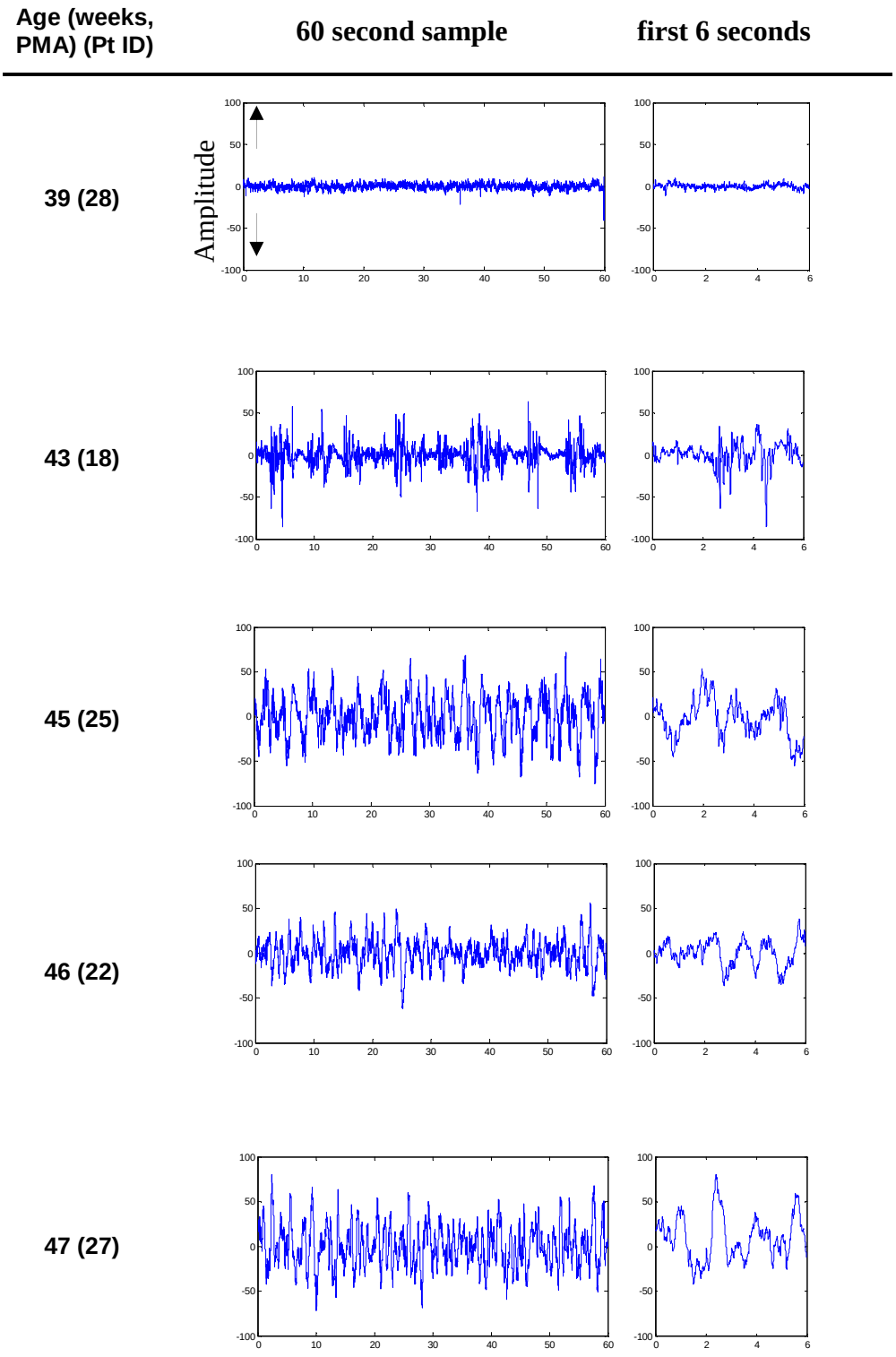
Before awakening had begun the signals were usually free of non-EEG artefacts and had steady baselines. Once awakening had begun however there were large changes in the baseline, bursts of EMG activity and non-physiological artefacts. Section 6.4.3.1 presents a summary of the epochs of EEG data excluded because of non-EEG interference.

The visual characteristics of 60 seconds of centro-parietal signal from each patient before sevoflurane was turned off are displayed in Figure 6-1 and demonstrate the steadiness (or otherwise) of the signals; a sample of one 6 second epoch is shown for

more detail. Table 6-1 lists and summarises the observed oscillations (in terms of their frequency, regularity and amplitude) until awakening began. In summary, the pre-awakening signals had a continuous low frequency oscillation of 0.5-2 Hz in all infants and the signal amplitude varied from 25-100 μV. In some infants the peaks and troughs of these low frequency signals were sharp resembling regular accidentals rather than smooth oscillations. In respect of higher frequencies there were two apparent patterns or trends that could be separated by age. The youngest infants had low amplitude signals whereas the oldest infants had appreciable amplitude in mixed frequencies between 3 and 20 Hz. In the older infants the appreciable amplitude pattern was prominent during anaesthesia but changed after sevoflurane was turned off. The amplitude gradually and steadily decreased until awakening began. In the youngest infants signal amplitude remained below 50 μV. As the age of infants increased there was a tendency for the amplitude of the signals to increase.

Figure 6-1: Raw EEG signal in each patient during anaesthesia after surgery

One minute and a 6 second sample of raw centro-parietal channel EEG just before sevoflurane had been turned off. Amplitude limits are +/- 100 µV.



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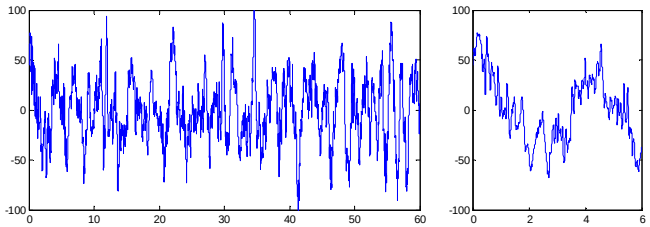

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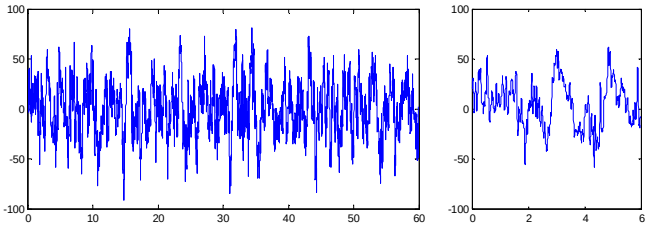

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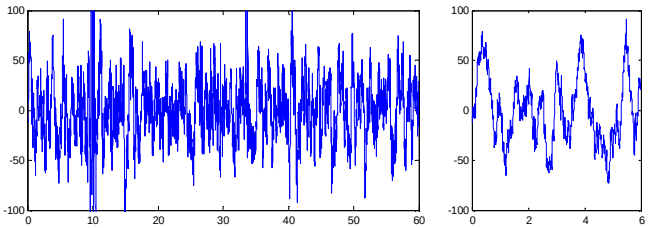

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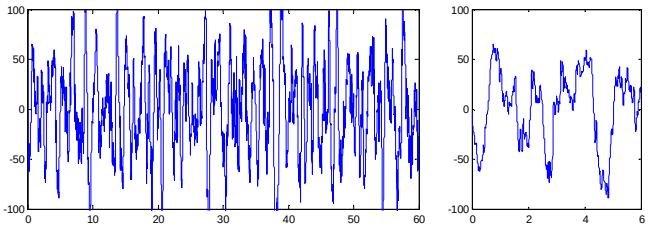

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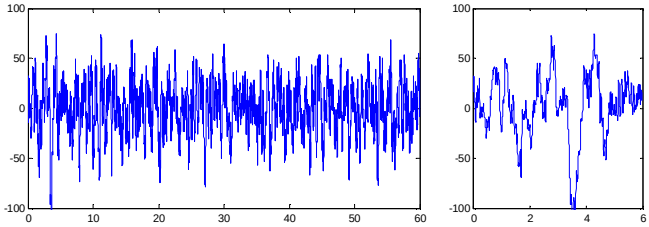

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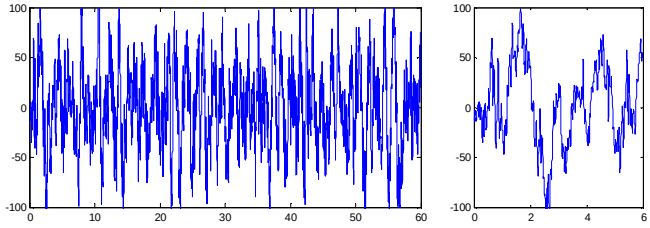

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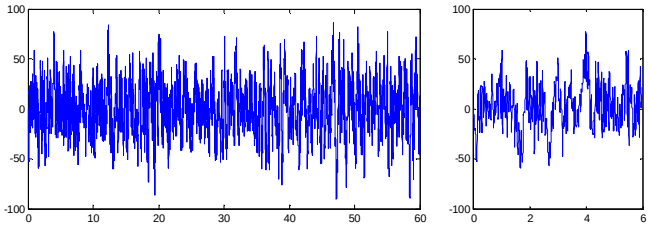

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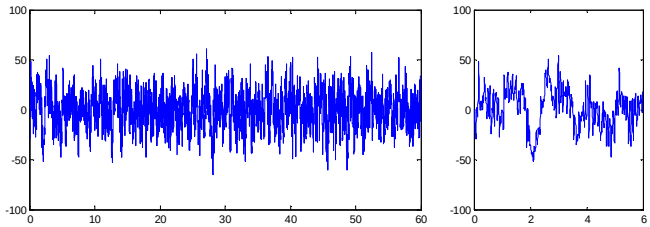
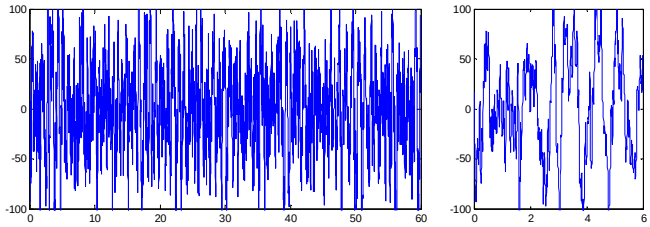
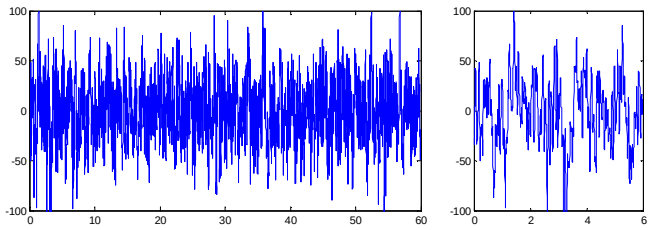


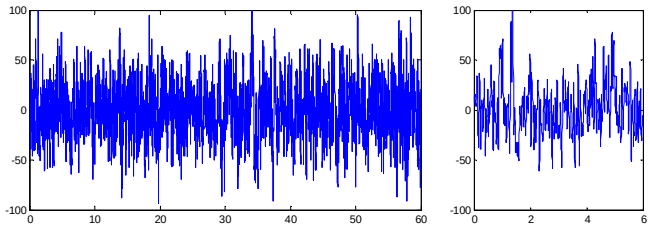
63 (11)



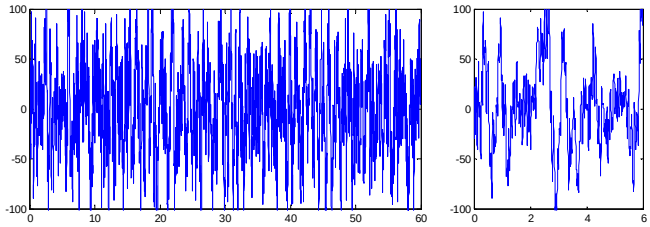
65 (12)



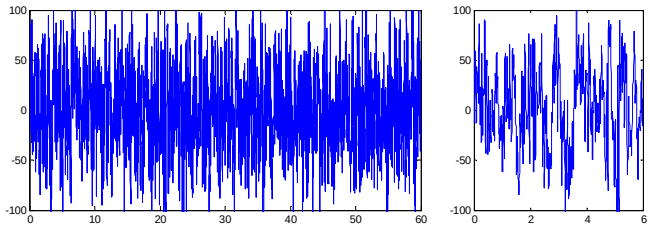
68 (21)



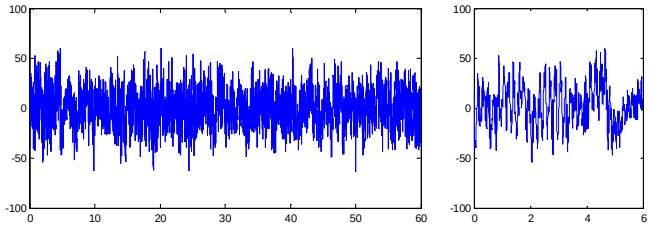
69 (30)



73 (32)



77 (13)



77 (15)

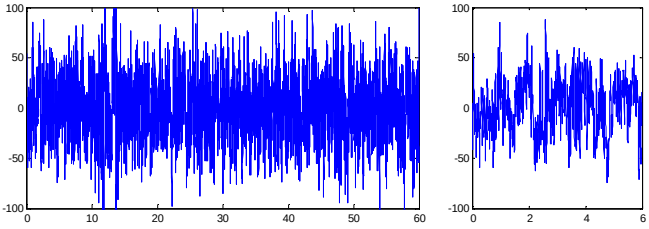


Table 6-1: Visual appearance of EEG signals before awakening began

PMA (ID)	LV	HV	Transients & other signals
	Signals are continuous and throughout unless stated otherwise		
39 (28)	<10µV&discontinuous, 10µV: <2Hz at 7 min 25µV:15Hz at 20 min	none	swings in baseline related to spontaneous breathing
43 (18)	<10µV: <0.5Hz &10-15Hz 25-30µV: 4-5Hz, = merging of bursts – become HV	75-100µV: 5Hz appearing after bursts have merged	30µV bursts: 4Hz, every 6s, merging (see Figure 6-3 & Figure 6-4)
45 (25)	<10µV: 20Hz	75-100µV: 0.5-1Hz	None
46 (22)	<10µV: 20Hz	50-75µV: 1Hz	None
47 (27)	<10µV: 12-15Hz	50-75µV: 1Hz	None
50 (26)	<5µV: 20Hz	75-100µV: 1Hz	None
20 (51)	15-50µV: 14Hz, increasing to 20Hz	50-75µV: 0.5-1Hz	None
51 (24)	<10µV:15Hz	50µV: 1-2Hz	100µV: baseline swings every 4-6 sec settling after 6 min
51 (23)	<10µV: 12Hz	50-100µV: 1-2Hz	None
52 (14)	<20µV: 15Hz, amplitude ↓	50-75µV: 1-2Hz, amplitude ↓ then ↑ before awakening	None

53 (19)	<20μV: 15Hz	50-200μV: 1-2Hz, amplitude ↓	None
53 (31)	<20μV: 18Hz, amplitude ↓	50-100μV: 1-2Hz, amplitude ↓	None
53 (29)	25-50μV: 15Hz, amplitude ↓	50-100μV: 1-2Hz, amplitude ↓	None
63 (11)	<50μV: 20Hz, amplitude ↓	100μV: 2-3Hz, amplitude ↓	None
65 (12)	<20μV: 20Hz, amplitude ↓	50-100μV: 12Hz, amplitude ↓	<50μV: saw tooth waves, 5Hz, lasting <2s, 5–6 min before awakening began
68 (21)	<20μV: 15Hz, amplitude ↓	50μV: 1Hz, amplitude ↓	None
69 (30)	<20μV: 18Hz, amplitude ↓	50-100μV: 1-2Hz, amplitude ↓	None
73 (32)	<20μV: 18Hz, amplitude ↓	50-100μV: 1-2Hz, amplitude ↓	Spikes (200μV) appearing at 10 min)
77 (13)	<25μV: 17Hz, amplitude ↓	100-150 μV: 1Hz, amplitude ↓	None
77 (15)	<50μV: 17Hz, amplitude ↓	100-150μV: 1-2Hz, amplitude ↓	None

6.4.2.2.1 Infants younger than 52 w

In the youngest patient in the series (patient 28), who was 39 weeks PMA, the EEG signal was limited to a low amplitude < 10 µV oscillation of 10-15 Hz. A regular change in baseline of occurring approximately every 2 seconds appeared after 6 minutes and was probably related to spontaneous breathing (Figure 6-2). In the next youngest patient in the series (patient 18), who was 43 weeks PMA, there was a background low amplitude < 10 µV oscillation of 10-15 Hz with bursts of higher amplitude activity of approximately 25-30 µV and 4-5 Hz (Figure 6-3). These bursts occurred approximately every 5-10 seconds and became more frequent, eventually merging to become continuous. Towards awakening the amplitude increased and there were periods of changing frequency and amplitude (Figure 6-4). Patient 22 (who was 46 weeks PMA) had a similar pattern. Figure 6-5 shows samples of EEG that were typical in Patients 20, 24 and 23 who were aged between 46 and 52 weeks PMA. All had features of continuous low amplitude background and higher amplitude low frequency oscillations. Their EEGs did not change during the period before awakening began.

Figure 6-2: Regular change in baseline EEG amplitude associated with respiration.

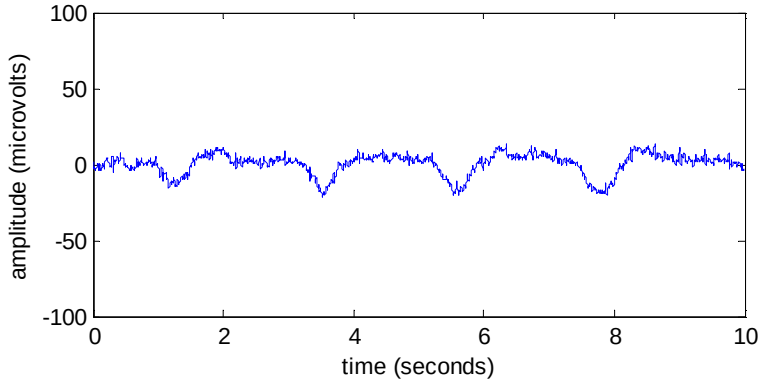


Figure 6-3: EEG showing LV background and HV bursts during anaesthesia

Features in recording from Pt 18 soon after sevoflurane turned off.

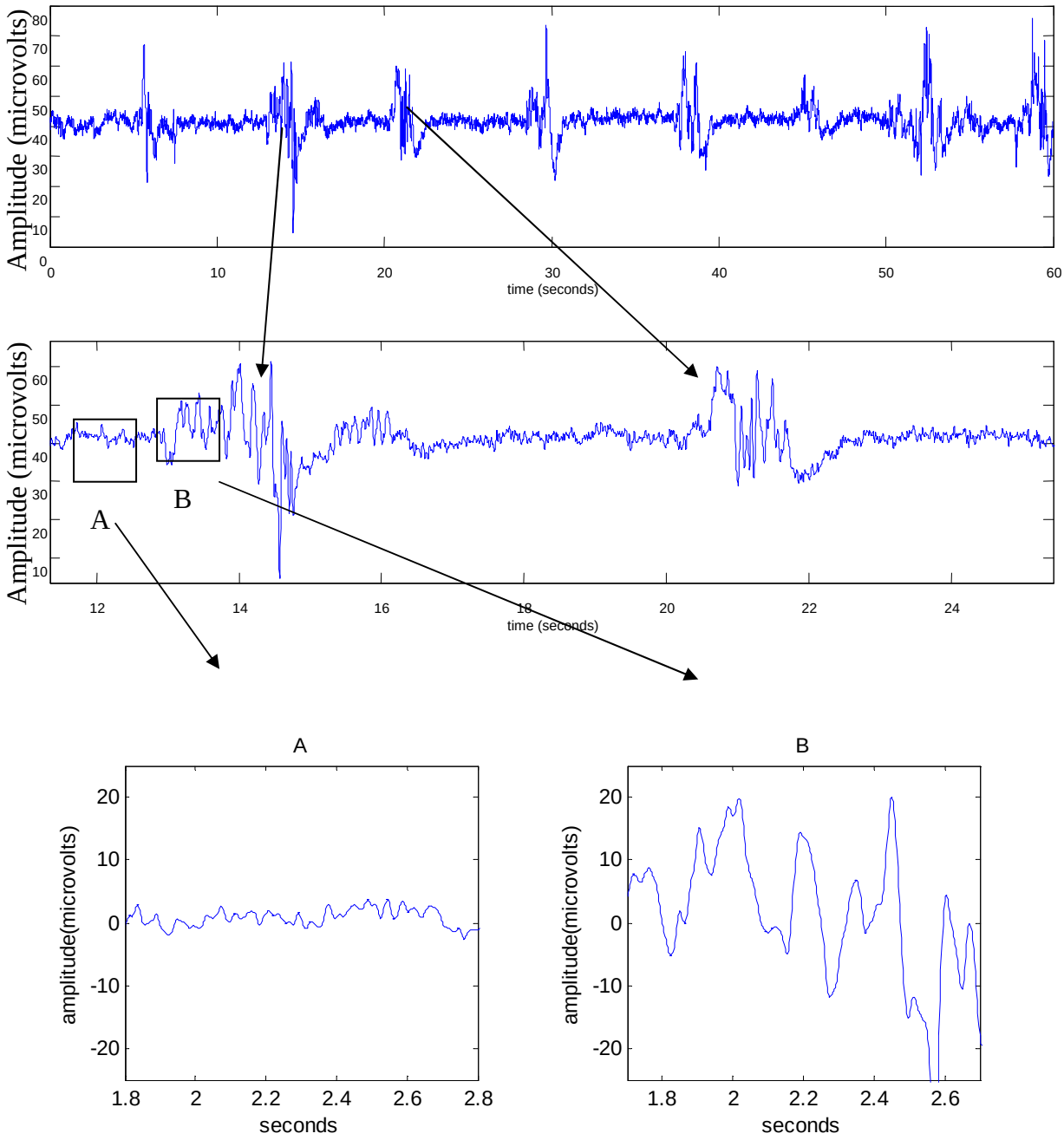
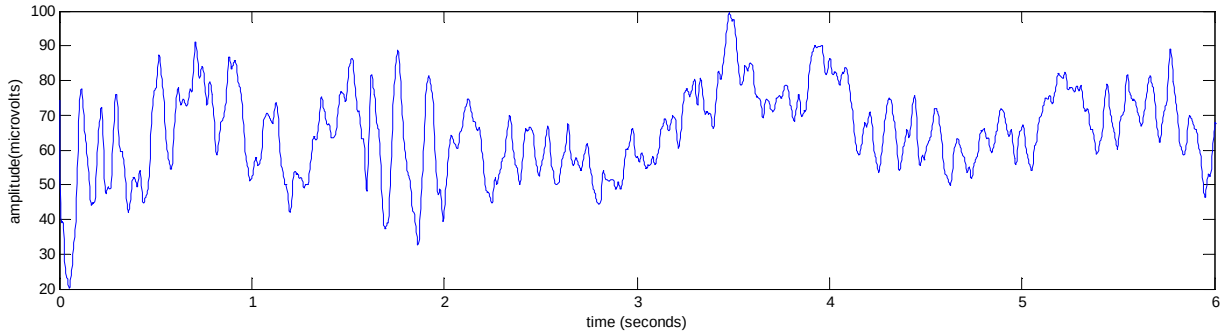


Figure 6-4: EEG frequency and amplitude changes before awakening began

Features in recording from Pt 18 one minute before awakening began:

A: Bursts merge and become a continuous oscillation



B: changing in amplitude and frequency.

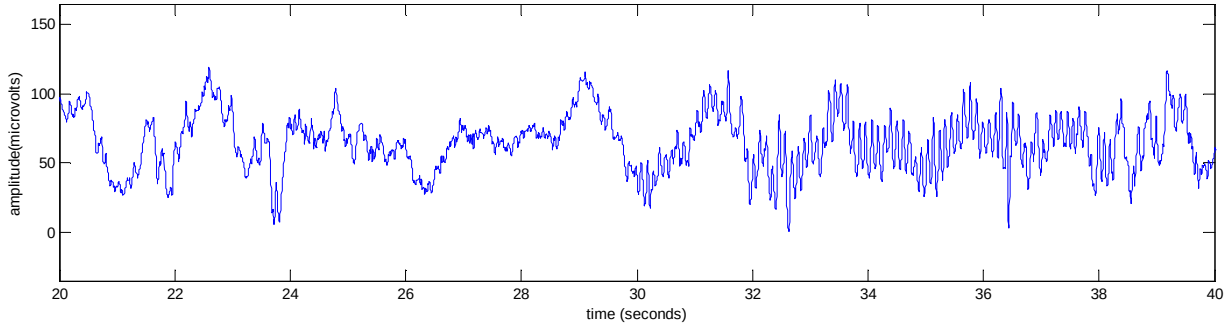
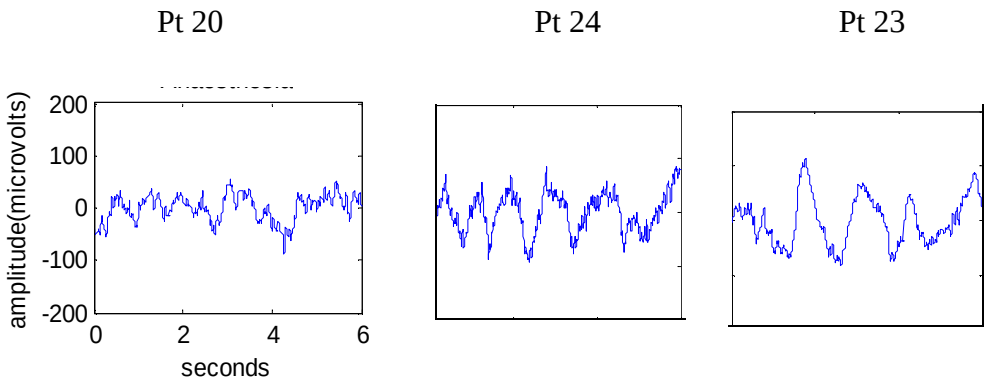


Figure 6-5: Typical EEG combination of low amplitude fast oscillation with higher amplitude slow oscillation during anaesthesia in 3 patients < 52 weeks old PMA



6.4.2.2.2 Infants older than 52 w

Patients 14, 19, 11, 21, 13 and 15 had similar patterns consisting of continuous background low amplitude fast oscillation (< 50μV, 20 Hz) and slow higher amplitude oscillations (50-150μV, 1-3Hz) that gradually decreased in amplitude before awakening. Samples of typical epochs are displayed in Figure 6-6. Patient 12, who was 65 weeks PMA, was unusual in that the higher amplitude oscillation was faster (12 Hz) and that bursts of low amplitude oscillation of 5 Hz became obvious approximately 3 minutes before awakening (see Figure 6-7). Signals from 2 infants older than 52 weeks PMA (13 and 21) have been selected and displayed in Figure 6-8 and to show the progression of amplitude (in the time domain) and frequency (in the frequency domain) over time starting from when sevoflurane was turned off until just after awakening had begun. In both patients just after sevoflurane was turned off there was an obvious frequency that had more amplitude than in the surrounding frequencies. The amplitude in this frequency tended to decrease before awakening began.

Figure 6-6: Typical EEG combinations fast and slow oscillation during anaesthesia

Examples from three patients older than 52 weeks PMA

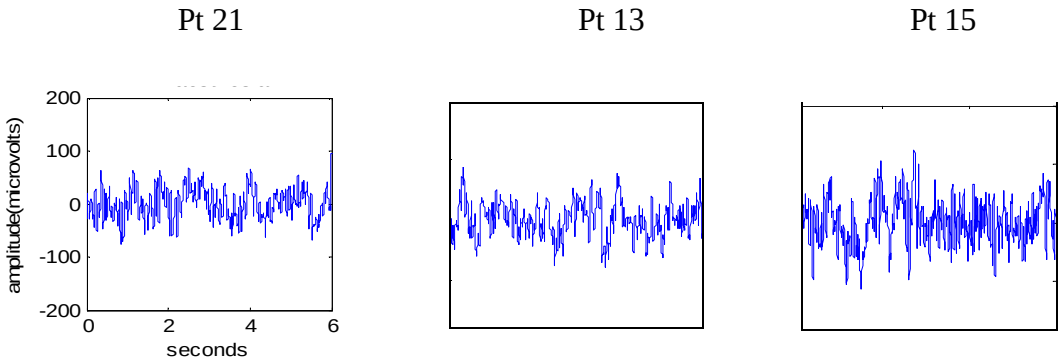


Figure 6-7: Patient 12. Changing EEG amplitude (middle epoch) approximately three minutes before awakening began

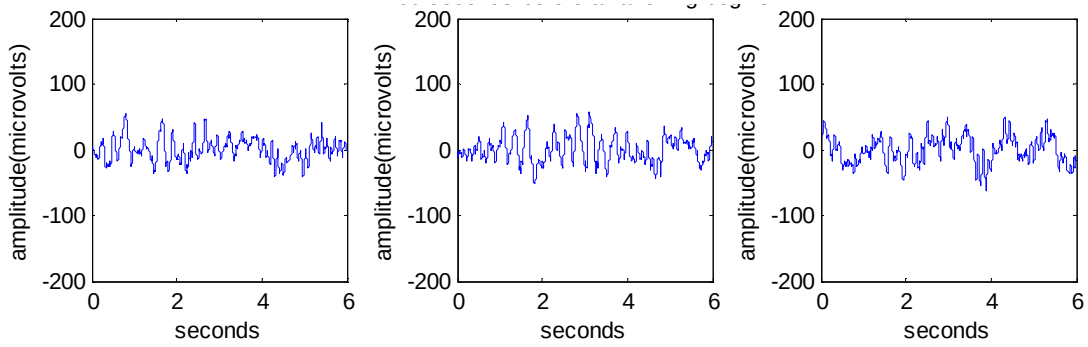
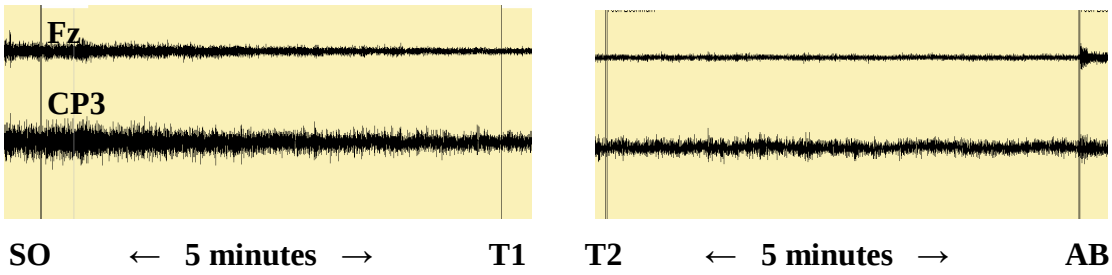


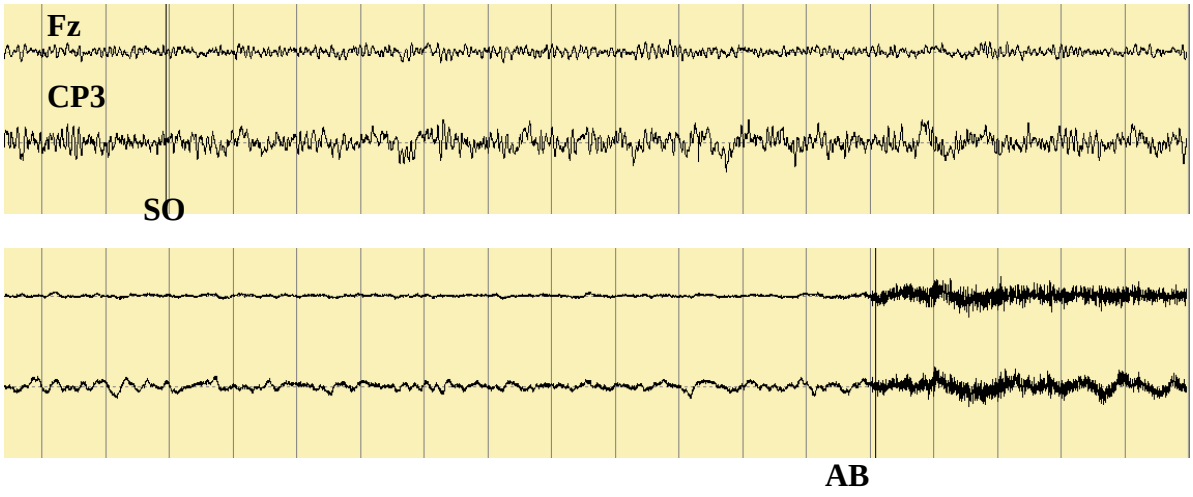
Figure 6-8: Typical original EEG signals showing change in amplitude over time

Grass Telefactor signals from an infant older than 52 weeks PMA (Pt ID 21, age 68 weeks PMA).

A: EEG recording from two channels (Fz and CP3). Vertical lines mark events SO (sevoflurane off), AB (awakening began) Time difference between T1 and T2 equals approximately 6 minutes.

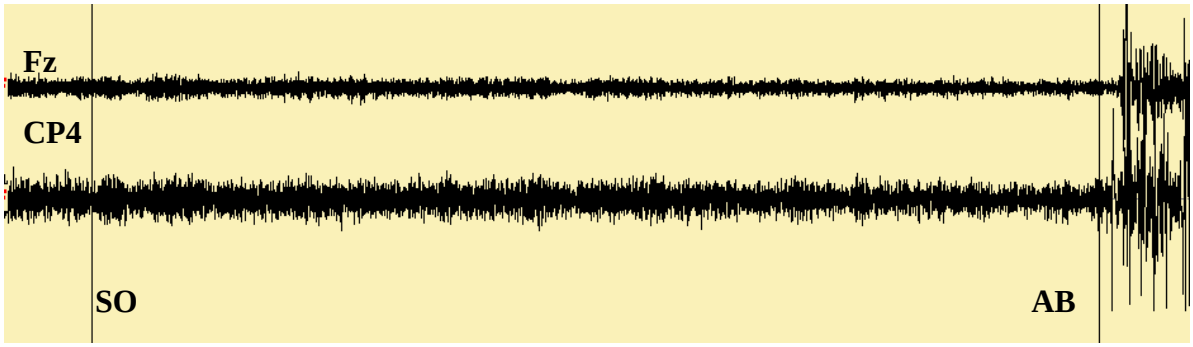


B: Same signal in more detail (vertical lines are spaced every one second).

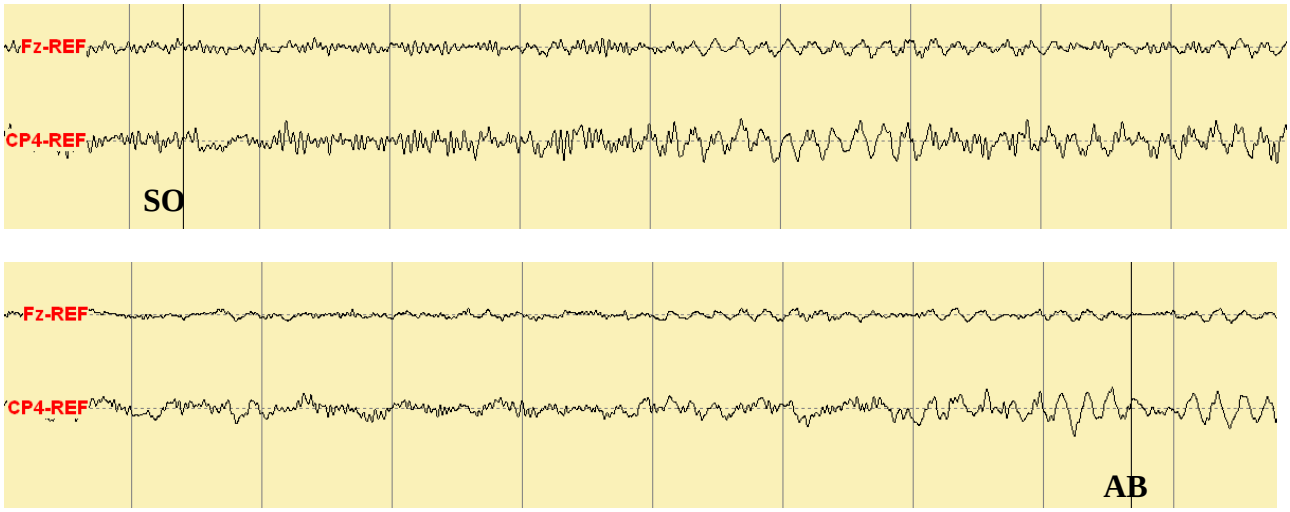


Grass Telefactor signals from another infant (ID 13 (age 77 weeks PMA)).

A: EEG recordings from two channels (Fz and CP4). Vertical lines mark the times when sevoflurane was turned off at SO and awakening began at AB (time between SO and AB was approximately 5 minutes)



B: Same signal in more detail (vertical lines are spaced every one second)

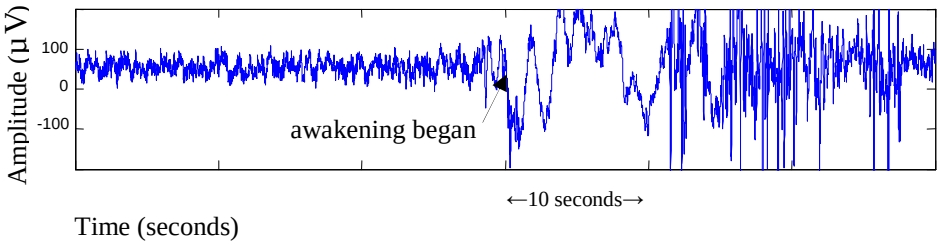


6.4.2.3 During awakening

Table 6-2 lists the EEG features that occur close to the time that awakening began. There was an obvious change in the EEG in only 9 of 20 infants and this did not show any obvious relationship to age. There were commonly large changes in baseline of 100-200 µV and these may represent movement artefact. Where movement related to awakening was vigorous there were obvious changes but not in infants who were slow to rouse Figure 6-9.

Figure 6-9: Two examples of EEG changes related to the beginning of awakening.

Obvious change in baseline and appearance of EMG activity in patient 11



Change in baseline before awakening began in patient 21

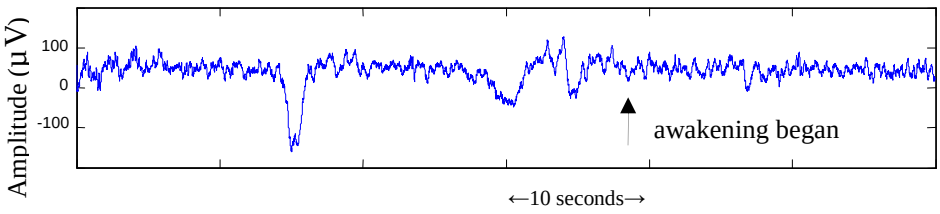


Table 6-2: Change of EEG signals near to beginning of awakening.

PMA (ID)	Description	Timing related to beginning of awakening
39 (28)	Shift in baseline (100µV)	Same epoch
43 (18)	Shift in baseline (100µV)	Same epoch
45 (25)	Shift in baseline (200µV)	16 epochs later
46 (22)	Shift in baseline (100µV)	160 epochs later
47 (27)	Shift in baseline (100µV)	Same epoch
50 (26)	Shift in baseline (>500µV)	28 epochs later
20 (51)	Minor shift in baseline	Same epoch
51 (24)	Non-physiological spike	Same epoch – shift in baseline 2 epochs later
51 (23)	EMG and minor shifts in baseline	EMG appears one epoch before
52 (14)	EMG and shifts in baseline	17 epochs later
53 (19)	minor spike-like shifts in baseline	19 epochs later
53 (31)	EMG and shifts in baseline	Same epoch
53 (29)	EMG and shifts in baseline	5 epochs later
63 (11)	EMG and shifts in baseline	Same epoch (see Figure 6-9)
65 (12)	EMG and shifts in baseline	2 epochs later
68 (21)	shifts in baseline	5 epochs before (see Figure 6-9)
69 (30)	shifts in baseline	1 epochs before
73 (32)	EMG and shifts in baseline	Same epoch
77 (13)	EMG and shifts in baseline	Same epoch
77 (15)	EMG and shifts in baseline	Same epoch

6.4.2.4 Before surgery

Inspection of raw EEG showed that signals were almost always steady with few accidentals, transients or non-physiological interference (only one patient had 3 exclusions in the samples). There were no recordings in patients 15, 22, 28 and 32 because of clinical time constraints.

6.4.3 Power spectra during anaesthesia

6.4.3.1 Excluded epochs and sequences

Table 6-3 presents the number of excluded epochs recorded from the centro-parietal channel in signals recorded after surgery. Many more epochs after awakening had begun had shifts in baseline signal and EMG artifact and therefore interpretation of the EEG at these times was uncertain. Consequently the frequency domain has not been analyzed in the signals after awakening began. The following results are from EEG sequences before awakening began.

6.4.3.2 Comparison of frontal and centro-parietal channels

The mean powers of all patients in selected frequency bands in both frontal and centro-parietal channels are presented in Table 6-4 and these data show that the differences between the channel band powers were not normally distributed (the means and medians were appreciably different). The mean band powers were log transformed and the differences are presented in Table 6-5. These data show that the total power and the band powers were approximately 4 times greater in the centro-parietal than in frontal channel and that the minimum 95% confidence interval of the geometric mean was 2.1.

Table 6-3: Epochs excluded from EEG analysis

	Before awakening		First minute after awakening began
PMA (ID)	Total	Number excluded	Number excluded
39 (28)	304	2	6
43 (18)	217	Nil	Nil
45 (25)	128	Nil	Nil
46 (22)	138	Nil	Nil
47 (27)	165	Nil	Nil
50 (26)	115	Nil	Nil
20 (51)	140	Nil	5
51 (24)	63	3 (EMG, spike, baseline shift*)	5
51 (23)	113	2 (EMG)	10
52 (14)	104	Nil	3
53 (19)	61	Nil	1
53 (31)	118	Nil	4
53 (29)	73	Nil	3
63 (11)	74	Nil	4
65 (12)	165	Nil	3
68 (21)	145	Nil	1
69 (30)	109	Nil	3
73 (32)	147	Nil	10
77 (13)	51	1 (baseline shift*)	10
77 (15)	82	3 (spikes), 1 (baseline shift*)	10

(* = epochs immediately before awakening began)

Table 6-4: Comparison of mean centro-parietal and frontal EEG band power before sevoflurane was turned off.

Frequency band (Hz)	Mean CP power	Mean F power	Mean difference	Median difference	SD of differences
1 to 28	5661.6	5112.5	549.1	527.9	1497.7
2 to 4	231.80	85.55	146.25	101.97	152.95
5 to 8	74.12	39.82	34.30	21.60	33.40
9 to 12	60.15	28.31	31.85	21.76	27.39
13 to 16	40.00	13.66	26.34	19.55	24.09
17 to 20	24.75	8.00	16.75	7.40	20.37
21 to 24	11.85	3.63	8.23	3.92	10.24
25 to 28	6.11	1.88	4.23	1.73	5.39

Table 6-5: Comparison of log10 mean centro-parietal and frontal EEG band power before sevoflurane was turned off.

Frequency band (Hz)	Mean difference	Median difference	SD of differences	Geometric mean	CI of geometric mean
1 to 28	0.64	0.71	0.45	4.33	2.1 to 8.91
2 to 4	0.61	0.67	0.35	4.06	2.79 to 5.89
5 to 8	0.57	0.59	0.28	3.70	2.74 to 4.99
9 to 12	0.62	0.62	0.32	4.14	2.95 to 5.83
13 to 16	0.70	0.67	0.33	4.96	3.47 to 7.08
17 to 20	0.68	0.70	0.31	4.78	3.43 to 6.68
21 to 24	0.66	0.66	0.22	4.56	3.59 to 5.78
25 to 28	0.57	0.60	0.21	3.71	2.95 to 4.67

6.4.3.3 Power distribution across the frequency range

Inspection of the power spectra at any time period showed that in almost all cases most of the power was within low frequency bands (less than 4 Hz). The power density in frequencies faster than 30 Hz was always less than 5 μV^2/Hz and was almost always less than 1 μV^2/Hz. In frequencies between 20 and 30 Hz only 6 out of 20 infants (ID 11, 21, 30, 32, 13, 15) had power more than 5 μV^2 centred on any frequency. Consequently only the powers within frequencies less than 20 Hz have been analysed and presented.

6.4.3.4 During anaesthesia, after surgery

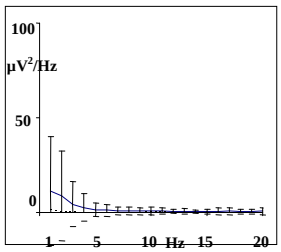
Close inspection of the power density spectra of each epoch during the 60 seconds before anaesthesia was turned off showed that infants could be divided into two groups: those who had appreciable power in the frequency range 5-20 Hz (P5-20Hz), and those who did not. Figure 6-10 shows the power density spectra for each patient arranged in age order and shows that P5-20Hz appears to be highest in the oldest infants.

Almost all PSDs had high power in the first and second frequency bands (centred on zero and one Hz) which could be related to direct current or artefact trend components of the signal. For this reason signals were further analysed with a longer window of 5 seconds to obtain narrower band power of 0.2 Hz and in almost each case, power in the zero and 0.2 Hz frequency bands was close to zero proving that any DC component was negligible. An example is presented in Figure 6-11.

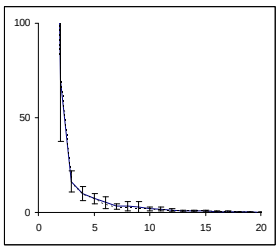
Figure 6-10: EEG power spectral density before sevoflurane turned off

Power spectral density from each infant calculated with frequency resolution of 1 Hz. Each graph has mean (solid line) and median (dotted line) with SD error bars of the power density of 10 epochs (one minute) before sevoflurane was turned off. The graphs are arranged in ascending order of infant age (PMA, w = weeks, (Pt ID)). All graphs have x axis scale 1-20 Hz and y axis scale 0 to 100 μV^2/Hz.

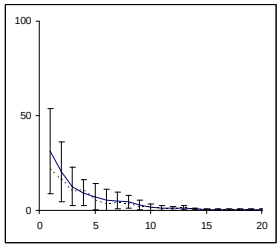
39w (20)



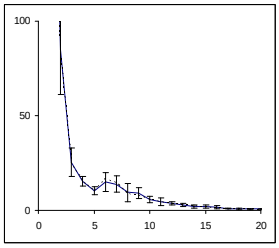
50w (26)



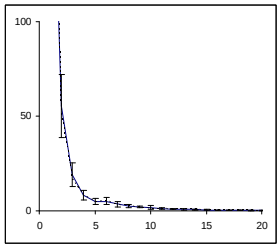
43w (18)



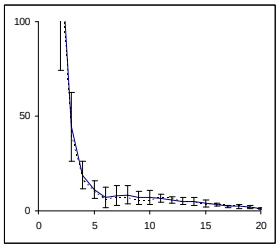
51w (20)



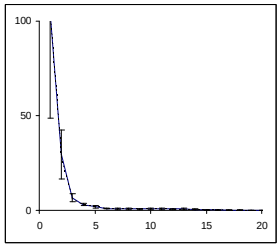
45w (25)



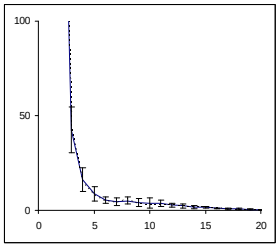
51w (24)



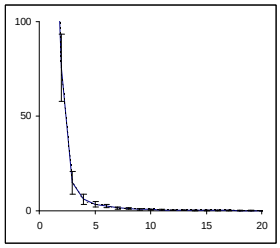
46w (22)



51w (23)



47w (27)



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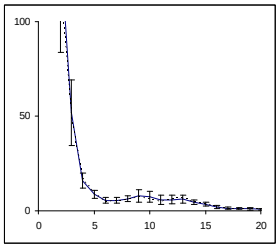

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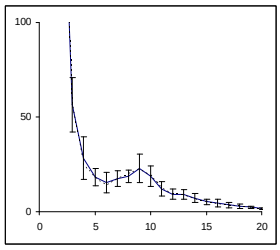
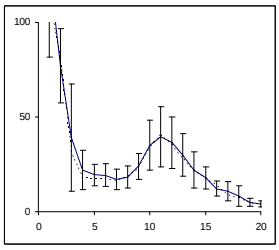


68w (21)



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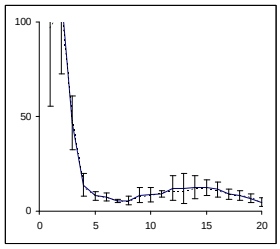
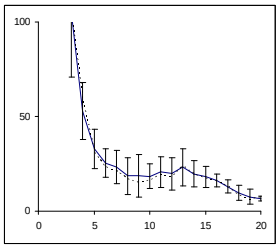
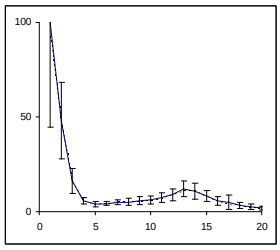


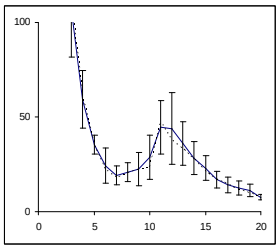
69w (30)



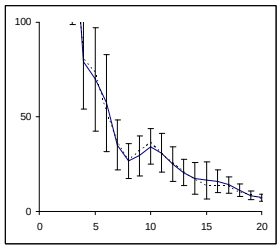
53w (29)



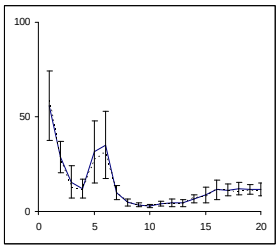
73w (32)



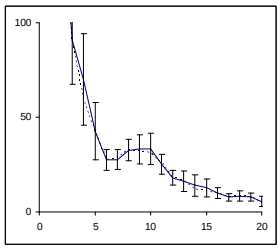
63w (11)



77w (13)



65w (12)



77w (15)

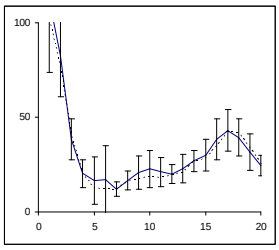
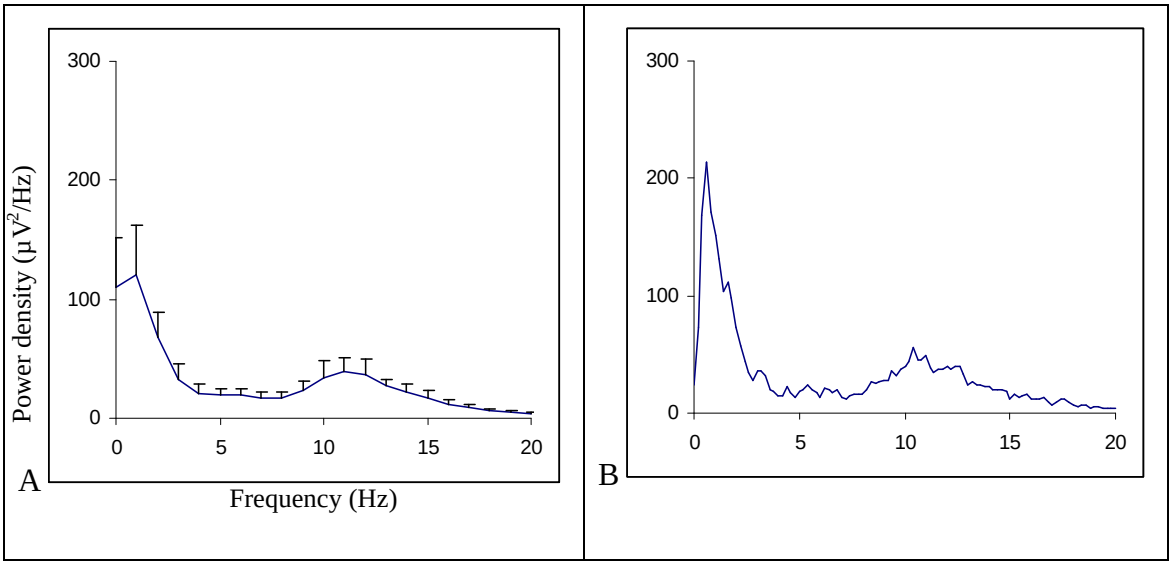


Figure 6-11: Effect of low and high frequency resolution on EEG PSD

PSDs of same EEG sample showing apparent DC in low frequency resolution PSD

A: Mean power density spectrum of 10 epochs each lasting 6 second (vertical lines are SDs).

B: Power density spectrum estimated from one period lasting 60 seconds showing much reduced DC component.



6.4.3.5 During anaesthesia before surgery and opioid

There were few obvious differences between power spectra before and after surgery except in patients 12, 13 and 21 who did not have prominent power in the 5-20 Hz frequency range before surgery. The mean total power in the frequency range 5-20 Hz of all patients (irrespective of age) before surgery was 154 μV^2 compared with 146 μV^2 after surgery. Log transformation reduced the difference between the means and medians although the SDs remained large. The geometric mean differences for the wide frequency bands are presented in Table 6-6 and show that the power in the frequencies less than 8 Hz were 2 to 3 times higher before surgery than after surgery. However, the powers in higher frequencies and in the 5-20Hz range were not statistically different (geometric mean difference for band power in 5-20 Hz range was 1.03, 95% CI 0.3 to 3.7). The mean difference in end-tidal concentration of sevoflurane between these periods was 0.04% (median 0.03, SD 0.63, range -1.5 to 1.35).

Table 6-6: Change in mean EEG band power from *before* to *after* surgery

Raw band power (distribution in all infants)			
Hz	**mean**	**median**	**SD**
1 to 20	955.09	592.45	996.17
1	657.39	473.19	788.24
2 to 4	290.25	130.06	354.76
5 to 8	26.28	12.27	58.35
9 to 12	-2.91	2.58	18.66
13 to 16	-10.12	-3.98	15.15
17 to 20	-5.80	0.00	10.94
5 to 20	7.46	10.93	55.50
Log10			
Hz	**mean**	**median**	**SD**
1 to 20	0.88	0.84	0.84
1	0.50	0.42	0.43
2 to 4	0.37	0.36	0.36
5 to 8	0.18	0.18	0.20
9 to 12	0.02	0.05	0.18
13 to 16	-0.10	-0.06	0.24
17 to 20	-0.09	-0.04	0.31
5 to 20	0.01	0.14	0.70
Geometric mean			
Hz	**mean**	**low CI**	**high CI**
1 to 20	2.28	1.63	3.18
1	3.16	1.88	5.33
2 to 4	2.34	1.51	3.64
5 to 8	1.50	1.17	1.91
9 to 12	1.06	0.85	1.31
13 to 16	0.80	0.59	1.08
17 to 20	0.82	0.56	1.20
5 to 20	1.03	0.29	3.67

6.4.3.6 Potential factors influencing P5-20Hz

The potential association between mean P5-20Hz and age is apparent from the PSDs in Figure 6-10. Furthermore the scatter plot in Figure 6-12 shows that not only may there be an association between age and band power but also that power of approximately 100 μV^2 separates infants younger and older than 52 weeks PMA. The association was tested using regression analysis and correlation values were higher for linear rather than logarithmic or exponential correlations (R^2 values were 0.712, 0.707 and 0.699 respectively).

Figure 6-12: Scatter plot of age (PMA (weeks)) versus EEG P5-20Hz

P5-20Hz = mean band power (5-20Hz) during 10 sequential epochs during steady sevoflurane anaesthesia both before and after surgery.

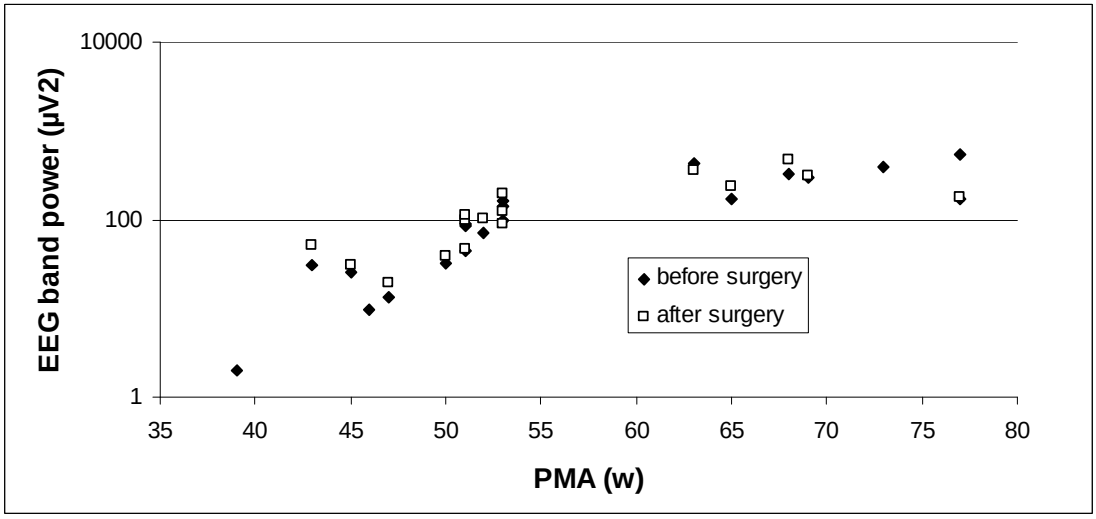


Table 6-7: Correlation between EEG P5-20Hz and other potentially important factors

		PMA	Wt	P5to20Hz	Length of surgery	Time to awakening	P_{et}Sevoflurane
PMA	R		.815	.844	-.023	-.424	.355
	P		.000	.000	.925	.063	.125
Wt	R	.815		.627	.117	-.387	.320
	P	.000		.003	.623	.092	.169
P5-20Hz	R	.844	.627		-.106	-.309	.219
	P	.000	.003		.657	.185	.353
Length of surgery	R	-.023	.117	-.106		-.530	.007
	P	.925	.623	.657		.016	.977
Time to awakening	R	-.424	-.387	-.309	-.530		-.247
	P	.063	.092	.185	.016		.294
P_{et}Sevoflurane	R	.355	.320	.219	.007	-.247	
	P	.125	.169	.353	.977	.294	

R = Pearson Correlation. Cp calculated only with P5-20Hz during bSO (i.e. only one value per infant). P was calculated with 2-tailed significance tests. P values <0.01 are highlighted in grey.

Other potentially important and influential factors may account for any apparent association and the following additional potential predictive factors were chosen to be examined by scattergraphs and correlation tests:

- Body weight
- Length of operation
- Time taken to awaken
- P_{et}Sevoflurane (before being turned off)

The strongest association was between EEG power and age (Table 6-7). There were no major differences between the parametric and non-parametric correlations and both suggest a positive association between P5-20Hz with both weight and age (Table 6-8). The additional predictive effects of other factors are presented in Table 6-9 and show that additional factors did not appreciably improve the predictive association of PMA. A plot of the residuals of the linear regression model showed a spread of residuals above and below the zero line but that this distribution was obviously wider in the older infants.

The effect of gender on P5-20Hz was analysed further. Figure 6-13 shows that female infants (n = 7) tended to be smaller and younger than males. Table 6-10 shows that gender had minimal effect on the predictive variables except for body weight; this factor tended toward significant difference ($p = 0.88$) but this may have been caused by one female infant who was the smallest in the sample; the non-parametric test did not find a significant difference.

Table 6-8: Summary of univariate linear correlation coefficients between EEG P5-20Hz and independent factors

Independent variables	**Pearson (p-value)**	**Spearman (p-value)**
PMA	0.844 (<0.001)	0.941 (<0.001)
Body weight	0.627 (0.003)	0.802 (<0.001)
P_{et}Sevo	0.219 (0.353)	0.349 (0.132)
Length of surgery	-0.106 (0.657)	0.099 (0.677)
Time taken to awaken	-0.309 (0.185)	-0.441 (0.052)

Table 6-9: Pearson correlation coefficients for effect of additional predictor variables on EEG P5-20Hz and the effect of adding a single predictor variable

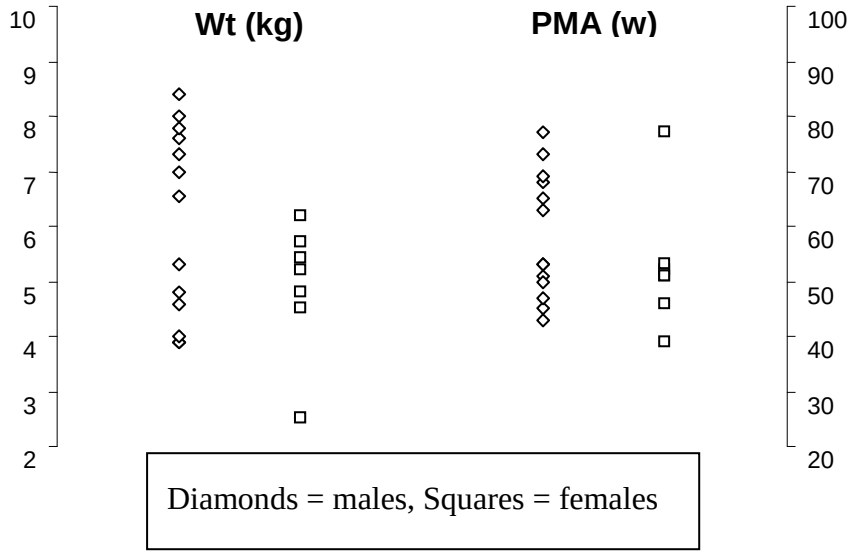
	R	**R^2**	**Adjusted R^2**
PMA alone	0.844	0.712	0.696
Additional predictor variable			
wt	0.85	0.723	0.691
P_{et}Sevo	0.848	0.719	0.686
Time to begin to awaken	0.846	0.715	0.681
Surgical time	0.848	0.72	0.687
Gender	0.847	0.718	0.685

Table 6-10: Effect of gender on predictive factors

	Gender	**Mean**	**SD**	**Mean diff**	**P (t test)***	**P (Mann-Whitney)**
PMA (weeks)	M	58.2	11.4	5.5	.332	.382
	F	52.7	11.8			
Wt (Kg)	M	6.1	1.7	1.2	.088	.234
	F	4.9	1.2			
EEG P5-20Hz (μV^2)	M	168.9	144.3	39.1	.639	.285
	F	129.7	185.8			
Surgical time (minutes)	M	137	64.4	-11.4	.624	.405
	F	148	38.1			
Time to begin to awaken (minutes)	M	12.1	5.1	-1.1	.743	.905
	F	13.2	7.6			
P_{et}Sevo (%)	M	2.3	.6	.1	.646	.843
	F	2.2	.4			

* Equal variances were not assumed (the variances for M and F body weight were appreciably different (F = 5.340, P = .033)).

Figure 6-13: Distribution of body weight and age according to gender



6.4.4 Power spectra changes after sevoflurane turned off

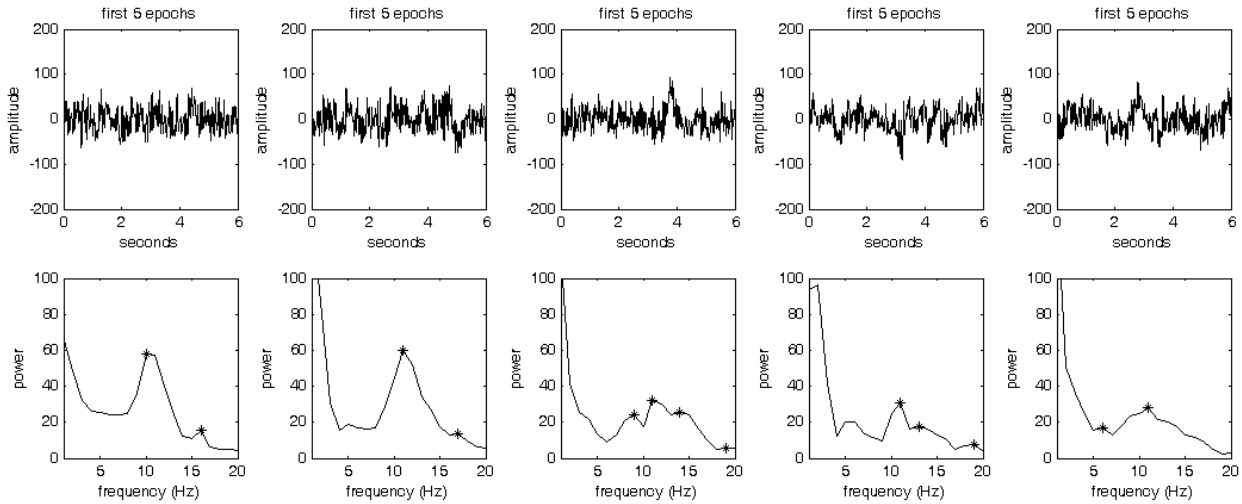
6.4.4.1 Power spectral array

Two trends of progression of the power spectra between turning sevoflurane off and the beginning of awakening were observed. In infants under 52 weeks PMA the distribution of power in the 5-20 Hz range did not change appreciably. In older infants however there was obvious power within the frequency range of 5-20 Hz for several minutes after sevoflurane had been turned off which then diminished at least one minute before awakening began. Figure 6-14 shows the change in raw signal and power spectrum in these two time periods. Examples of the progression of power spectra over time (power spectral array) are displayed in Figure 6-15.

Figure 6-14: Sequential epochs of raw EEG and power spectral density (Fres1Hz) in an infant with appreciable power in the frequency range 5 to 20 Hz.

(A) the first 5 epochs after sevoflurane turned off and, (B) the last 5 epochs before awakening began. Below each EEG plot is the power spectrum density (* mark any peaks). Amplitude units are μV and power density units are μV^2/Hz.

(A) As sevoflurane is turned off



(B) Just before awakening began

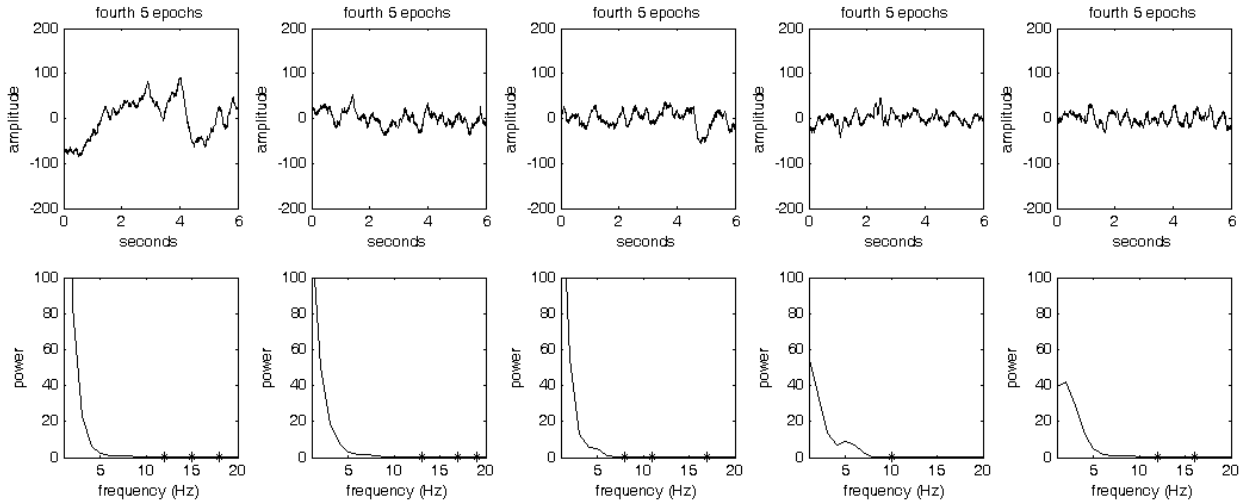
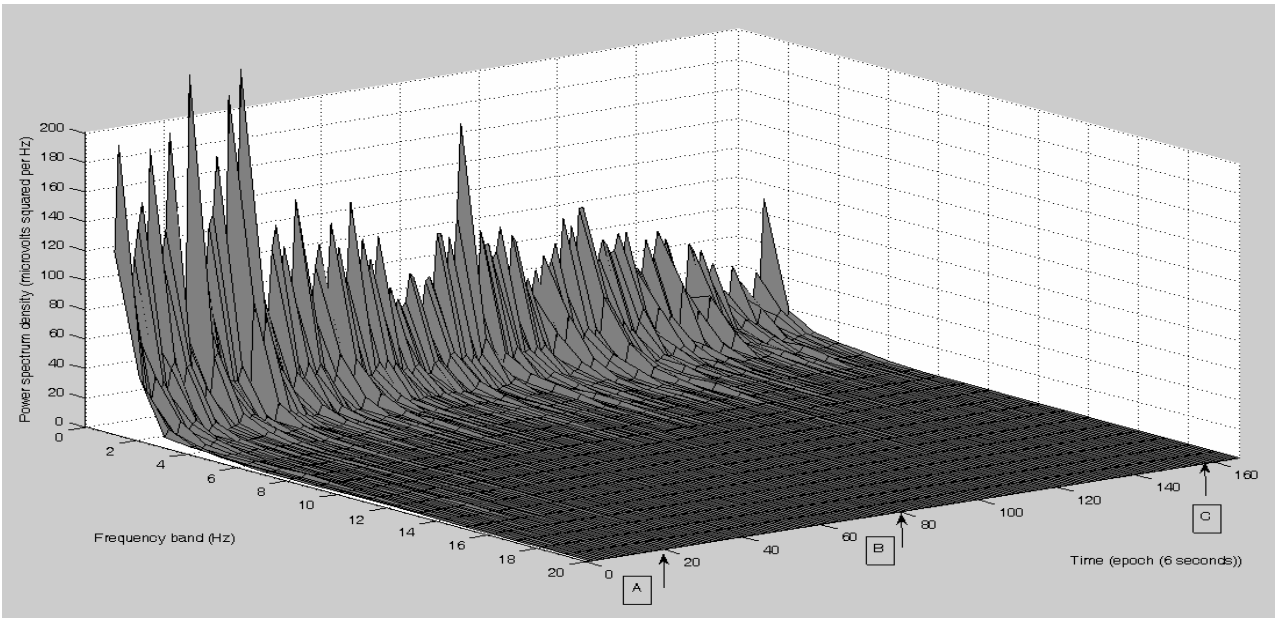


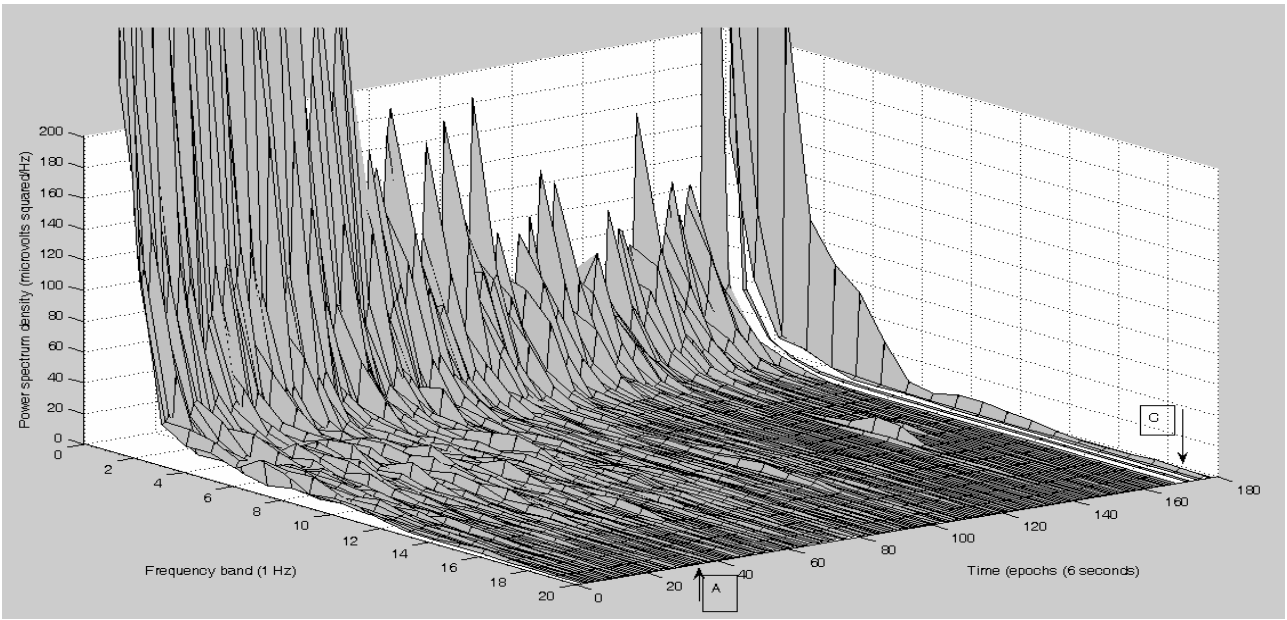
Figure 6-15: Examples of EEG power spectral arrays in four infants

Each graph shows the progression of the EEG power spectra (Fres1Hz) every 6 seconds from when sevoflurane was turned off until awakening began. Arrows mark the time of events: A = sevoflurane turned off, B = first movement, C = awakening began, D tracheal extubation. The graphs are labelled with the age and ID number of the infant.

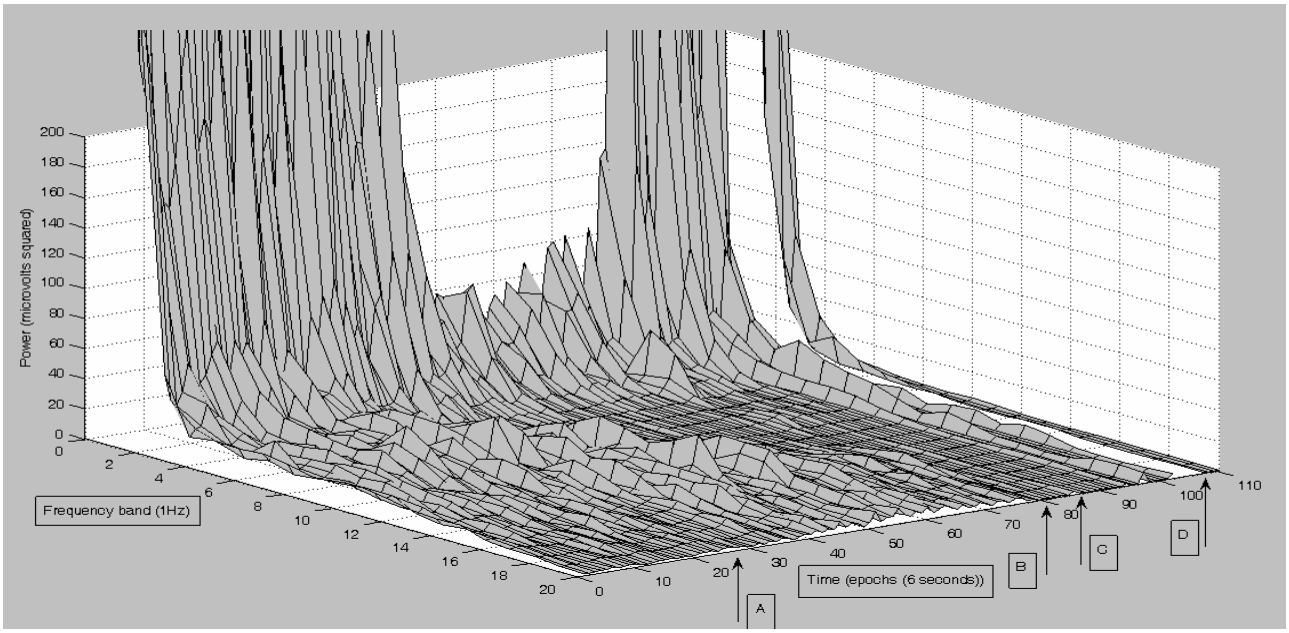
Age 46 weeks (ID 22)



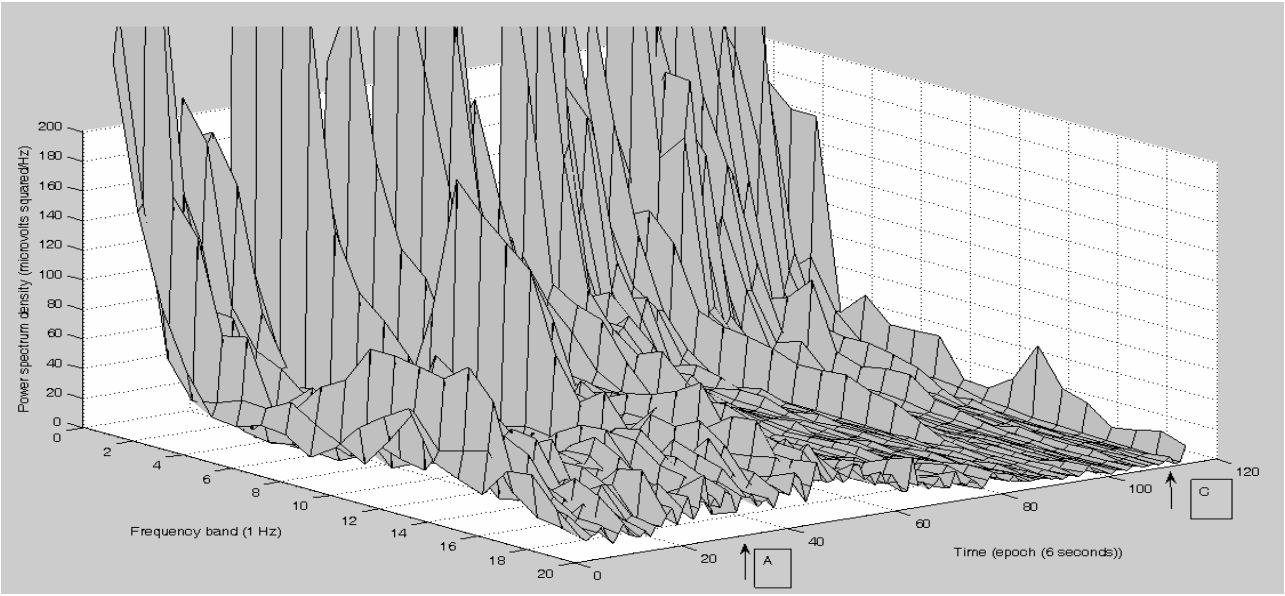
Age 51 weeks (ID 20)



Age 53 weeks (ID 19)



Age 77 weeks (ID 15)



6.4.4.2 Power within selected frequency bands

Table 6-11 shows the change in power within frequency bands for infants younger and older than 52 weeks between anaesthesia and just before awakening. Despite the wide confidence intervals there was a much larger decrease in power in infants older than 52 weeks PMA. Analysis of regression coefficients was chosen to compare the change in band power over time. The graphs below (Figure 6-16 and Figure 6-17) demonstrate an obvious difference in progression of band power over time between infants younger and older than 52 weeks PMA. The graphs show the power on a logarithmic scale for ease of presentation.

6.4.4.2.1 Infants less than 52 weeks PMA

The total power within the frequency range 5-20 Hz tended to remain less than 100 μV^2 and tended to decline before awakening began. Power within the frequency band 2-4 Hz varied between 20 and 200 μV^2 and also tended to decrease before awakening except for the two youngest infants (aged 39 and 43 weeks PMA).

6.4.4.2.2 Infants older than 52 weeks PMA

The power in the frequency bands 2-4 and 5-20 Hz decreased before awakening began. In Figure 6-17 the P5-20Hz the semi-log plot suggests that there is a log-linear reduction in power with time. Expansion of the axes demonstrates that by 60 epochs (10 minutes) after sevoflurane had been turned off (Figure 6-18). P5-20Hz had reduced to less than 10 μV^2 in all but 2 infants. Sevoflurane had decreased to less than 0.5% in all infants by this time.

Table 6-11: Difference in mean EEG band power between during anaesthesia and before awakening began

	Hz	**Mean (μV^2)**	**Median (μV^2)**	**Lower CI**	**Upper CI**
All patients	1 to 28	-477.63	-252.29	-723.83	-231.42
	1	-198.35	-126.87	-334.17	-62.53
	2 to 4	-87.26	-59.18	-215.56	41.03
	5 to 8	-52.48	-18.07	-95.49	-9.48
	9 to 12	-54.32	-24.29	-86.28	-22.35
	13 to 16	-36.22	-14.63	-54.92	-17.52
	17 to 20	-20.40	-4.37	-34.49	-6.31
	21 to 24	-8.51	-1.75	-14.19	-2.83
	25 to 28	-3.44	-0.62	-5.84	-1.04
	5 to 20	**-154.94**	**-73.98**	**-250.13**	**-59.75**
<52w	1	-206.20	-151.31	-423.79	11.39
	2 to 4	34.78	-23.12	-122.91	192.48
	5 to 8	-12.44	-9.43	-21.99	-2.89
	9 to 12	-9.19	-4.87	-15.71	-2.67
	13 to 16	-4.80	-2.20	-8.56	-1.04
	17 to 20	-1.47	-0.90	-2.56	-0.38
	21 to 24	-0.43	-0.21	-0.84	-0.03
	25 to 28	-0.08	-0.01	-0.22	0.06
	5 to 20	**-27.26**	**-18.44**	**-46.34**	**-8.17**
>52w	1	-155.62	-57.52	-357.21	45.98
	2 to 4	-122.47	-65.92	-254.44	9.50
	5 to 8	-51.82	-50.28	-89.64	-13.99
	9 to 12	-70.07	-71.40	-103.82	-36.31
	13 to 16	-54.35	-47.71	-80.28	-28.42
	17 to 20	-31.33	-28.04	-55.08	-7.57
	21 to 24	-12.23	-10.26	-20.11	-4.36
	25 to 28	-4.70	-5.13	-7.37	-2.02
	5 to 20	**-191.94**	**-130.38**	**-281.39**	**-102.49**

Figure 6-16: Progression of EEG power in two frequency bands (2-4 Hz and 5-20 Hz) in each infant younger than 52 weeks PMA

Power units are μV^2 (NB: scale is logarithmic). Epoch length = 6 seconds.

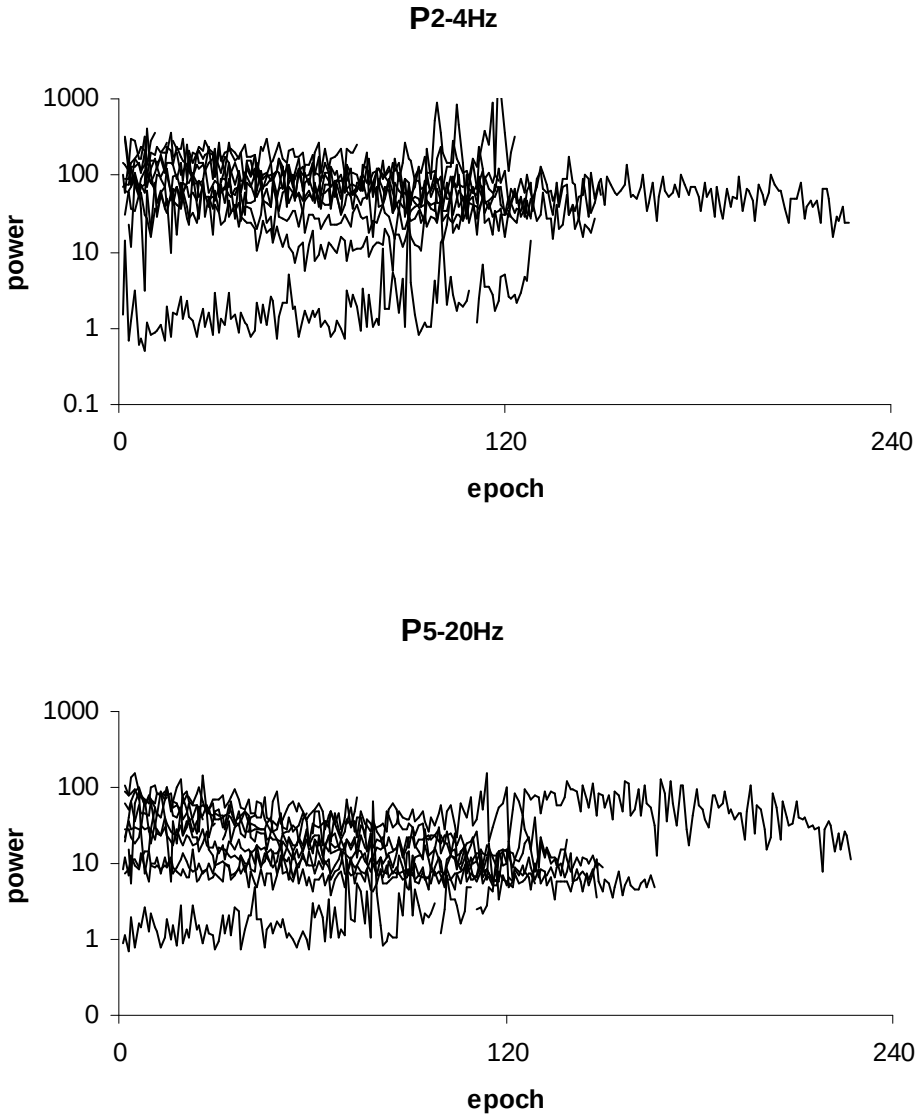


Figure 6-17: Progression of EEG power in two frequency bands (2-4 Hz and 5-20 Hz) in each infant older than 52 weeks PMA

Power units are μV^2 (NB: scale is logarithmic). Epoch length = 6 seconds.

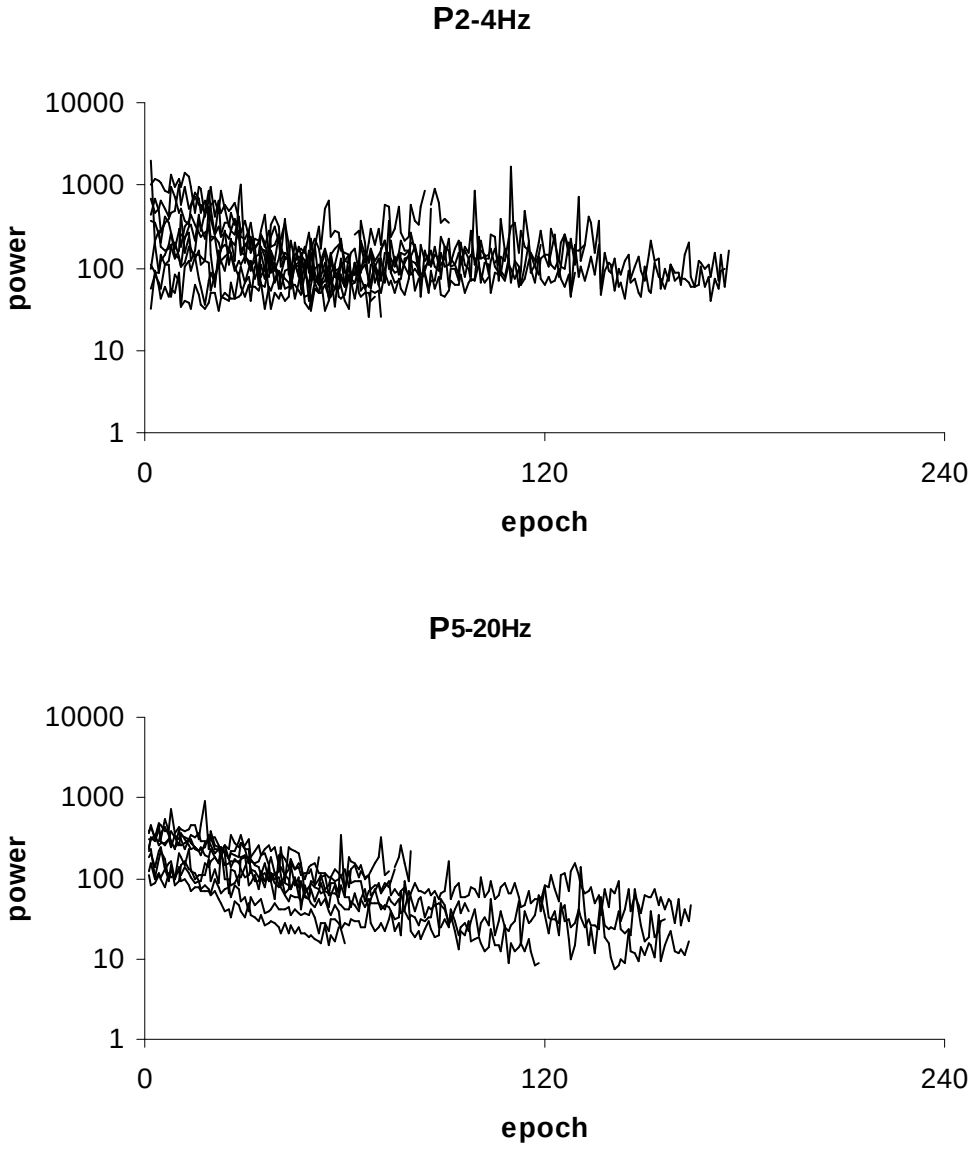
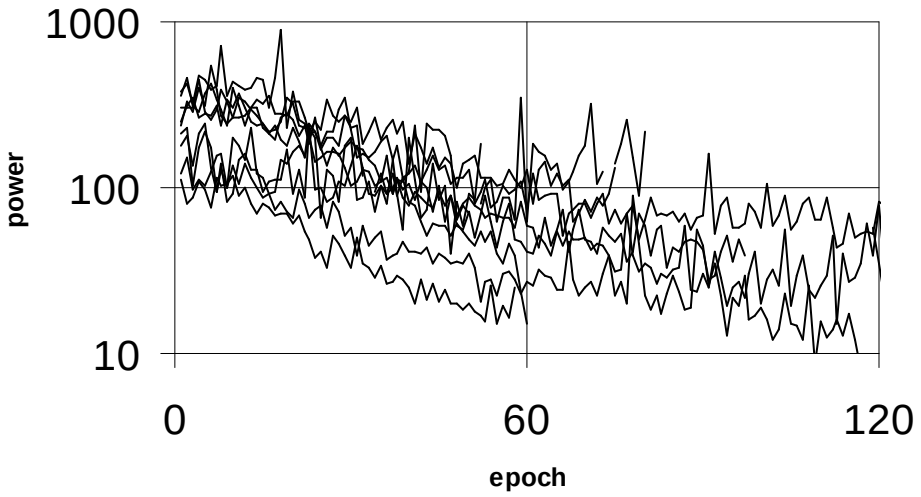


Figure 6-18: Progression of EEG band power in 5-20 Hz in each infant older than 52 weeks PMA

Power units are μV^2 (NB: scale is logarithmic). Epoch length = 6 seconds.



6.4.4.2.3 Statistical comparisons

The statistical differences between band powers during anaesthesia and before awakening are shown in Table 6-11; the upper confidence intervals for P5-20Hz differences are larger and furthest from zero any almost all other frequency bands. The correlation and regression coefficients for a linear model of the change in log10 power over the first 5 minutes (50 epochs) were calculated for each infant and are presented in Table 6-12. This limited time sequence was chosen because one infant began awakening by 5.2 minutes. All except one infant >52 weeks PMA had R values greater than 0.7. All but 2 infants >52 weeks PMA had negative gradients greater than 0.01. The mean gradient was -0.012 in older infants which, taking the antilog, is the equivalent of a decrease by approximately 1.032 (or to 97.3% of the previous value) for each epoch; for each 10 or 50 epochs the power has reduced to 75.9% and 25.8% respectively of the original value. The mean gradient in younger infants was -0.006 (compared to older infants by unpaired t test, p = 0.006). Data in Table 6-13 suggests that the log10 P5-20Hz is normally distributed. The log power at three periods in the

two groups were analysed by two way ANOVA. The between period ratio of variances was 6.92 which for 2 degrees of freedom has a P value of 0.03. Post hoc paired t tests compared the change in power from bSO to 5 min and bAB found P value less than 0.05 in both comparisons in both age groups (Table 6-14). The difference in power was appreciably greater in the older than the younger infants at both 5 minutes and just before awakening began. In the older infants the power reduced by factors of 3.9 and 5.9 at 5 minutes and just before awakening began respectively.

Table 6-12: Correlation and regression coefficients for log10 EEG P5-20Hz v time.

	Correlation				**Regression**				
ID	R	R^2	AdjR^2	SE	B	SE	p	Lower CI	Upper CI
28	0.204	0.042	0.022	0.180	-0.003	0.002	0.155	-0.006	0.001
18	0.007	<0.01	-0.021	0.197	<0.001	0.002	0.961	-0.004	0.004
25	0.573	0.328	0.314	0.087	-0.004	0.001	<0.001	-0.006	-0.002
22	0.413	0.17	0.153	0.111	-0.003	0.001	0.003	-0.006	-0.001
27	0.083	0.007	-0.014	0.096	0.001	0.001	0.565	-0.001	0.002
26	0.848	0.72	0.714	0.106	-0.012	0.001	<0.001	-0.014	-0.009
20	0.607	0.368	0.355	0.108	-0.006	0.001	<0.001	-0.008	-0.003
24	0.721	0.521	0.51	0.103	-0.008	0.001	<0.001	-0.01	-0.005
23	0.806	0.649	0.642	0.115	-0.01	0.001	<0.001	-0.013	-0.008
14	0.955	0.911	0.909	0.073	-0.016	0.001	<0.001	-0.017	-0.014
19	0.767	0.588	0.579	0.123	-0.01	0.001	<0.001	-0.012	-0.008
31	0.938	0.879	0.877	0.072	-0.013	0.001	<0.001	-0.015	-0.012
29	0.965	0.93	0.929	0.068	-0.017	0.001	<0.001	-0.018	-0.016
11	0.845	0.714	0.708	0.080	-0.009	0.001	<0.001	-0.01	-0.007
12	0.878	0.771	0.766	0.082	-0.01	0.001	<0.001	-0.012	-0.009
21	0.95	0.902	0.9	0.076	-0.016	0.001	<0.001	-0.017	-0.014
30	0.934	0.873	0.87	0.078	-0.014	0.001	<0.001	-0.015	-0.012
32	0.943	0.889	0.887	0.085	-0.016	0.001	<0.001	-0.018	-0.015
13	0.506	0.256	0.241	0.152	-0.006	0.001	<0.001	-0.009	-0.003
15	0.806	0.649	0.642	0.163	-0.015	0.002	<0.001	-0.018	-0.012

Infants are arranged in ascending age order.

Table 6-13: Distribution of log10 EEG mean P5-20Hz at three periods after surgery

	period	**Mean**	**SD**	**Median**
<52 weeks	bSO	1.39	0.51	1.44
	5min	1.17	0.40	1.25
	bAB	1.02	0.27	0.98
	gradient	-0.006	0.006	-0.005
>52 weeks	bSO	2.39	0.24	2.48
	5min	1.80	0.24	1.83
	bAB	1.62	0.37	1.60
	gradient	-0.012	0.004	-0.014

Table 6-14: Comparison of log10 EEG mean P5-20Hz between before sevoflurane turned off and before awakening

	period		**mean difference**	**lower CI**	**upper CI**	**P**
<52 weeks	5min	log 10	0.22	0.05	0.39	0.018
		antilog	1.65	1.12	2.43	
	bAB	log 10	0.37	0.04	0.69	0.03
		antilog	2.33	1.11	4.90	
>52 weeks	5min	log 10	0.59	0.50	0.68	<0.001
		antilog	3.90	3.16	4.82	
	bAB	log 10	0.77	0.54	1.00	<0.001
		antilog	5.89	3.51	9.89	

NB: bSO (one minute), 5min (4.5 to 5 minutes after SO, = 30 seconds), bAB (one minute)

6.4.4.3 Prominent frequencies

In Table 6-15 the infants with appreciable P5-20Hz, a prominent frequency was usually apparent. In some infants the prominent frequency was unchanging, yet in others it tended to increase. The prominent frequency and its power during anaesthesia in each patient were plotted against age (see Figure 6-19). In all except 2 infants over 52 weeks PMA, power in the prominent frequency was greater than 20 $\mu V^{2.}$ All younger infants had power in the prominent frequency less than $20\mu V^2$. When anaesthesia is washed out, power in the prominent frequency clearly decreases over time in older infants but not obviously in younger infants (Figure 6-20). The power in the prominent frequency is usually less than 10 μV^2 by 6 to 7 minutes. The prominent frequency itself changes little over the first five minutes after sevoflurane is turned off (Figure 6-21) although the increase in frequency over time has a correlation coefficient of 0.816 (R^2 0.667) and a gradient of 0.062 Hz per epoch (or 0.62 Hz per minute) ($p = <0.001$).

Figure 6-19: Scatter plot of age versus power in EEG prominent frequency

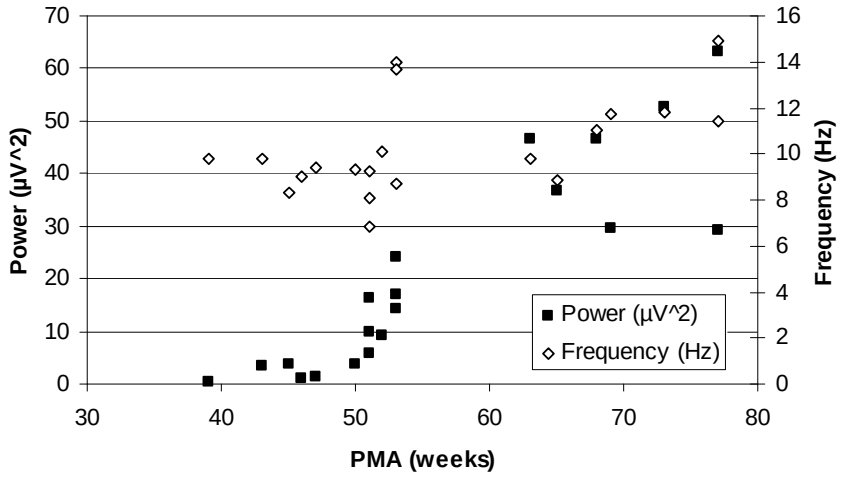


Table 6-15: Mean EEG prominent frequency, and its power, before sevoflurane turned off

Prominent frequency (Hz)	**Power of prominent frequency (μV^2)**	**Ratio of the prominent to background power**	**Age (weeks, PMA)**	**Pt ID**
0.29	9.78	2.75	39	28
9.8	3.49	2.05	43	18
8.3	3.82	2.57	45	25
9.0	1.11	1.85	46	22
9.4	1.31	1.77	47	27
9.3	3.79	1.93	50	26
6.8	16.15	3.56	51	20
8.1	5.81	2.30	51	24
9.22	9.86	1.87	51	23
10.1	9.34	2.14	52	14
8.7	24.12	2.50	53	19
14	14.2	2.54	53	31
13.7	17.16	2.03	53	29
9.8	46.43	1.88	63	11
8.88	36.58	1.92	65	12
11.0	46.45	2.55	68	21
11.7	29.73	1.66	69	30
11.8	52.65	2.32	73	32
11.4	29.35	3.22	77	13
14.9	63.13	2.16	77	15

Figure 6-20: Progression of EEG power in prominent frequency between 5 and 20 Hz Power units are μV^2 (NB: scale is logarithmic). Epoch length = 6 seconds.

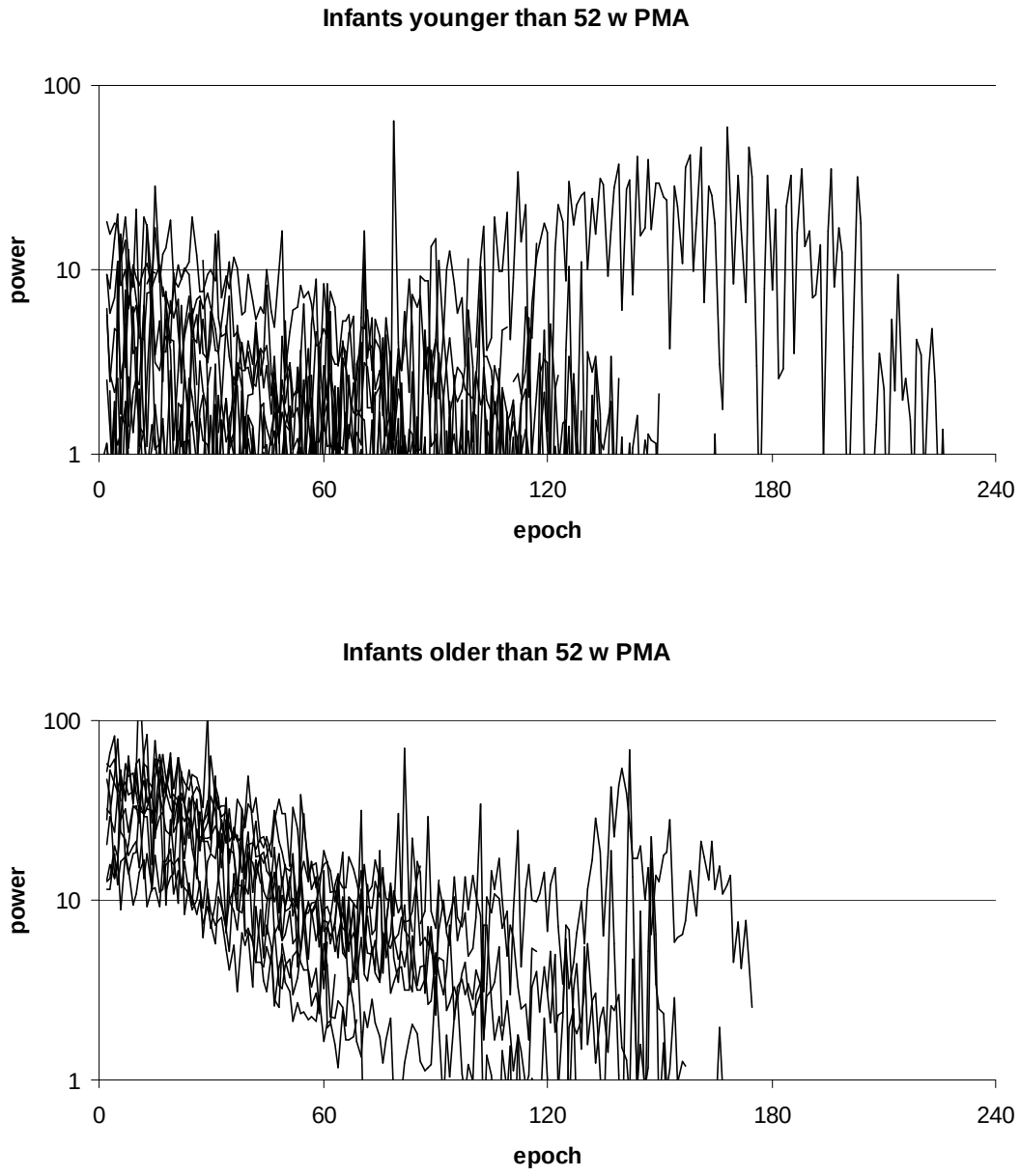
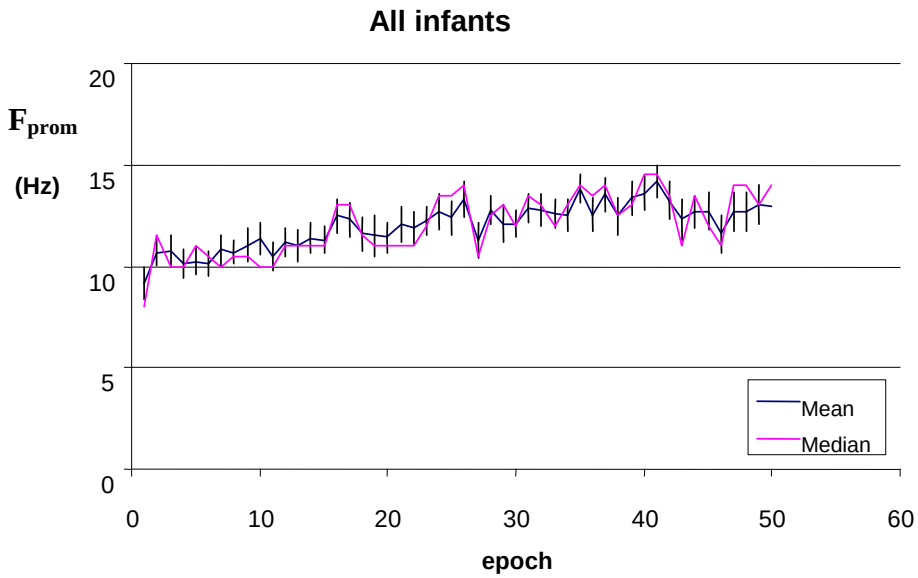


Figure 6-21: Progression of mean and median EEG prominent frequency power in all infants.

F_{prom} = prominent frequency. Vertical bars are SDs. Epoch length = 6 seconds.



6.5 Discussion

EMG signals have a frequency range and amplitude that easily obscures the EEG. In these series of infants awakening was usually associated with EMG and large changes in baseline amplitude. Consequently interpretation of these signals was limited. Moreover, once movement has occurred sophisticated monitoring is “too late” and it is reasonable to focus the search for changes in EEG before rather than after awakening began. An important observation is however that the visual appearance of the EEG did not change as awakening began in 6 infants; in these, change was delayed by 5 or more epochs later.

The choice of EEG channel is important. In this series, the amplitude in either of the centro-parietal channels was always higher than that in the frontal channels. The band

powers were also higher. Indeed the power in the frontal channels was often so low in the frequency range 5- 20 Hz that it was unlikely to show any appreciable change before awakening began. These findings contrast with other workers who have found either that frontal power is higher than central. These differences may be related to frequency band and age group.

Davidson and colleagues report that during anaesthesia (and surgery) the forehead mean log power was significantly greater than central. However this was the mean power rather than the power of any particular frequency or frequency band. Also, their data represented a mean for all children. When specified age groups were considered EEG power was higher in the frontal channels in toddlers aged 6 to 24m but lower in infants less than 6 months. Finally, the steady state may not be the same in all infants because there was a range of surgery taking place and various anaesthetic and analgesic drugs were used.

In another study by Lo et al children and infants have many EEG channels applied and the authors state that there was a frontal predominance of power although data supporting this statement was not presented.[159] All patients in Lo's series had either sevoflurane or isoflurane anaesthesia without any opioid supplementation.

The EEG of a newborn who is naturally sleeping often has an irregular tracé alternant pattern. This was noted in only one of the infants presented here; he was 40 weeks PMA. Otherwise signals were almost always continuous. In Davidson's series characteristic was described in all infants less than 6 months of age and the difference in our findings may relate to the depth of anaesthetic used. EEG discontinuity was not mentioned in Lo's study.

The visual appearance of the EEG in infants during anaesthesia has not been described in the literature. In this series accidentals were detected in only 5 out of 20 infants and accounted for only a few excluded epochs. The separation of infants according to visual identification of patterns of frequency has also not been reported before. Low frequency oscillations were almost always present but the presence of high frequencies was not appreciable until 52 weeks PMA.

Examination of the power across the measured frequency range of 1-70 Hz showed that power was minimal in frequencies higher than 20 Hz. Power with higher

frequencies may be useful in detecting the awake state[108], as described in adults, but they were not present before awakening began in this series of infants. The PSDs displayed in Figure 6-10 clearly show that the majority of the power lay within the frequencies less than 5 Hz and that in older infants there is appreciable power in the 5-20 Hz range. Investigators of the EEG often describe the PSD in terms of total power (TP), mean power (MP), MF and SEF. These measures however do not fully describe the power spectrum. For example, the SEF and MF are influenced most by frequencies with high power and will not readily be able to distinguish power changes in frequencies containing low power. TP and MP also do not distinguish between spectra of different shapes. The distribution of power within frequency bands is more helpful in this regard. Lo and colleagues have used the total power within α, β, δ and θ bands whereas Davidson and colleagues used total power within 2-20 Hz. Neither of these approaches however is able to identify a specific spectrum shape and therefore the finding in this series that older infants have a prominent frequency between 5 and 20 Hz cannot be confirmed by data from other studies.

An attempt has been made to establish whether the spectrum shape is present in the EEG before surgery took place and before opioids were administered. Ideally the comparison between the EEG power spectra at these two times should be made when other conditions are similar, for example sevoflurane concentration. This is not feasible and therefore comparison of EEG data at these times cannot be conclusive. In addition, the selection of the time of the EEG sampling before surgery is troublesome and potentially open to bias. The times chosen in this study tried to identify a steady state period immediately before surgical drapes where applied. It is possible that the steady state was not steady and that EEG characteristics varied.

The relationship of EEG power to age has been considered by Davidson and colleagues. They identified a clear relationship of band power in the 2-20 Hz range with age during surgical depth of anaesthesia. In their study infants less than 100 days old had power less than 100 μV^2. This is similar to the finding of this thesis bearing in mind that power was in the 5-20 Hz range, infants were anaesthetised with sevoflurane alone, and that they were undisturbed after surgery. Considering these differences, especially that the depth of anaesthesia was not controlled, the

relationship of EEG band power to age may not depend greatly on depth or whether isoflurane or sevoflurane is used. However EEG power is dependent on concentration of anaesthetic in adults and this is likely to be true also in infants.

Lo and colleagues state that they measured power at various steady state concentrations of sevoflurane yet they contradict this statement by saying that the anaesthetic was not changed by their study protocol. The findings of their study are difficult to interpret because the length of time spent at various concentrations of anaesthetic has not been stated.

In this chapter infants who were older than 3 months (52 weeks PMA) had EEG band power in 5-20 Hz range during sevoflurane anaesthesia and this decreased soon after sevoflurane was turned off. The precise concentration of sevoflurane in the brain cannot be measured but is assumed to be close to the end-tidal concentration. Some effect from sevoflurane in the spinal cord may be present however and this may mean that the brain concentration is not all important. This thesis found that by 5 minutes, when P_{et}Sevoflurane had reduced to approximately 0.5% P5-20Hz had reduced in all infants (>52 weeks) to less than 100 μV^2. In Davidson's study P2-20Hz did not decrease in infants <6 months old but did decrease in infants aged 6-24 months. The decrease was demonstrated by comparing power at 2 time points and not by examining the trend over a time sequence. Lo and colleagues studied infants and children up to 3 years of age and, showed that as sevoflurane concentration decreased during awakening, alpha and beta power increased. These differences may be because the concentration of sevoflurane used was much higher (mean P_{et}Sevoflurane was 3.2%) probably because no opioids were used. Another reason why the change in band powers was different to those presented in this thesis was that Lo and colleagues calculated the mean power from across many channels.

One other study reported change in EEG band power during emergency. Murray and colleagues studied children recovering from propofol sedation in intensive care and found that the power decreased in frequencies higher than 12 Hz.[160] Further studies of controlled emergence from anaesthesia may help confirm the value of EEG band power in charting recovery of consciousness.

The description of prominent frequency has been described before but not for sevoflurane. In children alpha waves have been described by both Constant[144] and James,[141] but neither prominent alpha nor beta waves have been described during anaesthesia in infants. In a recent report on the investigation of a new benzodiazepine in sheep the power within the beta range was used as a measure of sedation.[300]

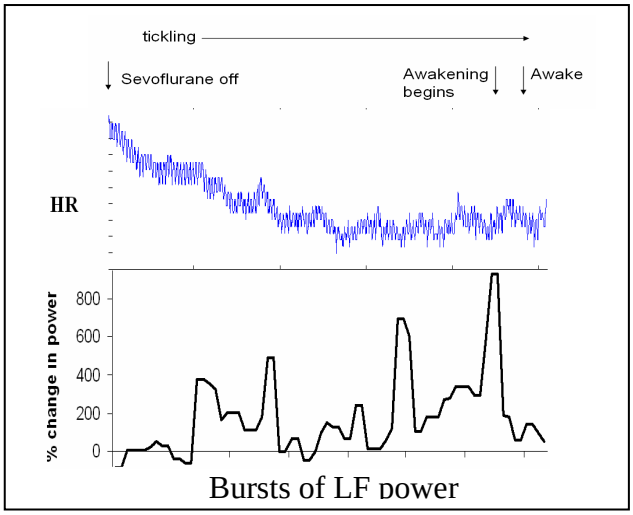
6.6 Conclusions

- EEG power was larger in the centro-parietal than the frontal channels.
- The EEG after awakening is difficult to interpret because of interference.
- EEG characteristics during anaesthesia before and after surgery are similar
- Before awakening most EEG power lies in the low frequency range.
- In the range 5-20 Hz EEG power during sevoflurane anaesthesia increases with age
    - In infants less than 52 weeks PMA the power is negligible
    - In infants older than 52 weeks PMA the EEG power is greater than100 μV^2
        - This band power decreases during sevoflurane wash-out and before awakening began.
        - Awakening did not begin until P5-20 was less than 100 μV^2.

7 Characterisation of HRV changes

THESIS THUMBNAIL

- Background
- Hypothesis
- General methods
- Model of awakening
- EEG characteristics
- HRV characteristics
- Assessment of prediction
- EEG and HRV changes with stimulation
- EEG power and age



7.1 Introduction and aims

HRV is associated with autonomic nervous system activity. The previous chapter describes the EEG changes during awakening. This chapter examines the HRV changes that may indicate autonomic *arousal* as sevoflurane levels decrease and as awakening began. The main aims of this chapter are to determine if HRV changes before awakening began and if any HRV characteristics could be used to warn of or predict awakening.

7.1.1 Objectives

- To determine HRV characteristics during awakening from anaesthesia after surgery.

7.2 Methods

7.2.1 Subjects and general methods

The subjects and general methods are those described in the previous chapter. Three ECG channels were recorded from self-adhesive skin electrodes placed on the shoulders and the left side of the chest. Signal processing is described in section 4.4.4.3.

7.2.2 Statistical methods

Initially, descriptive statistics were used to show any trend over time between four periods. Periods lasted 1 minute and started from:

- One minute before sevoflurane turned off (bSO)
- 5 minutes after sevoflurane had been turned off (5aSO)
- One minute before awakening began (bAB)
- One minute after awakening began (aAB).

Where differences were appreciable in any variable, the variable was calculated for each period and plotted to identify any trend of change over the time. Statistical methods used in analysis of EEG data were applied.

7.3 Results

7.3.1 Visual appearance of raw signals

ECG data was successfully collected in 19 infants (not collected in one due to error). All R waves were easily visually identified except in 8 patients during aAB because of artifacts and interference related to movement. ECG recordings of these periods were not analyzed.

7.3.2 Time domain

Table 7-1 summarizes the heart rate variation over four one minute periods. The minimum and maximum heart rates in any infant, and at any time during these times, were 83 and 179 per minute respectively. Before anaesthesia was turned off only one infant had an SDiffNN greater than 25 milliseconds. During later periods 3, 7 and 7 infants had SDiffNN greater than 25 milliseconds during 5aSO, bAB and aAB respectively.

Figure 7-1 shows distribution of mean heart rate at each one minute period (mean heart rate calculated from the RR intervals of successive beats). Figure 7-2 shows the distribution of change in mean heart rate at these times. In comparison with bSO, there was a small but statistically significant decrease in mean heart rate (mean change of 4.8 beats per minute, CI -7.52 to -2.07) during 5aSO; an increase in heart rate after awakening began (mean change 11 beats per minute, CI 3.6 to 21.5); but the mean heart rate did not change significantly from bSO through till bAB.

Table 7-1: HRV time domain variables of all infants at four periods after surgery

	bSO	**5aSO**	**bAB**	**aAB**
Mean NN	0.5109	0.5358	0.5201	0.4833
SDNN	0.0036	0.0095	3.5241	6.0047
Mean HR	119.37	114.57	118.3273	128.4007
SDHR	0.8209	1.9544	3.5241	6.0047
RMSSD	0.0036	0.0062	0.0121	0.0181
Infants with any NN25	1	3	7	7
Infants with pNN25 > 10%	0	0	2	0

Figure 7-1: Distribution of mean heart rate during one minute just before sevoflurane was turned off

Mean heart rate = mean of beat to beat heart rates over one minute. Mean heart rate =/> category label and < next category label. n = number of infants.

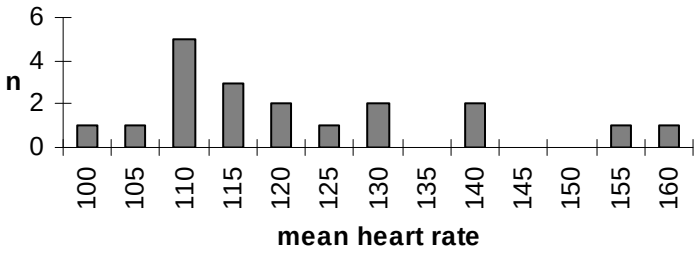
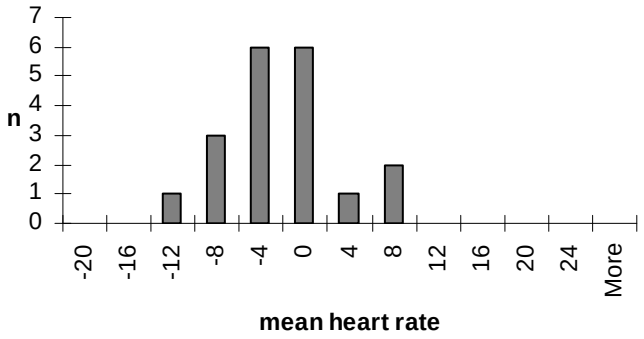


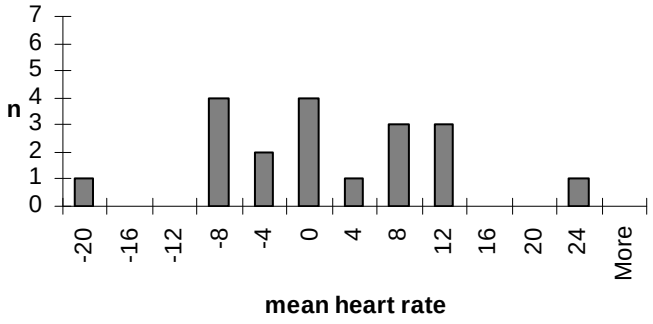
Figure 7-2: Change in mean heart rate after sevoflurane turned off

Mean heart rate (mean of beat to beat heart rates over one minute) =/> category label and < next category label. n = number of infants. Comparisons made within each infant between one minute before sevoflurane turned off (bSO) and:

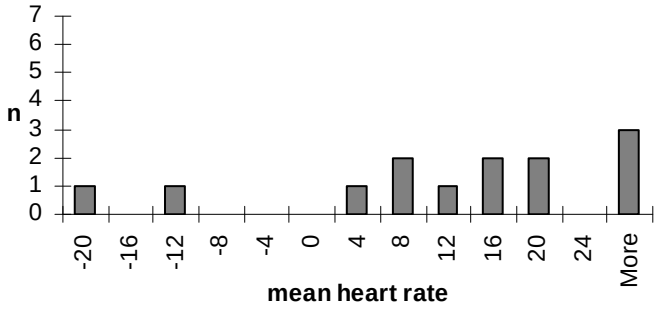
(1) 5 minutes later (5aSO) (mean change -4.8, CI -7.5 to -2.1)



(2) before awakening began (bAB) (mean change -3.3, CI -8 to 1.5)



(3) after awakening began (aAB) (mean change 12.5, CI 3.3 to 21.8)



7.3.3 Frequency domain

7.3.3.1 Power spectrum density

For ease of presentation in graphs and tables, the power units, s^2, have been multiplied by a factor of 10^6. The figures below show that ranges of powers for all infants within each frequency band were wide and not normally distributed. Most signal power lay within frequencies less than 0.4 Hz. No infant had appreciable power in frequencies over 1Hz and therefore powers in frequencies greater than 1 Hz are not presented. Figure 7-3 shows the relationship of mean band power (with SD) to frequency during bSO and demonstrates wide SDs across all frequencies. Figure 7-4 shows the relationship of power (median with 25^{th} and 75^{th} percentiles of all infants) to frequency after sevoflurane was turned off. There is an obvious increase in power in frequencies (<1Hz) after sevoflurane was turned off and when awakening began. Further analysis was performed on power within wider frequency bands.

Figure 7-3: Distribution of HRV power density in all infants during one minute before sevoflurane turned off

Vertical lines represent one SD. Power density units = $seconds^2.10^{-6}/Hz$

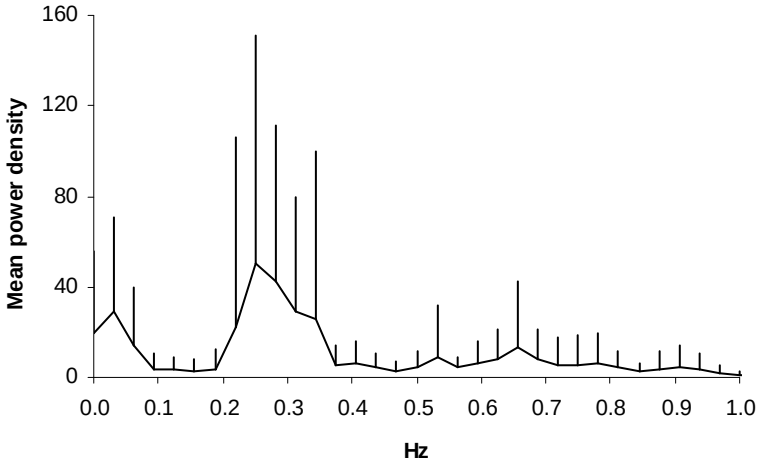
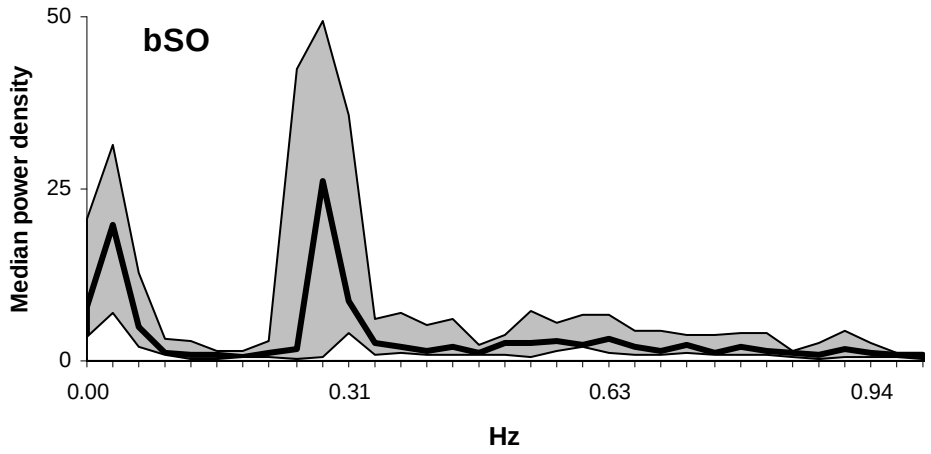


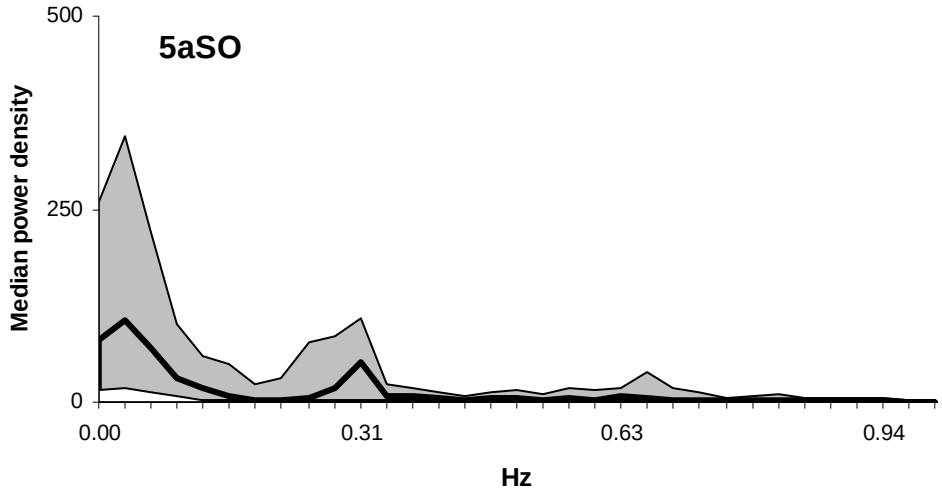
Figure 7-4: Median HRV power density at four periods after surgery

Grey shaded areas represent the limits of 25th and 75th percentiles. The black line in the shaded areas joins all medians. Power density units = seconds^2.10^{-6}/Hz. Frequency resolution = 0.3125 Hz. NB: the scales of the y axes are different. The y axis scale in bSO is one tenth of the scale in 5aSO and one fiftieth of the y axes in the other 2 graphs.

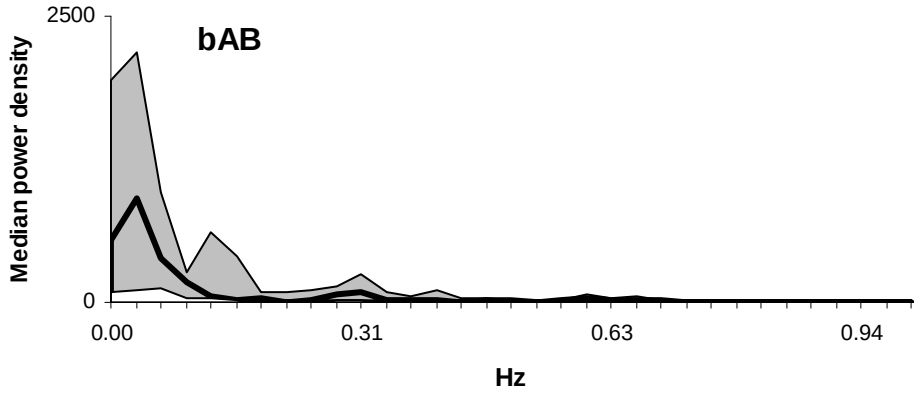
(1) Before sevoflurane turned off (bSO).



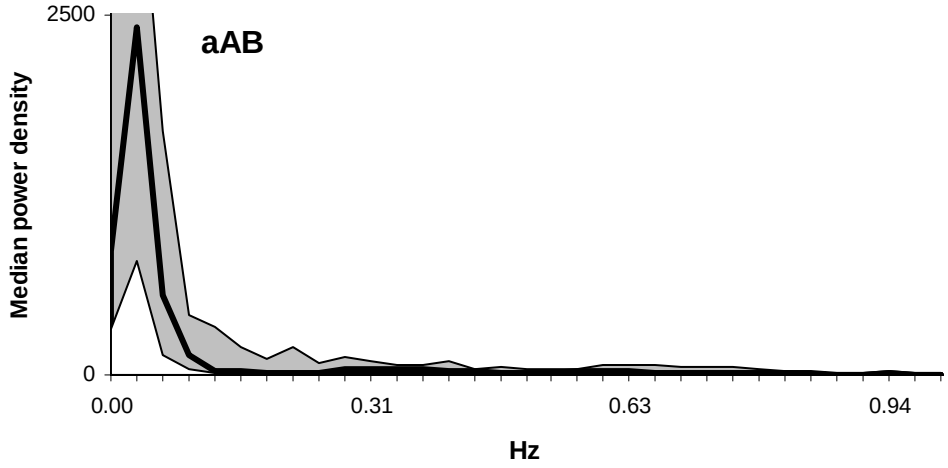
(2) 5 minutes after sevoflurane turned off (5aSO)



(3) Before awakening began (bAB)



(4) After awakening began (aAB)



7.3.3.2 Band power

Table 7-2 shows the distribution of band power during bSO, and that the means are markedly different to the medians for raw power, but not after they have been log10-transformed. The power within frequencies greater than 1 Hz was much smaller than in other frequency bands.

Table 7-2: Distribution of HRV band powers during one minute before sevoflurane was turned off

	LF (0.03-0.15 Hz)	**HF (0.19-0.41 Hz)**	**vHF (0.44- 1 Hz)**	**xHF (>1 – 2 Hz)**
Raw band power (s^2)				
mean	53.2	186.3	101.4	3.0
median	27.1	74.3	44.9	2.2
SD	79.3	244.3	146	3.3
max	334.7	800.6	527.4	14.5
min	0.8	6	21.7	0.3
Log10 band power				
mean	1.4	1.9	1.8	0.2
median	1.4	1.9	1.6	0.3
SD	0.6	0.6	0.4	0.5

7.3.3.3 Change in power spectrum

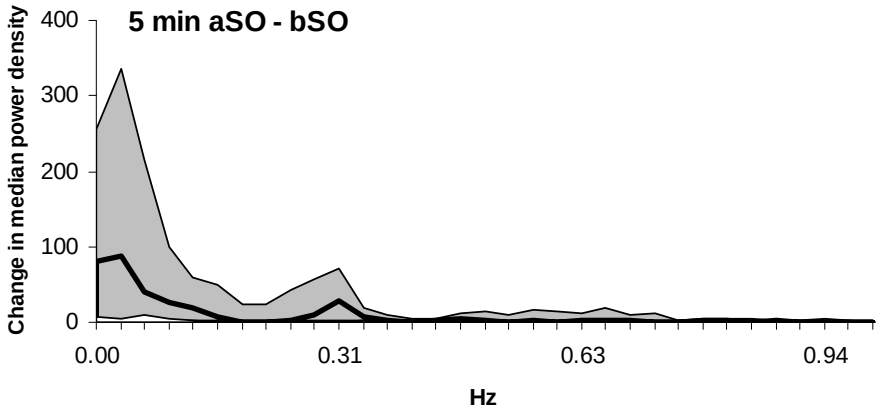
Figure 7-5 represents the change in power from bSO to 5aSO, bAB and aAB, within each infant, across the spectrum of frequencies (<1Hz) and confirms the trend for an increase in power after sevoflurane has been washed out. The main increases appear to be within the LF and HF frequency bands.

Figure 7-5: Change in median HRV power density

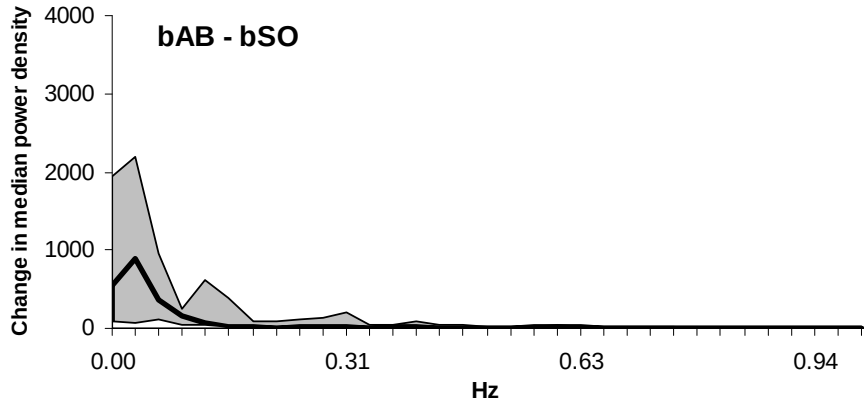
The black line in the shaded areas joins all medians. Grey shaded areas represent the limits of 25th and 75th percentiles. Power density units = seconds^2.10^{-6}/Hz. Frequency resolution = 0.3125 Hz.

(1) Change from before sevoflurane was turned (bSO) off to 5 minutes later (5aSO)

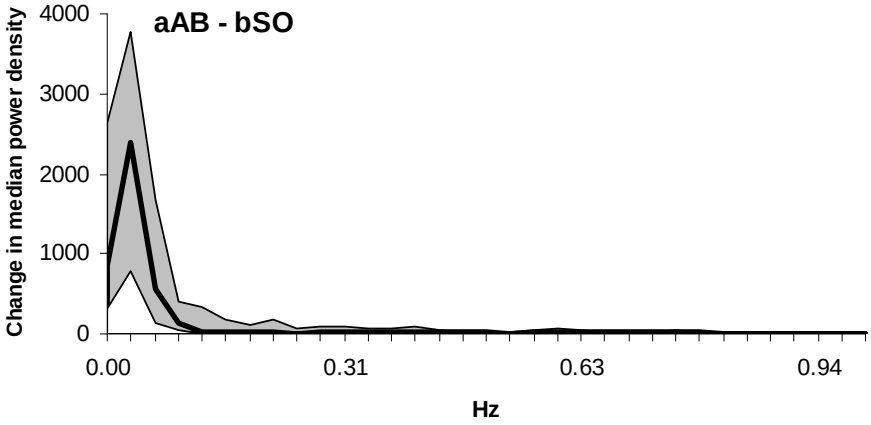
NB: the scale of the y axis is one tenth of y axes in the other graphs.



(2) Change from before sevoflurane was turned (bSO) off to before awakening began (bAB)



(3) Change from before sevoflurane was turned (bSO) off to after awakening began (aAB)



7.3.3.4 Change in band power – comparisons at specific times

The changes in band power (raw and log transformed) in the 3 times after sevoflurane was turned off (5aSO, bAB and aAB) compared with the power during sevoflurane anaesthesia (bSO) were calculated and are displayed in Table 7-3, Table 7-4 and Table 7-5. These data show that raw power is unlikely to be normally distributed; the means are substantially different to the medians and the SD's are large. The means in log10 data however are similar to the medians although the SD's are similar to the means. Further analysis with histograms and Normal plots supported the assumption that log10 transformed band power is normally distributed.

The change in log10 power was significant and appreciable in all frequency bands and at all times. At bAB the LF band power was 45 times higher than that at bSO (95% confidence limits 16.59 to 122.7).

Table 7-3: Change in HRV band power from before sevoflurane turned off (bSO) to 5 minutes later (5aSO)

5aSO-bSO	**LF (0.03-0.15 Hz)**	**HF (0.19-0.41 Hz)**	**vHF (0.44- 1 Hz)**	**xHF (>1 – 2 Hz)**
Change in raw band power (s^2)				
mean	1336.37	432.06	150.95	1.34
median	144.60	137.56	56.96	0.24
SD	2530.71	861.48	253.36	3.28
max	8016.34	3320.64	1086.85	9.48
min	-33.96	-126.34	-19.22	-2.94
Change in log 10 band power				
mean	0.89	0.42	0.37	0.08
median	0.79	0.3	0.27	0.06
SD	0.83	0.56	0.41	0.23
CI of mean	0.51 to 1.28	0.16 to 0.68	0.18 to 0.56	-0.12 to 0.29
Antilog				
Geometric mean change	7.85	2.66	2.34	1.21
CI of geometric mean	3.24 to 19.04	1.46 to 4.83	1.51 to 3.63	0.76 to 1.95

Table 7-4: Change in HRV band power from before sevoflurane turned off (bSO) to before awakening began (bAB)

bAB-bSO	**LF (0.03-0.15 Hz)**	**HF (0.19-0.41 Hz)**	**vHF (0.44- 1 Hz)**	**xHF (>1 – 2 Hz)**
Change in raw band power (s^2)				
mean	4087.79	1994.00	497.61	5.51
median	2325.78	206.35	149.54	3.63
SD	4936.15	5231.36	957.98	9.07
max	16287.53	22102.57	3204.68	37.79
min	16.89	-498.66	-25.66	-6.70
Change in log10 band power				
mean	1.65	0.69	0.64	0.42
median	1.99	0.42	0.59	0.46
SD	0.93	0.91	0.54	0.56
CI of mean	1.22 to 2.09	0.26 to 1.11	0.39 to 0.89	0.15 to 0.68
Antilog				
Geometric mean change	45.12	4.84	4.35	2.61
CI of geometric mean	16.59 to 122.7	1.82 to 12.87	2.44 to 7.74	1.42 to 4.78

Table 7-5: Change in HRV band power from before sevoflurane turned off (bSO) to after awakening began (aAB)

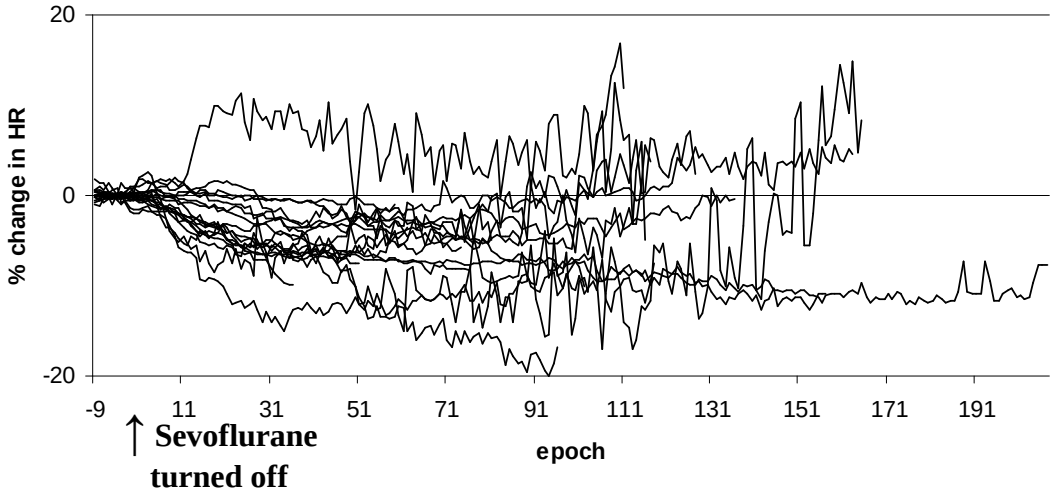
aAB-bSO	**LF (0.03-0.15 Hz)**	**HF (0.19-0.41 Hz)**	**vHF (0.44- 1 Hz)**	**xHF (>1 – 2 Hz)**
Change in raw band power (s^2)				
mean	6815.66	806.42	645.67	80.13
median	3430.54	287.44	156.46	13.18
SD	8797.54	1518.13	1117.39	159.07
max	30087.14	4657.64	3922.48	539.26
min	139.12	-515.90	-2.12	-1.99
Change in log10 of band power				
mean	1.92	0.54	0.81	0.99
median	2.04	0.81	0.74	0.85
SD	0.77	0.97	0.70	0.90
CI of mean	1.52 to 2.31	0.04 to 1.04	0.45 to 1.17	0.53 to 1.45
Anti-log				
Geometric mean change	82.32	3.47	6.44	9.75
CI of geometric mean	33.12 to 204.6	1.11 to 10.92	2.80 to 14.82	3.36 to 28.26

7.3.3.5 Change in HRV band power - time sequence

Comparing power at specific times has shown an overall change but does not describe the change in power throughout the whole study period. The PSD therefore was calculated for the whole period from bSO until awakening. Every R wave fiducial point was checked visually to make sure that it was correctly identified by the MATLAB program. R wave identification was unreliable in more than 20% of beats in 3 infants and these data were not processed. There was one ectopic beat. The HR was calculated in every epoch (epoch length = 6 seconds) by converting the mean of the RR intervals in epoch. The percentage change in mean HR from baseline (bSO) is presented in Figure 7-6 and shows that during the first minute the heart rate was steady. In the subsequent 8 minutes (approximately) the HR decreased in all but one infant. Thereafter there was often an increase before awakening began.

Figure 7-6: Progression of % change in HR

HR = mean beat by beat heart rate over one 6 second epoch (beats per minute)

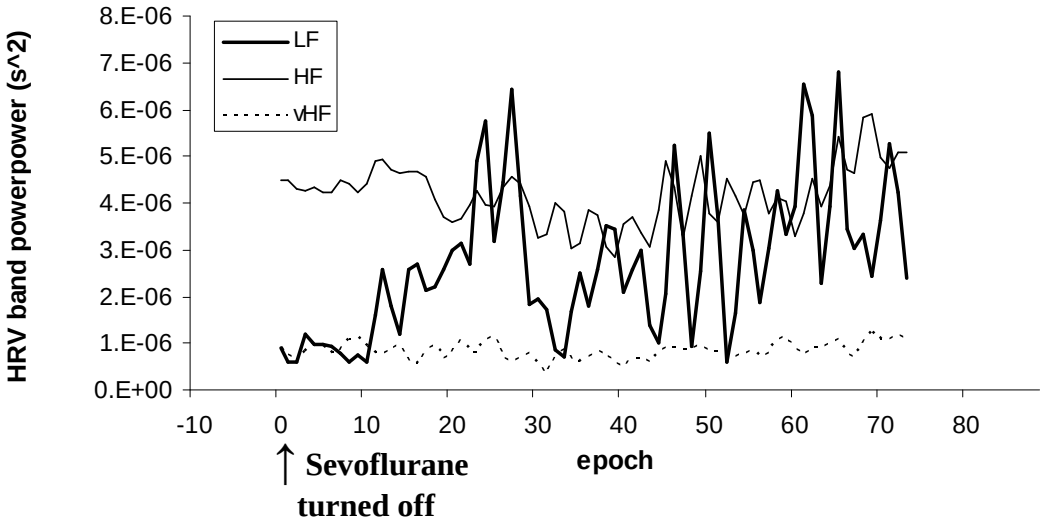


The PSD was calculated in each period of length of one minute using the Welch method with a window length of 30 seconds and 0.25 overlap. This enabled a frequency resolution of 0.033Hz, over a range of 2 Hz (sample frequency of interpolated RR interval sequence = 4 Hz). Each PSD in the sequence therefore represents the previous minute of HRV. To obtain a time sequence of PSDs, a PSD was calculated every 6 seconds later in the time sequence. The band power frequencies were similar to those used previously.

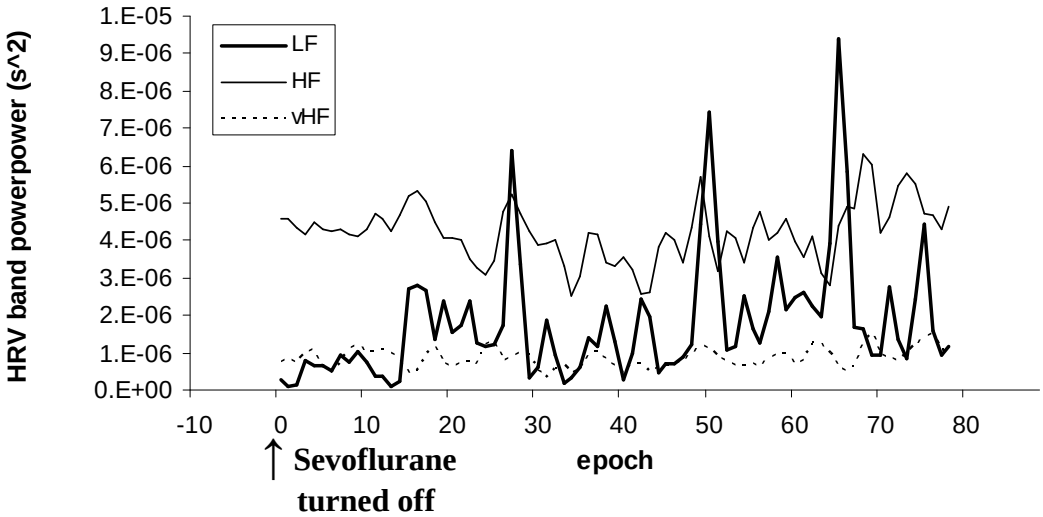
The percentage change in band power from baseline band power was plotted over time. Baseline band power was taken as the mean band power from the first 10 PSDs in the sequence; these represent two minutes of steady state starting one minute before and ending one minute after sevoflurane was turned off. An example of the progression of % change in HRV band power is presented in Figure 7-7; the figure also shows the progression of RR intervals over the same time period. This infant (Pt 11) is typical in that the LF power increase is irregular. A reduction in the period length to 30 seconds (Welch window length unchanged at 30 seconds) changes the sequential change in PSD to show that the irregular increase appears to be in a burst pattern.

Figure 7-7: Typical irregular progression of HRV band power and corresponding RR interval sequence

(A) HRV band power progression. Period length = 60 seconds. First powers represent previous 60 seconds.



(B) HRV band power progression. Period length = 30 seconds. First powers represent previous 30 seconds.



(C) Progression of ECG RR intervals

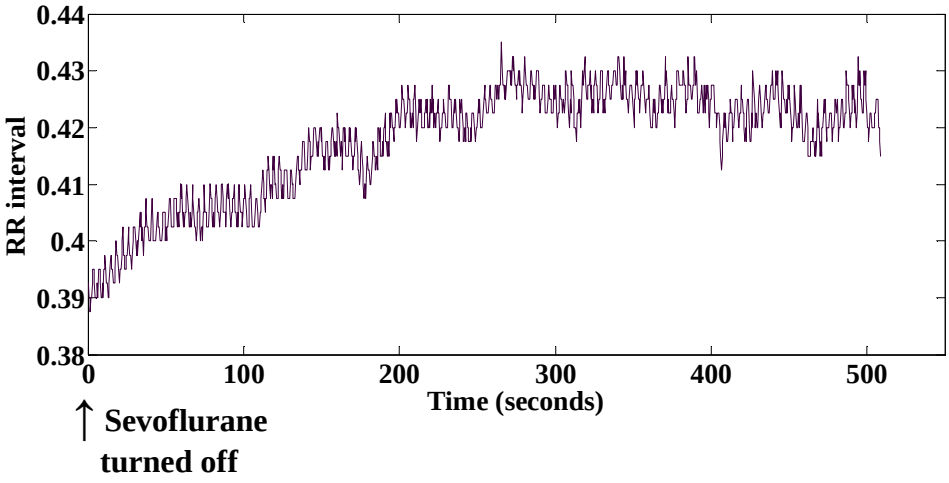


Figure 7-8 demonstrates the progression of change in power for all infants and shows that there is a general but irregular trend for the band power to increase with time. Note that the y-axes scales are different. Band power was filtered with a simple median filter (length = 3 data points) but this did not make the plots appreciably less irregular. The range of power in the LF band was 10 and 100 times that of HF and vHF band power respectively emphasising that the majority of the power is in the LF range. Figure 7-9 shows the same graphs but with more detail in the low power range, and these demonstrate that in many infants the power remains low and varies around the *zero* change: power may decrease as well as increase by up to 100% below and above the baseline mean value.

The time of the first appreciable increase in band power was estimated. Mean baseline band power and SD were calculated. Epochs were identified with band power that exceeded a limit of mean + (2* SD) of baseline band power. The beginning of appreciable change after the baseline period was estimated as the 2nd epoch of raw band power exceeding the limit (epochXL). The second epoch was chosen because the change in band power was irregular and one isolated increase in band power may have been misleading. The mean epochXLs were not appreciably different. Mean epochXLs (SD) were 27.9 (18.3), 33.3 (31) and 32.7 (17.7) for LF, HF and vHF respectively.

Figure 7-8: Progression of % change in HRV band power

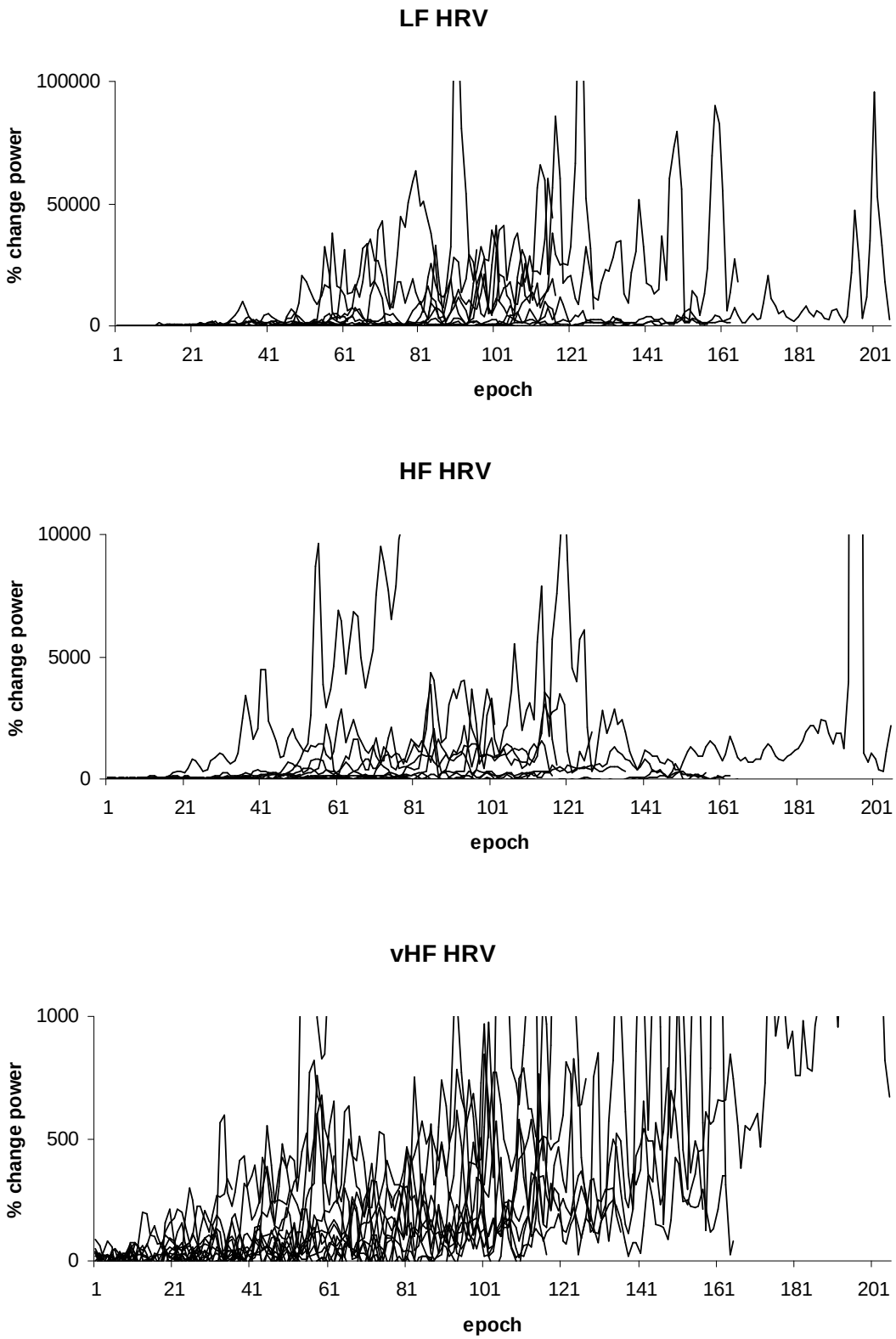
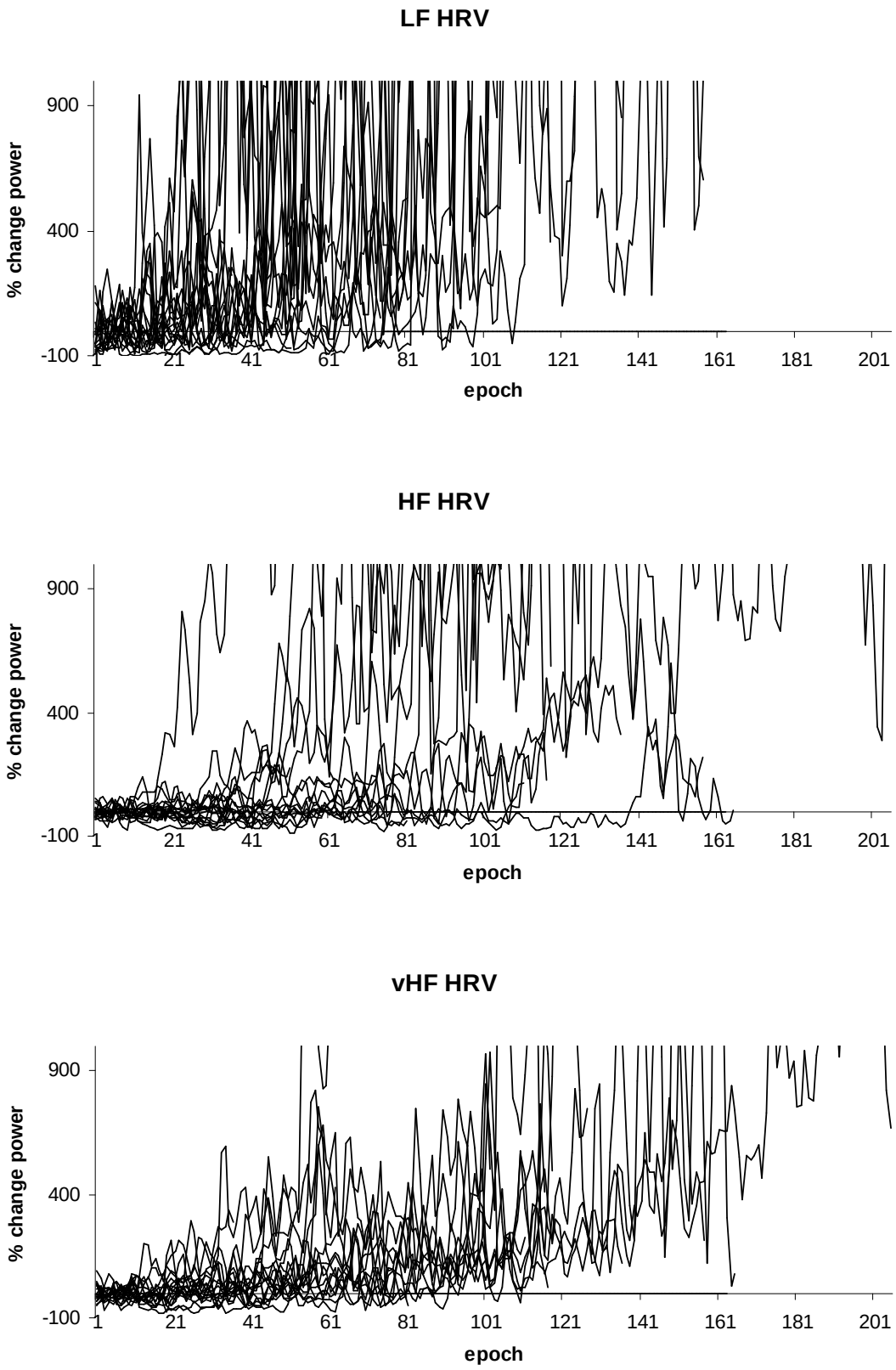


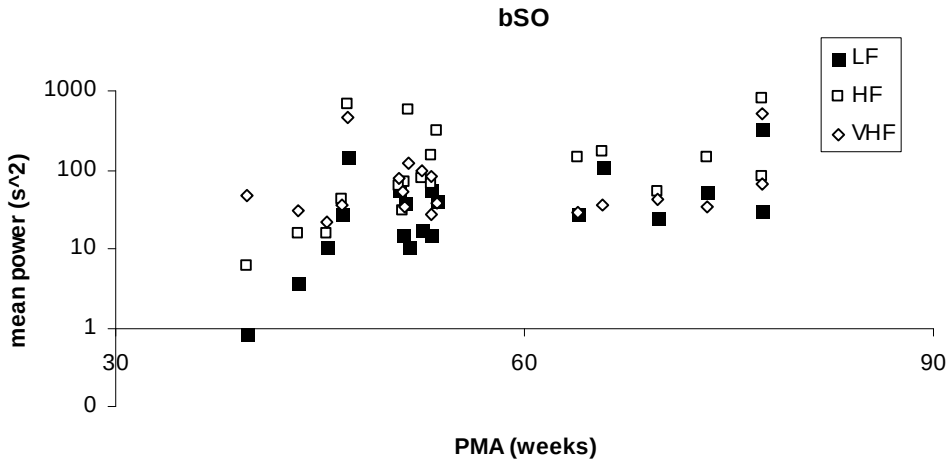
Figure 7-9: Detailed progression of % change in HRV band power



7.3.3.6 Effect of age on band power during anaesthesia

A survey of any association of age and HRV band power found low correlation coefficients for all band powers for common regression models (linear, log, exponential, quadratic, growth). The highest R^2 value was 0.422 for a logarithmic model of the effect of PMA on LF band power at bSO. Figure 7-10 shows that there is a weak trend for band power to be higher in older infants.

Figure 7-10: Relationship of age to HRV band power during anaesthesia (bSO)



7.4 Discussion

There are practical difficulties with HRV. R wave identification needs visual checking before RR intervals can be considered to be accurate. After awakening began, R wave identification was sometimes too difficult and consequently some RR intervals could not be measured. Before awakening began, RR intervals could be identified in almost all epochs. Checking RR intervals was easily achieved by plotting them and any mistakes in R wave identification, or any ectopic beats, could be readily identified and indices could then be rechecked. This was practical in all infants for short data sequences because the number of false R wave indices was less than 100. HRV PSDs and band powers could therefore be calculated and compared at specific short periods (see section 7.3.3.4). However when checking long sequences (section 7.3.3.5) the number of false R waves was many more than 100 in 3 infants and, for practical reasons, these sequences were not studied.

Time domain variables at specific times did not show any useful features that changed reliably with time. HR tended to decrease as soon as sevoflurane was turned off but by 7 or 8 minutes later it increased in some infants. HRV band power showed some potentially useful changes related to time after the sevoflurane was turned off. During anaesthesia HF band power was most prominent, and appreciably greater than LF power. Approximately one minute after sevoflurane is turned off power in all three frequency bands began to increase and by 5 minutes the mean power had increased significantly. However, there was appreciable variation in power.

First, the variation in band power during steady state anaesthesia is appreciable with most infants showing a variation of 100% greater or less than the mean and this can be seen in the first minute after sevoflurane has been turned off (Figure 7-9). Consequently attempting to estimate the time of an increase in band power will depend upon the chosen limit that the band power must exceed. Choosing the limit is arbitrary and a limit of 2*SD more than the mean seems reasonable but may not describe the time of an important increase in power; the limit may be set too low or too high and there is no measure of how long the increase lasted.

Second, LF power, in particular seems to vary in bursts and quantification of these may be a better way to describe the change in band power. There is a substantial increase in the group mean band powers before awakening began and the greatest increase was in the LF range. However the range of increase was wide and some infants did not increase their power at this time. This may be a feature of the burst characteristic of LF power in that the power was outside the burst at this time.

Band power tends to be higher in older than in younger infants but this relationship is weak and rests upon steady state mean HRV band power.

7.5 Conclusions

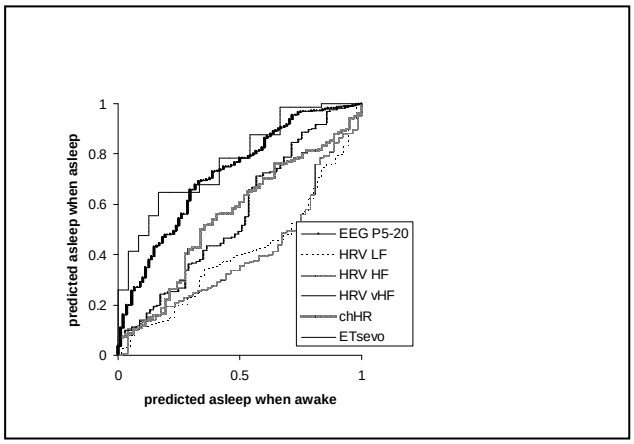
- HRV frequency domain band power changes in a characteristic fashion after sevoflurane is turned off.
- Power in LF increases considerably more that HF and vHF but the increase appears in bursts.
    - Measurement and comparison of LF power at specific times may not describe the change in LF power in a sequence of data.
    - The identification and quantification of bursts may be more useful.

8 Further observations

8.1 Assessment of prediction

THESIS THUMBNAIL

- Background
- Hypothesis
- General methods
- Model of awakening
- EEG characteristics
- HRV characteristics
- Assessment of prediction
- EEG and HRV changes with stimulation
- EEG power and age



8.1.1 Introduction and aims

EEG and HRV changes during emergence for anaesthesia may be useful but their ability to determine change in conscious level needs to be tested. The standard statistical methods of Receiver Operating Characteristic (ROC) and prediction probability (PK) were applied to the data obtained from 20 infants described in section 5.4.

8.1.2 Methods

In these infants, studied in section 5.4, sevoflurane was turned off after surgery was complete and emergence occurred at a variable time thereafter. It was assumed therefore that there was a monotonic (always increasing) change in both conscious level and expired sevoflurane concentration. Note that the movement after awakening began usually created interference with EEG and ECG recordings and also prevented accurate end-tidal sevoflurane recordings. Consequently, in the scenario of emergence, during the *awake* phase, data without movement artifact was usually not

possible and therefore data was categorized into the following 3 ‘levels’ or ‘stages’ of emergence:

- Sleep (all times before first movement)
- Movement (from first movement until 60 seconds before awakening began)
- Before awakening began (60 seconds before awakening began until awakening began)

In each infant the variable being tested was matched with the emergence level. Variables tested included:

- End-tidal sevoflurane concentration
  measured once per minute from when sevoflurane was turned off until awakening began
- EEG power in 5-20Hz frequency band (P5-20Hz)
  calculated for each epoch (length 6 seconds) from when sevoflurane was turned off until awakening began
- HRV power in LF, HF and vHF frequency bands
  calculated for each epoch (each value represents previous 60 seconds) from one minute after sevoflurane was turned off until awakening began)
- Mean % change in heart rate
  Calculated from mean RR interval over each epoch (length 6 seconds) and compared with mean RR during one minute before sevoflurane turned off, from when sevoflurane was turned off until awakening began

For EEG, HRV and heart rate there were 10 data items (for each infant) representing the period *before awakening began* compared with variable numbers of data items for *sleep* and *movement* levels of emergence. For end tidal sevoflurane there was one data item representing the minute *before awakening began*; variable numbers of data items represented other levels of emergence.

Data are presented separately for infants younger and older than 52 weeks PMA.

8.1.2.1 Histograms

Data were plotted to show their distributions in levels of emergence. These plots may allow visual estimation of how well a variable might distinguish between sleep and *before awakening began.*

8.1.2.2 Receiver operating characteristic (ROC)

Analysis was performed using the statistical software SPSS version 16 and a free-access Excel spreadsheet from the internet website www.anaesthetist.com. ROC is a graphical representation of how sensitivity and 1-specificity change as the value of the "cut off" varies. Sensitivity and 1-specificity are also known as "true positive" and "false positive" rates respectively. Two scenarios were considered according to whether the detection of "sleep" as opposed to "awake" was intended. "Sleep" was chosen as the outcome of greatest interest because it may be more important to make sure that the infant is asleep (anaesthetised) during surgery rather than awake during awakening. In this scenario the true (TPR) and false (FPR) positive rates are equivalent to the following:

- TPR = predicted asleep when actually asleep
- FPR = predicted asleep when actually awake

Alternatively, if it is considered important to predict awakening then the following can be calculated:

- TPR = predicted awake when actually awake
- FPR = predicted awake when actually asleep

In the first scenario, the ROC may be used to protect a patient from being wrongly considered asleep and in the second, the ROC could be used to protect the patient from be being falsely considered awake. The purpose of the ROC in these two scenarios is to protect the patient from inadequate and excess anaesthesia respectively. To achieve these aims the FPR should be minimal. The cut-off predictor variable value was estimated at which the FPR was 0.05 (=95% specificity). The corresponding TPR was calculated at this cut-off value. The area under the ROC curve was estimated using SPSS together with its 95% confidence intervals; it is a

measure of the difference between the ROC curve and the line of equality, which has an area of 0.5, and therefore for statistical significance (P=0.05) 95% confidence intervals should not enclose 0.5.

8.1.2.3 Prediction probability

Prediction probability (PK), described by Smith and colleagues, has become a standard tool to estimate of the ability of an anaesthetic depth indicator to detect or predict the true observed *depth*.[301] The test outcome is the probability that the predictor variable correctly predicts the rank order of any pair of observed *depths*. Commonly, in the literature, the model to be tested has both the predictor variable and the depth ideally monotonically (always) increasing during emergence (for example BIS increases as the patient awakens): under this assumption if, in any data pair, both the predictor variable and the observed depth change in the same direction the pair are considered concordant. The PK is a statistic that is based on the ratio of the probability of concordance to the combined probabilities of concordance, disconcordance and tied predictor variables. PK varies between 1 (all pairs concordant) and zero (all pairs disconcordant). In the model presented here EEG power and end tidal sevoflurane levels are decreasing and the PK presented inn the results is 1 minus the calculated PK. PK was calculated using the Excel macro PKMACRO made available by Smith and colleagues. [301] For PK estimation the mean EEG power, HRV and heart rate were calculated for each minute so that these data could be compared with end-tidal concentration data. The PKDMACRO was used to estimate the difference between PK values within each age group.

8.1.3 Results

8.1.3.1 Histograms

Figure 8-1 shows the distributions of end-tidal sevoflurane and P5-20Hz during *sleep* compared with one minute *before awakening began*. Of all the histograms of the predictor variables, this is the best example showing how the variable in question distinguishes *sleep* from *before awakening began*. Histograms of EEG power in the 5-20 Hz band are also shown in Figure 8-2.

Figure 8-1: Histograms of distributions of end-tidal sevoflurane infants during sleep and before awakening began.

0 = asleep and movement alone, 1 = before awakening began.

Frequency = number of epochs in all infants

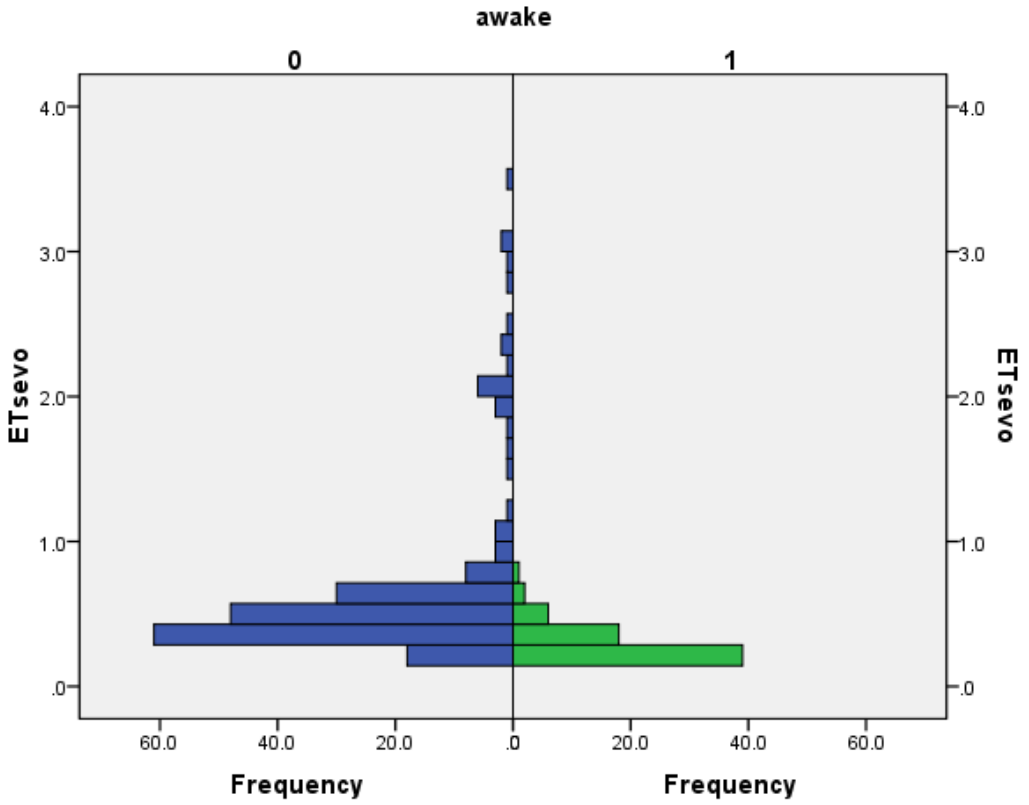
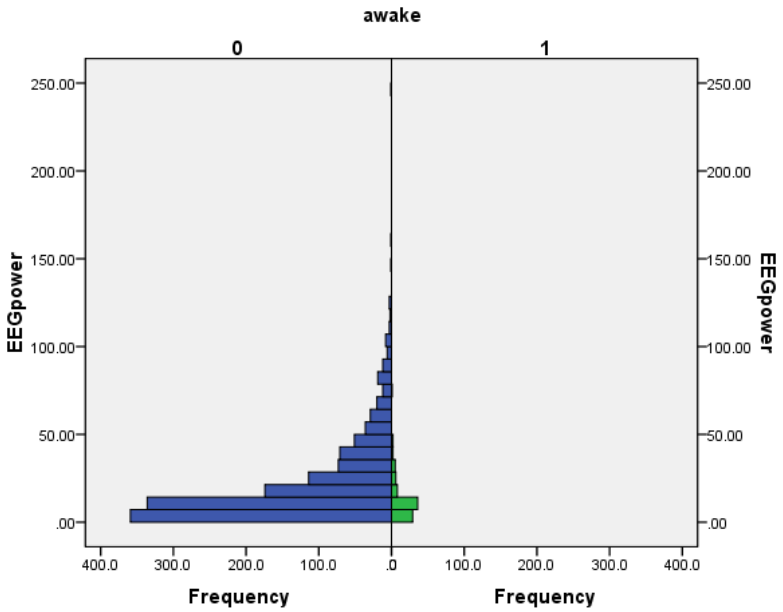


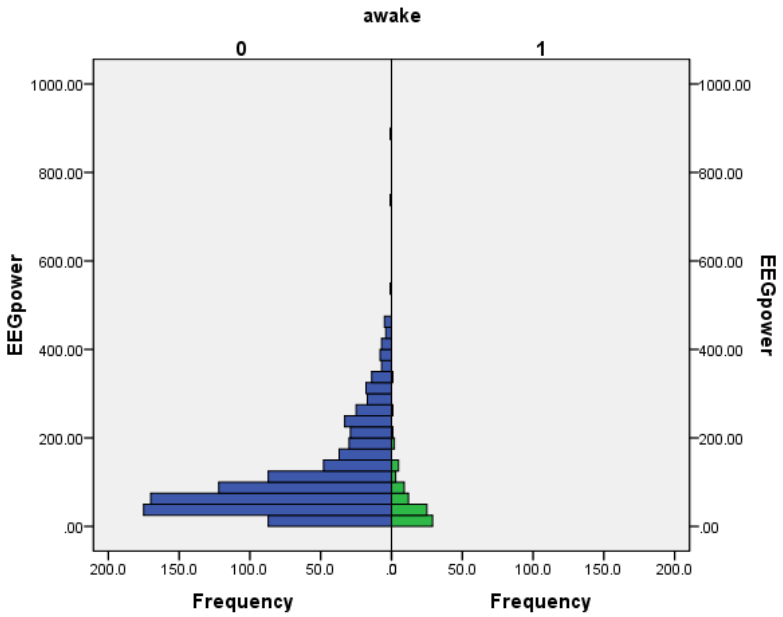
Figure 8-2: Histograms of distributions of EEG power (5-20Hz) infants during sleep and before awakening began.

0 = asleep and movement alone, 1 = before awakening began. Frequency = number of epochs in infants of two age groups

A: Infants younger than 52 weeks PMA.



B: Infants older than 52 weeks PMA.



8.1.3.2 Receiver operating characteristics

Data are presented separately for infants younger and older than 52 weeks PMA. ROC curves are in Figure 8-3. Cut-off values and their corresponding sensitivities are presented in the following tables if the area under the ROC curves was greater than 0.55. ROC data for predicting sleep i.e. in the scenario of aiming to make sure that the infant is asleep (anaesthetised) during surgery are presented in Table 8-1 and Table 8-2. In summary, these data show that end-tidal sevoflurane concentration predicts sleep better than any other predictor variable. Of the other variables EEG P5-20Hz predicts sleep best; HRV and change in heart rate were poor at predicting sleep. The areas under the ROCs for LF and HF HRV were less than 0.45 which means that they could be used to predict the absence of sleep, i.e. awakening. ROC data for the prediction of awakening for infants older than 52 weeks by these predictor variables are presented in Table 8-3.

Table 8-1. ROC data for prediction of sleep during emergence in infants < 52 weeks PMA

Predictor variable	Area under curve	95% CI		Cut-off value for specificity 0.95	Sensitivity at cut-off
End tidal sevoflurane	0.924	0.88	0.97	> 0.35%	0.83
EEG P5-20	0.59	0.54	0.64	> 35.9	0.2
HRV LF	0.46	0.38	0.54	-	-
HRV HF	0.53	0.46	0.6	-	-
HRV vHF	0.53	0.45	0.6	-	-
% change in HR	0.51	0.45	0.57	-	-

Table 8-2: ROC data for prediction of sleep during emergence in infants > 52 weeks PMA

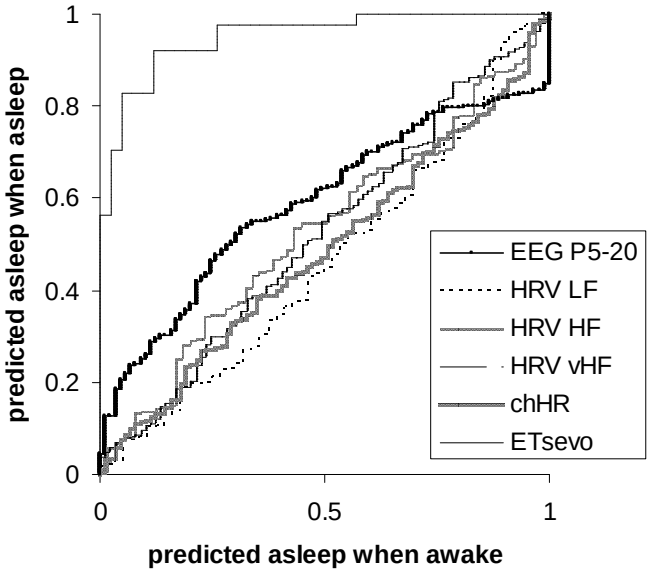
Predictor variable	Area under curve	95% CI		Cut-off value for specificity 0.95	Sensitivity at cut-off
End tidal sevoflurane	0.741	.634	.848	> 0.7	0.42
EEG P5-20	0.72	0.66	0.78	>182	0.2
HRV LF	0.37	0.29	0.45	-	-
HRV HF	0.35	0.29	0.4	-	-
HRV vHF	0.44	0.36	0.51	-	-
% change in HR	0.55	0.47	0.63	-	-

Table 8-3: Selected ROC data for prediction of awakening during emergence in infants > 52 weeks PMA

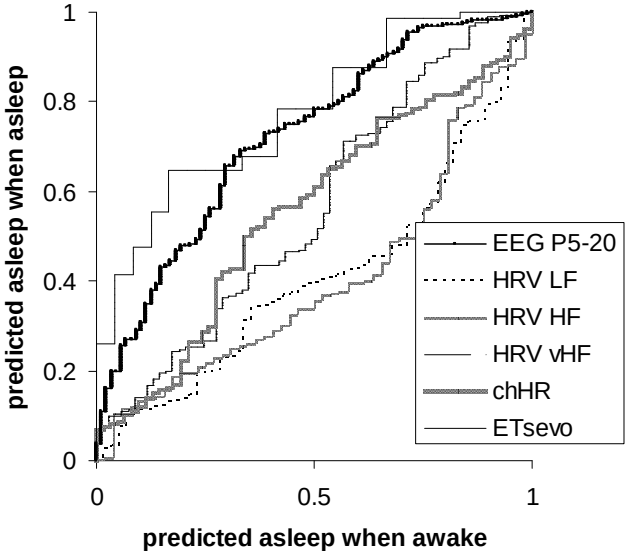
Predictor variable	Area under curve	95% CI		Cut-off value for specificity 0.95	Sensitivity at cut-off
HRV LF	0.63	0.71	0.55	$>9.8*10^{-7}$	0.83
HRV HF	0.65	0.71	0.6	$>2.6*10^{-6}$	0.88

Figure 8-3: Receiver operating characteristic curves

A: Infants younger than 52 weeks PMA.



B: Infants older than 52 weeks PMA.



8.1.3.3 Prediction probability

Table 8-4 summarises the PK values for each predictor variable and shows that the end-tidal sevoflurane had similar prediction probability to all other variables except EEG power in infants less than 52 weeks PMA. Statistical comparison of PK values between the groups is not possible because the numbers of data items are different in each group. However, Table 8-4 shows that EEG P5-20 Hz and HRV variables performed better in the older than in the younger infant. For % change in heart rate, increasing heart predicted conscious level in young infants contrasting with a decreasing heart rate in older infants. PKs were compared using the PKDMACRO macro (for paired data). Within each age group the predictor variables were compared with and end-tidal sevoflurane and the PK differences are summarised in Table 8-5. These data show that end-tidal sevoflurane is better at predicting conscious level than EEG power in young infants but not in older infants; this supports the concept that EEG power in the 5-20Hz frequency band could be used to predict conscious level in infants older than 52 weeks PMA. HRV and % change in heart rate predictor variables were not statistically different from end-tidal sevoflurane in either age group.

Table 8-4. PK for variable to predict increasing conscious level

PK values in this table were calculated from all available data. PK = prediction probability (0.5 = equal chance of predicting increasing or decrease conscious level during emergence). CI calculated from the PK -/+ 1.98*SE (SE = standard error calculated using the *jackknife* method).

	Infants < 52 weeks PMA		Infants > 52 weeks PMA	
Predictor	PK	CI	PK	CI
End tidal sevoflurane	0.35 0.65*	0.27 to 0.43	0.21 0.79*	0.11 to 0.31
EEG P5-20	0.49 0.51*	0.39 to 0.59	0.29 0.71*	0.2 to 0.39
HRV LF	0.77	0.73 to 0.81	0.82	0.77 to 0.87
HRV HF	0.64	0.58 to 0.69	0.79	0.75 to 0.83
HRV vHF	0.69	0.64 to 0.74	0.76	0.71 to 0.82
% ch in HR	0.64	0.59 to 0.69	0.37 0.63*	0.31 to 0.44

*PK values calculated for reversed conscious level values so that the predictor variable and the conscious level are changing in the same direction.

Table 8-5: Comparison of predictor variable PK with PK for end-tidal sevoflurane

Infants < 52 weeks PMA					
	PK	SE	PK diff	Lower 95% CI	Upper 95% CI
End tidal sevoflurane	0.678*	0.053			
EEG P5-20	0.51*	0.055	0.17	**0.058**	**0.278**
HRV LF	0.751	0.045	0.033	-0.113	0.179
HRV HF	0.662	0.056	0.041	-0.099	0.181
HRV vHF	0.677	0.053	0.021	-0.121	0.163
% ch in HR	0.065	0.055	0.091	-0.063	0.245
Infants > 52 weeks PMA					
	PK	SE	PK diff	Lower 95% CI	Upper 95% CI
End tidal sevoflurane	0.814*	0.86	0.08		
EEG P5-20	0.719*	0.054	0.095	-0.015	0.205
HRV LF	0.731	0.103	0.07	-0.17	0.31
HRV HF	0.656	0.11	0.124	-0.156	0.404
HRV vHF	0.678	0.103	0.128	-0.13	0.386
% ch in HR	0.708*	0.099	0.087	-0.171	0.345

*PK values were calculated for reversed conscious level values so that the predictor variable and the conscious level are changing in the same direction. Data in this table are restricted to infants in whom data was available for all variables (some infants did not have HRV data). Non-significant confident intervals are in bold.

8.1.4 Discussion

The problem of movement artifact prevents access to predictor variables during awakening itself. Nevertheless the minute before awakening began could be regarded as a period that may predict whether an infant will awaken. Comparison of predictor data in this period with the data prior to this time could determine whether predictor variables are useful. The results of the ROC and PK data in this section support findings elsewhere in this thesis that EEG power is more useful in older than in younger infants. Nevertheless, in the ROC data, end-tidal sevoflurane is more predictive than any other variable. Submitting the data to PK analysis however showed that all predictor variables were similar except for EEG power in infants <52 weeks age PMA which was significantly less predictive than end-tidal sevoflurane.

ROC is founded on sensitivity and specificity data describing how a variable predicts an event. In the situation of awakening, it was considered more important to predict the presence of sleep and, moreover, to avoid the prediction sleep when the infant was indeed awake. HRV in older infants however was better at predicting awakening and in the avoidance of predicting awake when the infant was indeed asleep.

The advantage of the PK analysis over ROC is that it can analyze multiple observed conscious levels and is not restricted to a dichotomous outcome of an event. There are problems however with both the ROC and PK statistical analysis. First the scenario is not steady state and test-retest opportunities are not possible; the conscious level is therefore always increasing in this model. Secondly, data is not independent and it should be for PK analysis. This is recognized and accepted by the developers and other workers who have used it; no alternative statistical process has been proposed. Third, the data were not equally spread amongst infants; this makes it difficult to compare the groups of infants and the outcomes may be biased by infants in whom more data was collected.

8.1.5 Conclusions

- ROC analysis found that prediction of a sleep state was highest using end-tidal sevoflurane
- PK analysis found that prediction of a change in conscious level was similar in all variables except EEG power in infants less than 52 weeks PMA

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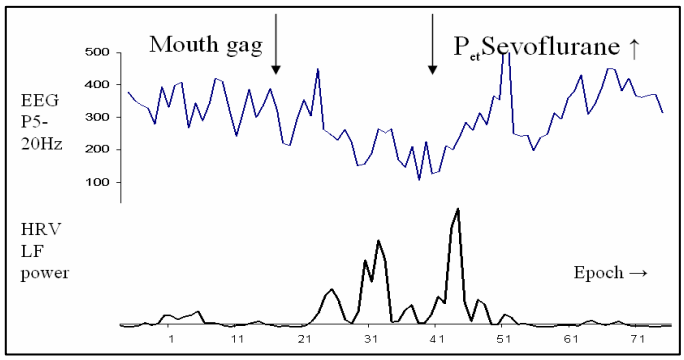
8.2 Potential value of EEG P5-20Hz and HRV LP

THESIS THUMBNAIL

- Background
- Hypothesis
- General methods
- Model of awakening
- EEG characteristics
- HRV characteristics
- Assessment of prediction
- **EEG and HRV changes with stimulation**
- EEG power and age



8.2.1 Introduction and aims

The characteristics of EEG and HRV during awakening from sevoflurane anaesthesia may also occur during surgery if anaesthesia levels are inadequate. If so, increasing analgesia or hypnotic drug doses may reverse them.

8.2.2 Objectives

- To investigate how P5-20Hz and HRV LP react to intraoperative stimuli and changing P_{et}Sevo
- Do P5-20Hz and HRV LP have the potential to monitor depth of anaesthesia?

8.2.3 Methods

An infant older than 52 weeks PMA age was monitored throughout surgery using EEG and ECG the study monitoring as described in 4.3.4. Clinical details of potential awakening were noted.

8.2.4 Case report

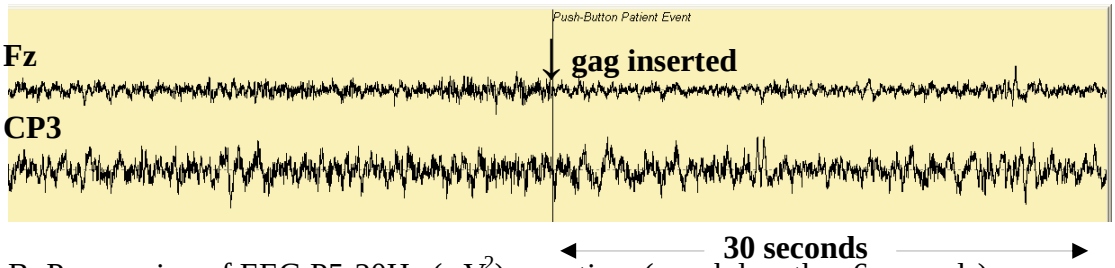
The infant was 64 weeks PMA (gestation 39 weeks), male, 8.5kg, and required repair of cleft palate. Anaesthesia was induced and maintained with sevoflurane delivered in oxygenated air. Atracurium facilitated tracheal intubation. Fentanyl analgesia was used during surgery (initial dose 1.5mcg/kg). Study monitoring was applied soon after tracheal intubation.

8.2.4.1 Response to pain

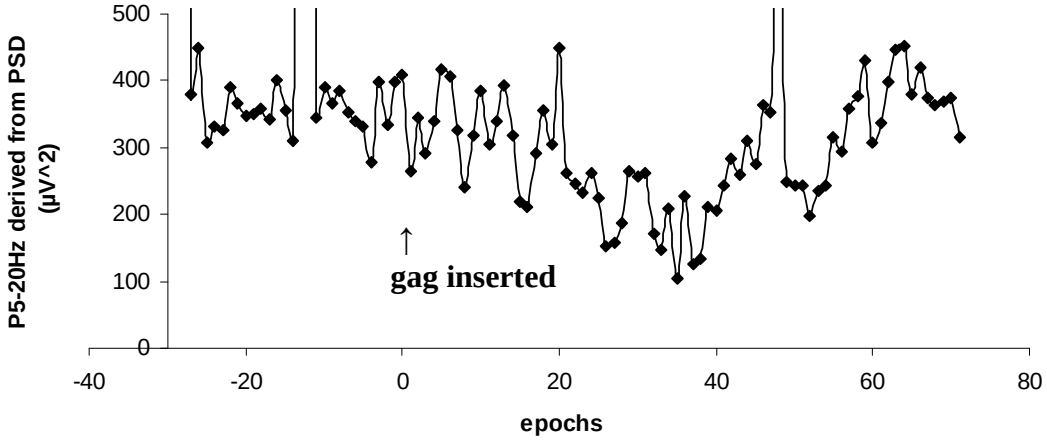
After anaesthesia had been established for at least 15 minutes the surgeon positioned a gag in the mouth. The gag caused pressure on the gum margin and was followed a few seconds later by an appreciable increase in the infant's heart rate (Figure 8-4). This was assumed to be a response to pain. The anaesthetist responded by administering fentanyl (0.5mcg/kg) and increasing the inspired sevoflurane concentration (P_{et}Sevoflurane had been 2.2 % and it increased to 2.4 % 5 minutes later). Figure 8-4 (A) shows raw EEG signals over this period and there was a decrease in amplitude in the raw signal of the frontal channel. There was a fall in P5-20Hz in the CP3 channel to almost 100μV^2 but by 2 minutes later, when extra fentanyl and sevoflurane had been administered, this had increased to over 200 μV^2. HRV LF band power showed some burst activity before the response to pain but increased power by over 35 times the baseline during the response to pain. LF band power reduced to baseline soon after extra fentanyl and sevoflurane had been given.

Figure 8-4: Change in raw EEG, EEG P5-20Hz, RR interval, mean heart rate and HRV band power in response to painful stimulus (gag insertion)

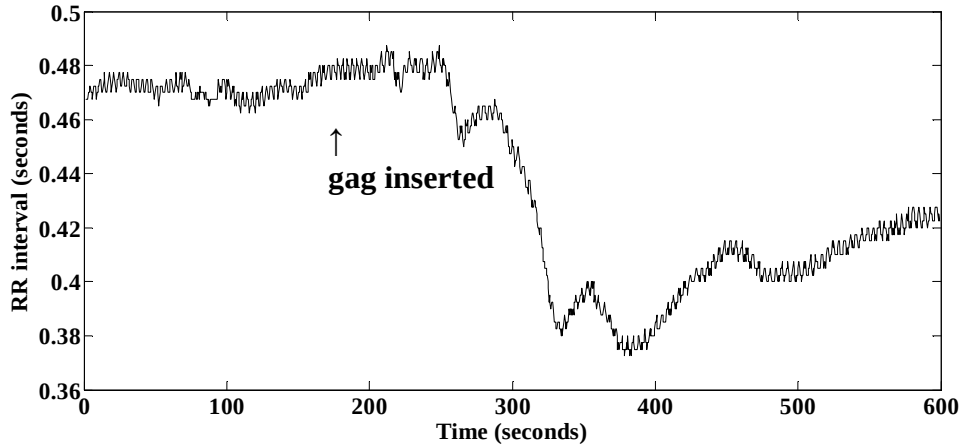
A: EEG recordings from two channels (Fz and CP3) copied from the Grass Telefactor recording of an infant aged 64 weeks PMA.



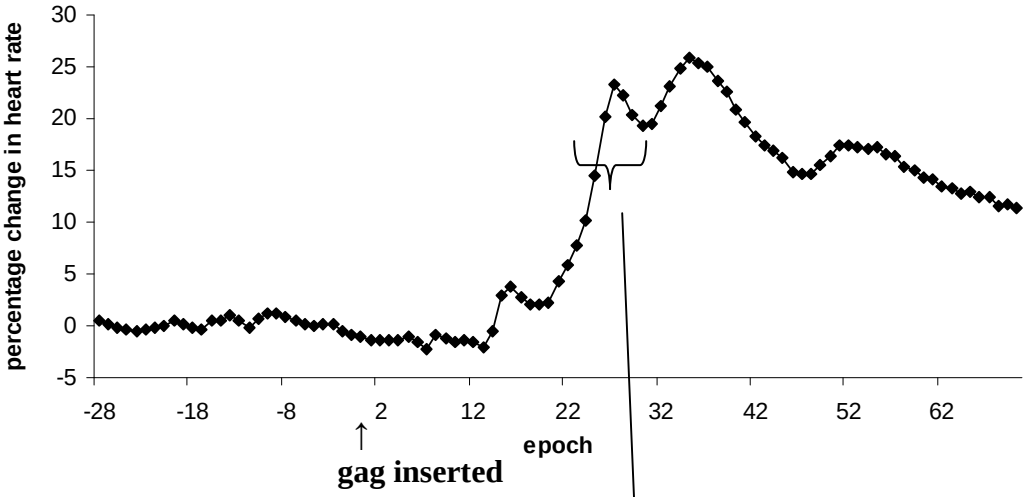
B: Progression of EEG P5-20Hz (μV^2) over time (epoch length = 6 seconds).



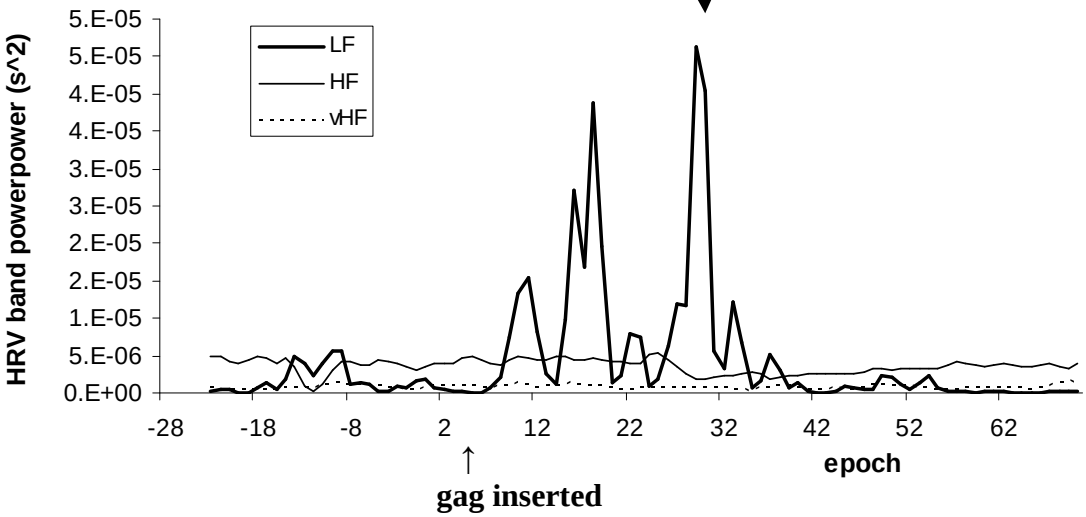
C: Progression of RR interval



D: Progression of % change in mean heart rate (= mean heart rate in each epoch)



E: Progression of HRV band powers over time. Each epoch marks the end of the 30 second period over which the band power has been calculated. Long arrow connects the power representing the RR intervals over the previous 30 seconds (5 epochs)

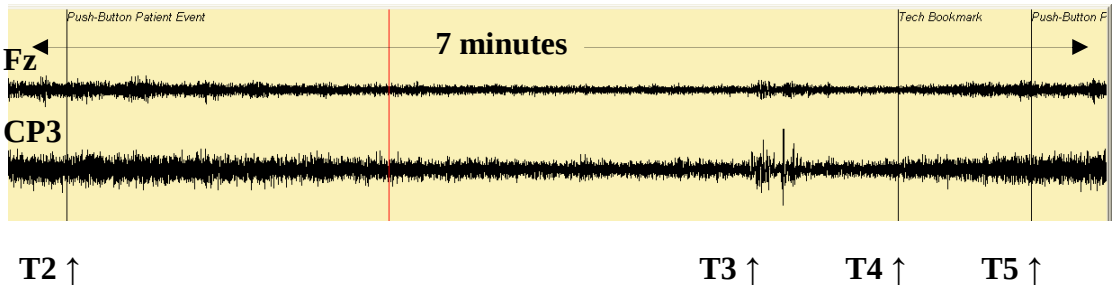


8.2.4.2 Awakening and re-establishing anaesthesia

After surgery and during awakening, anaesthesia had to be re-established for clinical reasons. This was because there was bleeding from the nose and the pharynx and cleft repair had to be inspected and suctioned. Tracheal extubation was delayed until the bleeding ceased. Bleeding ceased spontaneously and recovery was unremarkable thereafter. EEG and HRV recording took place during these events process and findings during re-establishment of sevoflurane are presented in Figure 8-5 (A, B, C, D and E). In (A) the decrease in raw signal amplitude is obvious during sevoflurane wash-out and it increases approximately to baseline levels when sevoflurane has been re-established. In (B) the power spectrum array also shows an obvious prominent frequency and power that decreases and increases with sevoflurane wash-out and wash-in. The change in P5-20Hz, in (C) follows the same trend over time. The mean (SD) P5-20Hz over 10 epochs in bSO, bAB and one minute later was 323 (54), 43(11), 243 (39) μV^2 respectively. The heart rate in (E) clearly increases as awakening began and LF HRV band power also increases at this time. HRV LF power returns to baseline as anaesthesia is re-established. vHF band power increases in activity after anaesthesia is re-established and may reflect underlying native respiratory rate undetected clinically.

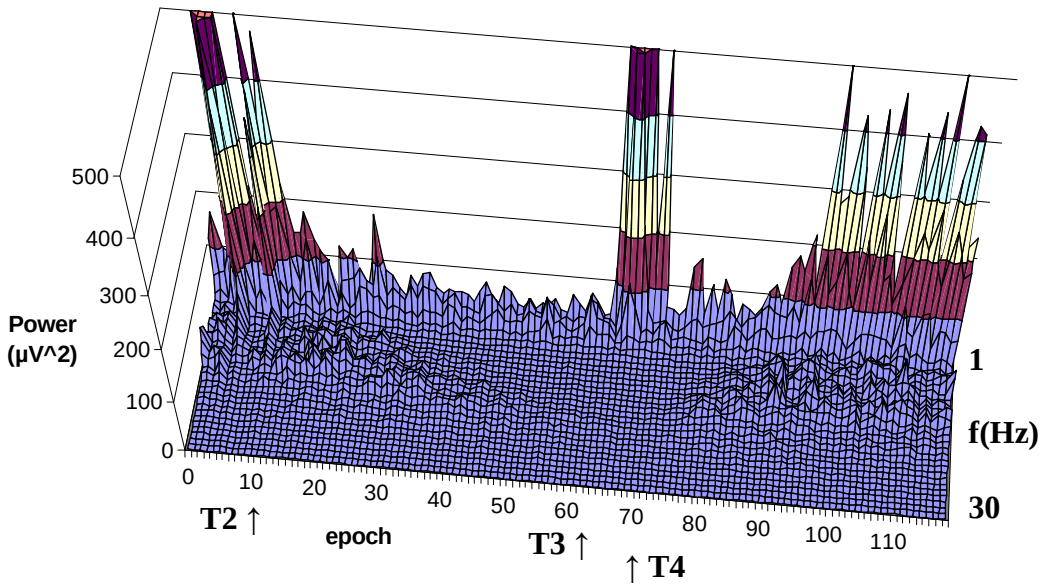
Figure 8-5: Change in raw EEG, EEG power spectra, EEG P5-20Hz, HRV band power and heart rate in response awakening and restoration of anaesthesia

A: EEG recordings from two channels (Fz and CP3) copied from the Grass Telefactor recording of an infant aged 64 weeks PMA.T2 marks time of sevoflurane turned off, T3 = awakening began, T4 = sevoflurane turned on, T5 = one minute later. Length of sample recording is 7 minutes.



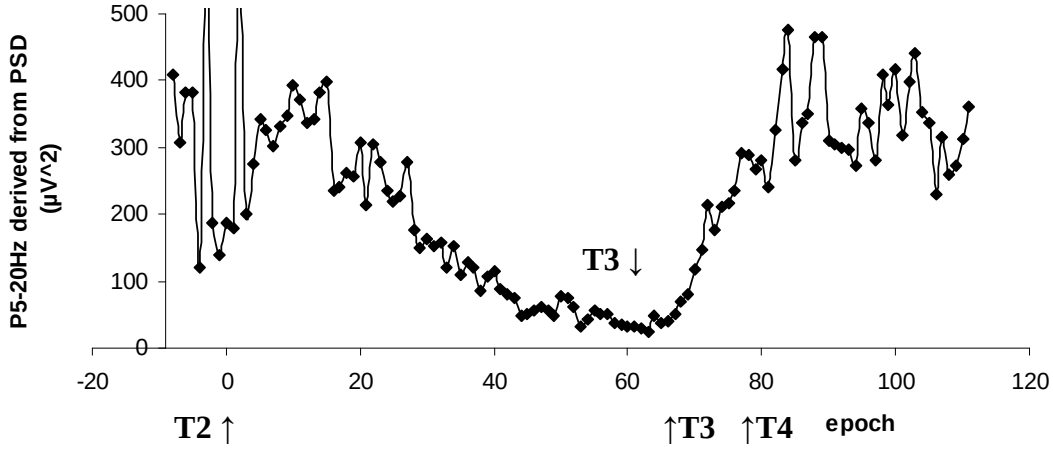
B: EEG power spectrum array of same infant. Power units are μV^2.

T2 marks time of sevoflurane turned off, T3 = awakening began, T4 = sevoflurane turned on.

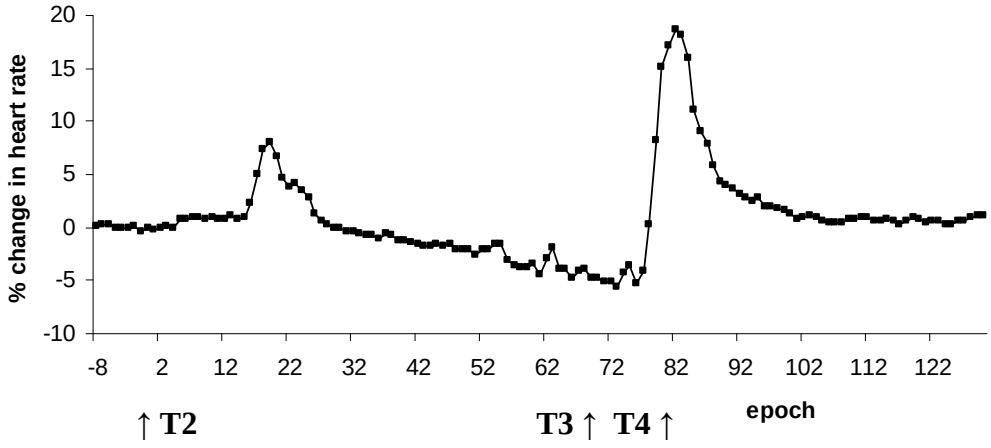


C: Progression of ECG P5-20Hz (μV^2) in same infant over same time period.

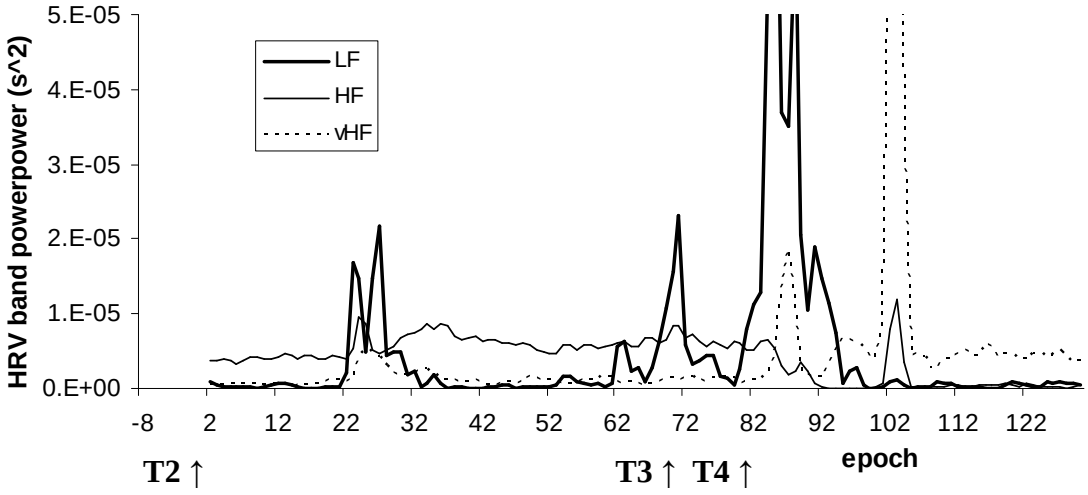
T2 marks time of sevoflurane turned off, T3 = awakening began, T4 = sevoflurane turned on.



D: Progression of % change in heart rate (mean heart for each epoch (6 seconds))



E: Progression of HRV band powers over time. T2 marks time of sevoflurane turned off, T3 = awakening began, T4 = sevoflurane turned on. Each epoch marks the time of the end of the minute over which the band power has been calculated.



8.2.5 Discussion

This case report provides supportive evidence that both EEG P5-20Hz and LF HRV could monitor depth of anaesthesia in infants older than 52 weeks PMA.

Both EEG P5-20Hz and LF HRV power changed during sevoflurane wash-out in the characteristic manner described in previous chapters. By chance, anaesthesia had to be re-established because of bleeding at the operative site, and study monitoring captured the EEG and HRV changes during sevoflurane wash-in; P5-20Hz increased and HRV LP decreased to their pre-sevoflurane wash-out range.

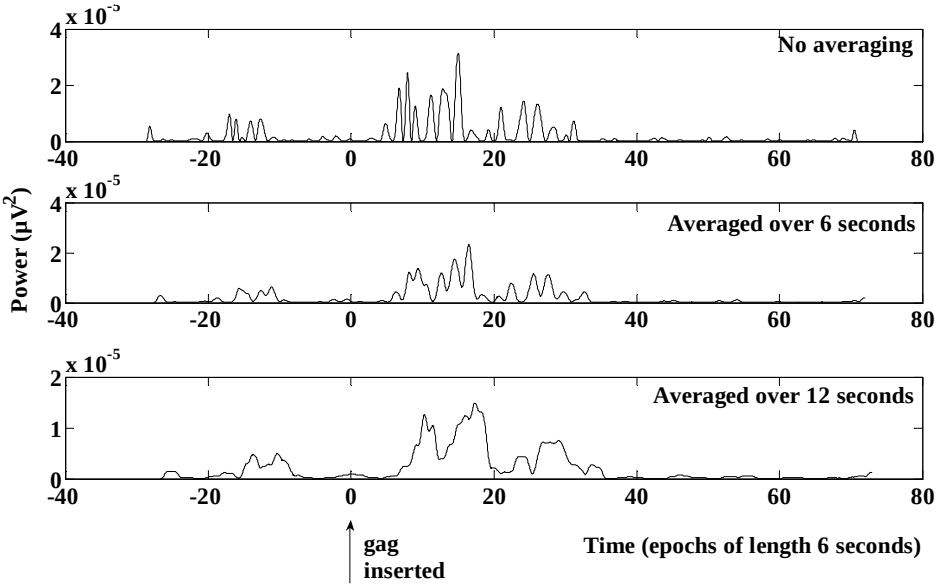
Both EEG P5-20Hz and LF HRV power changed with a painful stimulus during sevoflurane anaesthesia. Both variables changed in a similar manner to the changes seen during the washout of sevoflurane at the end of anaesthesia and this suggests that intraoperative awakening was possible. Not all infants may respond to a mouth gag and this may be because the degree of the pain may be important. If so, the efficacy of the anaesthesia technique will be influential. The analgesia and hypnotic components of the anaesthetic technique agent may have different effects on response to pain. It is likely that fentanyl, known to be a potent analgesic, is more important than

sevoflurane in preventing a response to pain. A study of dose of fentanyl required to prevent a decrease in EEG P5-20Hz and LF HRV bursts may be interesting but a similar study would also be necessary to determine the effect of various inspired concentrations of sevoflurane.

The time taken by each variable to respond to a stimulus is dependant on the method of calculation. There is an inevitable delay in the ability of LF band power to detect a change in RR interval because of the length of the period over which the LF power is calculated. This delay can be reduced by minimising the Welch window length of the FFT but the reasonable minimum window length is limited by the need to distinguish the power in the LF and HF bands. If distinguishing band powers is important a window length of 18 seconds (3 epochs) is the minimum. If the contribution of HF power to the total HRV is small or constant, it may be reasonable to use shorter windows. A window of 6 seconds long (one epoch), will produce wide frequency bands in which the 2^{nd} 3^{rd} and 4^{th} frequency bins would represent power centered on 0.125, 0.25 and 0.375 Hz respectively and these would encroach into the high frequency range (0.19 to 0.41Hz).

The RR interval sequence itself can be filtered to estimate power within a chosen frequency band. In order to estimate the power in a filtered signal the mean signal power should be estimated over at least one wavelength, and therefore at least 10 seconds would be needed to estimate power of a 0.1Hz signal. Figure 8-6 shows that LF power derived from RR intervals can be calculated for individual RR intervals but that averaging the signal over 12 seconds (2 six second epochs) produces a progression of power similar to that found by the PSD method shown in Figure 8-4.

Figure 8-6: Progression of LF band power (derived from band pass filter of RR intervals) with and without moving average.



This encourages the use of a monitor of EEG band power and assessment of its value in a larger cohort of infants undergoing painful surgery. Such a tool may help to modify anaesthesia technique.

8.2.6 Conclusions

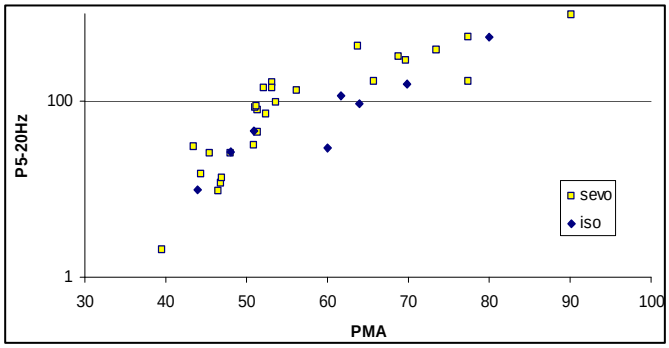
In this case report

- P5-20Hz decreased and HRV LP increased during sevoflurane wash-out
    - These changes were reversed when sevoflurane anaesthesia was re-established.
- P5-20Hz decreased and HRV LP increased in reaction to a painful stimulus
    - These changes could be reversed by both intravenous fentanyl and an increase in P_{et}Sevoflurane
- P5-20Hz and HRV LP have the potential to monitor depth of anaesthesia

8.3 The relationship between age and P5-20Hz during anaesthesia

THESIS THUMBNAIL

- Background
- Hypothesis
- General methods
- Model of awakening
- EEG characteristics
- HRV characteristics
- Assessment of prediction
- EEG and HRV changes with stimulation
- EEG power and age



8.3.1 Introduction and aims

The finding in section 6.4.3.6 that P5-20Hz is associated with, and increases with, age was in a small sample number of infants (n = 20) . More infants need to be studied to confirm and investigate the relationship of age to EEG band power during steady state anaesthesia.

8.3.2 Objective

- To confirm and further investigate the association between age and P5-20Hz

8.3.3 Methods

Three sets of EEG data were combined.

- Nine infants had been studied (see section 5.3) of whom 6 had had sevoflurane and 3 isoflurane. EEG data was recorded after surgery was completed and at the same anaesthetic dose used for surgery.
- Twenty infants anaesthetised with sevoflurane studied in chapter 6.
- EEG data from 14 infants and children were supplied by investigators in Royal Melbourne Childrens Hospital in Australia.

8.3.3.1 Processing Melbourne data

Demographic details of these patients are presented in Table 8-6. Five had had sevoflurane and 9 had had isoflurane anaesthesia. The investigators recorded EEG during under steady state anaesthesia during non stimulating surgery. Data had been recorded using a ReBrim EEG monitor that had analogue filters to exclude signals lower than 2 Hz and higher than 88 Hz. The sampling frequency was 512 Hz. The processor was 12 bit. The digitized data was digitally filtered to include signals below 28 Hz only and then decimated to reduce the sampling frequency to 64 Hz. Three channels were recorded; one frontal (Fz) and two centro-parietal (CP3 & CP4). The data was raw and was supplied in excel spreadsheets. Data was processed using the bespoke Matlab programs used in this thesis. A three minute period of steady state anaesthesia was identified in each patient from the clinical details supplied. Each signal was visually inspected. The amplitude in the centro-parietal channels was obviously higher than the frontal and therefore only centro-parietal channels were processed further. P5-20Hz was calculated in each 6 second epoch in both centro-parietal channels and plotted over time to check that the P5-20Hz did not have obvious unsteadiness. The mean P5-20Hz of both channels, and all epochs of the 3 minutes was calculated.

8.3.4 Results

In Figure 8-7 there appears to be a linear relationship between P5-20Hz and age until 100 weeks PMA (equivalent to age 14 months). Figure 8-8 shows the relationship in more detail for infants less than 14 months old. All infants less than 53 weeks PMA have power less than 10 μV^2. All infants older than 52 weeks, except one, have power greater than 100μV^2. These findings do not seem to be affected by the choice of anaesthetic agent.

8.3.5 Conclusions

- The combined data support the initial finding that P5-20Hz is related to age.

Table 8-6: Demographic details of infants and children studied in Melbourne

Age	**G**	**Operation**	**Anaesthesia**	**N_2O**	**Airway device**	**Opioids**	**LA block**
1m	M	Inguinal hernia repair	Isoflurane		ETT		Caudal
2m	M	Inguinal hernia repair	Isoflurane		ETT		Caudal
2m	M	Inguinal hernia repair	Sevoflurane		nil		Caudal
5m	M	Hypospadias repair	Isoflurane	Yes	ETT	Morphine	Caudal
6m	F	Excision extra digit	Isoflurane	Yes	LMA		Ring
10m	M	Oesophageal dilatation	Isoflurane	Yes	ETT		
18m	M	Eye examination	Isoflurane	Yes	LMA		
2y	M	orchidopexy	Isoflurane	Yes	LMA		Caudal
3y	M	Change of plaster	Sevoflurane	Yes	LMA		
3y	M	Squint correction	Isoflurane	Yes	ETT	Morphine/ Fentanyl	
4y	M	Release trigger thumb	Isoflurane	Yes	LMA		
6y	F	Cholecystectomy	Isoflurane	Yes	ETT	Morphine/ Fentanyl	
7y	M	Inguinal hernia repair	Sevoflurane	Yes	LMA	Fentanyl	Caudal
9y	M	circumcision	Sevoflurane	Yes	LMA	Morphine	Penile

G = gender

Figure 8-7: Scatter plot of P5-20Hz against PMA in combined children and infants

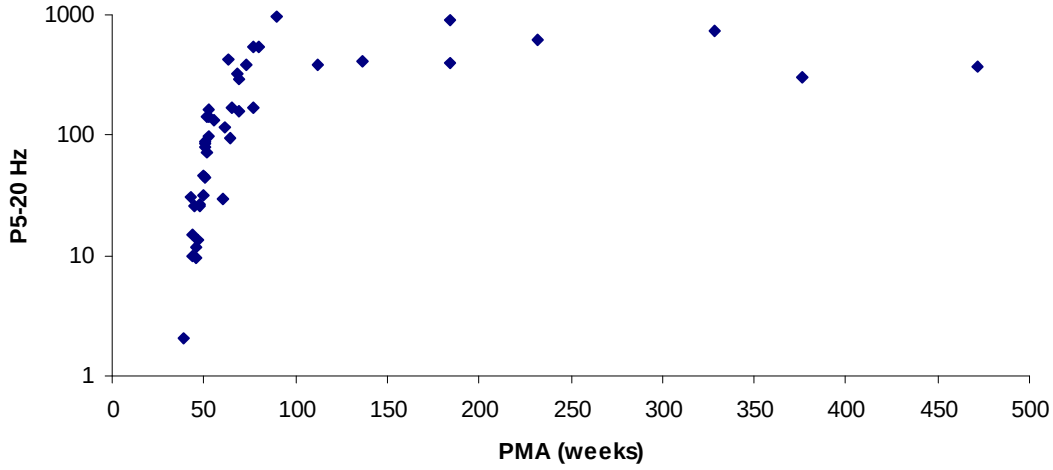
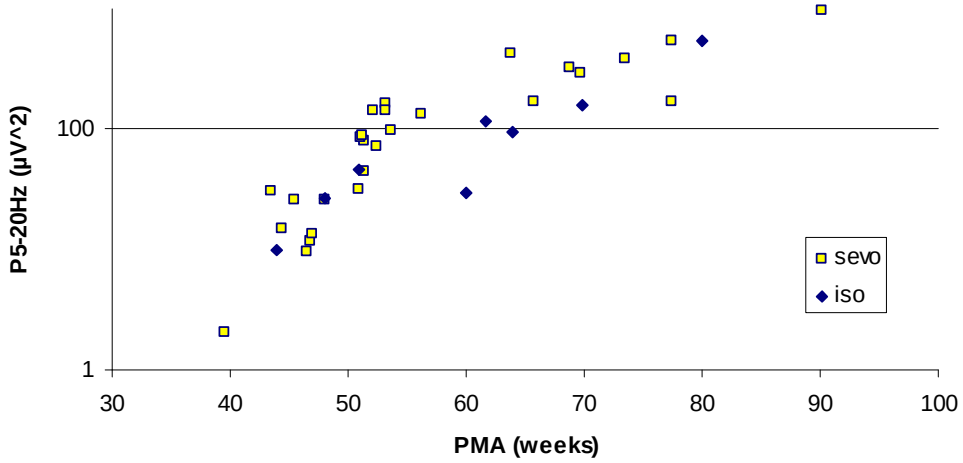


Figure 8-8: Scatter plot of P5-20Hz against PMA in combined infants



9 Discussion and future directions

At the beginning of this thesis the aim was to identify and investigate EEG and HRV characteristics that may detect or predict awakening of infants from anaesthesia. Characteristics have been defined but, by necessity have been obtained on limited numbers of infants.

Major impediments to research of this subject have not only been the limited numbers of infants who require anaesthesia (even in a major paediatric hospital) but also that many infants who do require surgery have had to be excluded because of abnormal neurological and cardiovascular systems. Parental consent was not always given, probably because anxiety at the time of surgery prevented them considering anything other than essential decisions. Explaining the reasons for the research, i.e. “that we need to investigate methods of monitoring depth of anaesthesia in order to try and avoid giving inadequate or excessive doses of anaesthesia drugs” may not have seemed important enough to parents who believed that any interference with normal practice increases risk and is therefore not justified. It is possible that more time spent in preparation of parents could improve their understanding and help them overcome their natural reluctance to consider the risk implications of altering anaesthesia management. This however will mean that recruitment will need planning which has been difficult in this work because of reliance on the organisation of surgery. Certainly, to generate dose response data, the dose of anaesthesia needs to be altered in a defined and controlled fashion involving a protocol that takes account of the possible influence of timing and order or dose changes; dose response changes would need to be randomised. In the current research era this demands more intense administrative resources and employment of salaried researcher. The work of this thesis was limited to observations made on routine – or almost routine – anaesthesia practice. Minor deviations from the routine involved application of extra non-invasive monitoring, videoing events, additional minutes of anaesthesia while study monitoring was applied and, at the end of surgery, recording a few minutes of steady state anaesthesia. It is also true, perhaps, that infants awakened more slowly in the

study than in routine practice when they would normally be stimulated by pharyngeal suctioning and their tracheas extubated at a different level or dose of anaesthesia. This too, might have been an interesting set of observations but, because movement creates interference on the EEG and ECG signals, recording at this time is unlikely to generate useful data.

Such difficulties in this field have probably hindered other researchers and may explain why few data are published. Indeed those that are published are also largely observational and the authors have been unable to clearly define the conditions under which their observations have been made. In respect of EEG characteristics Davidson and colleagues studied their infants (and children) throughout the perioperative period but have limited their report to the intraoperative recordings and those during emergence.[143] Their chosen steady state was during surgery itself and they assumed that this was the depth of anaesthesia appropriate to surgery. Whether surgery caused EEG changes is unknown. Lo and colleagues randomised infants and children to receive isoflurane or sevoflurane anaesthesia but otherwise their study was observational.[159] They too studied the EEG during anaesthesia but their methods are unclear and contradictory in that they state the anaesthesia management was not changed by their observations yet they had steady state anaesthesia at decreasing concentrations of anaesthetic. Constant and colleagues studied the EEG at induction, and successfully recorded EEG in children sedated with midazolam before anaesthesia was induced. They showed that induction caused EEG changes similar to those seen in adults.[144]

The technical aspects of EEG monitoring during anaesthesia may also have prevented research interest. Application of electrodes to hirsute scalps is time consuming and can cause variation in signal impedance making interpretation difficult. Diathermy and other electrical interference can reduce the value of EEG monitoring.

HRV, also, has received little attention from researchers in anaesthesia depth. Constant and colleagues showed that sevoflurane suppresses HRV LF power (and arterial blood pressure variability LF power) and that during emergence power increases many-fold. Blues and Pomfrett have studied HRV in children being induced with halothane but restricted their calculations to the respiratory component (i.e.

HF).[302] They found that HRV HF power reduced with increasing anaesthesia depth. Oberlander and colleagues studied HRV band powers (LF, HF and LF/HF ratio) in infants and found that halothane suppress all of these variables.[303] Variability in HRV band power was observed by all of these authors yet none reported that LF HRV power may have a burst pattern. In a study testing the HRV effects of propofol anaesthesia in children having painful procedures, Toweill and colleagues found that LF power increased during painful episodes irrespective of the propofol dose.[304] Maenpaa and colleagues have used HRV in adults and found changes associated with sevoflurane and propofol anaesthesia are the same.[215]

That so few data are available in infants with this interesting monitoring modality is surprising but, as for EEG, may be explained by tedious technological problems. R wave identification is crucial and will need to be visually checked. Ectopic beats may need to be replaced or ignored. Moreover the evidence to support the separation of sympathetic and parasympathetic nervous systems influence on LF and HF band powers is debated and therefore interpretation is uncertain.[305]

In the outset of this thesis, the choice of EEG and HRV, rather than other measurements, was made because these are non-invasive and they were available and relatively inexpensive. Such considerations make their investigation important because if they were useful, they could be readily used in clinical practice. Limiting this work to the investigation of raw signals and their frequency domain band power analysis is justified in that such data are essential before other more complex analysis can be undertaken. The investigation of BIS or any other processing method that obscures the raw signal may be misleading, difficult to understand and interpret, and may not be accepted by clinicians. Frequency domain analysis from this thesis provides essential background knowledge for investigation of other EEG derived variables.

The following summarises the findings of this thesis and discusses the strengths and weaknesses of methods and results. Each major step in the thesis is considered separately and finally a plan for future direction of investigation is presented.

9.1 Definition of awakening

Certainty of conscious level in non communicating individuals is not possible, and therefore valid surrogate markers of potential conscious level are almost certainly needed. Possibly the most persuasive marker of consciousness is the ability of a person to react to verbal command. Other researchers have not found this to be practical especially in the youngest infants.[255] This may be possible in infants who have become accustomed to their mothers voice. [59] Packaging a *mothers voice* into an auditory stimulus could, in theory be used in an infant during anaesthesia. The infant would need to be able to respond in an appropriate manner but a response to command seems implausible. Yet any response to a mothers voice as distinct to a response to any other noise would be supportive of conscious processing of an auditory stimulus. Muscle relaxants could not be used although EMG interference may be troublesome. The isolated forearm technique could be adapted for infants. Initial response to skin stimulation is probably a spinal response.

Awakening, defined by the experts group, produced a definition that was practical and readily used to separate beginning of awakening from a quiet state. Neither state is certain to represent awake nor sleep, but at least they have been defined by an independent group whose main professional interest is in the observation and control of conscious level. “Beginning of awakening” was an easily identifiable reference point in the continuum of conscious level. The experts may have modified their views if they had been challenged by other members of the group, or if they had been asked to consider other published opinions. Nevertheless the criteria that they chose are similar to those described by other investigators and clinicians (see Table 2-3). Over time, people change their views. Further questioning and challenging of the expert group could have reduced their commitment to the task and further questioning therefore ended after 2 rounds of questions.

9.2 Development of a model of awakening and its application to conscious level monitoring

9.2.1 Steady state

Steady state anaesthesia depends, in the main, on the dose of anaesthesia and the stimulation. The drug concentration in the target organ is theoretically possible to measure (end-tidal sevoflurane for example) but the context is important. The longer the length of time at which the steady end-tidal concentration has been achieved the greater the confidence that the body has achieved equilibrium. The effect on the brain may not be steady however because stimulation changes. Tracheal irritation from a tube can vary especially if it is moved. Surgical pain changes as does the concentration of analgesia at the effect site. Indeed a perfect steady state is only theoretically possible, and may not be truly relevant to the clinical situation. In the real situation, stimulation demands changes in concentration of anaesthesia or analgesia drugs (or both) and the anaesthetist attempts to balance anaesthesia with stimulation.

In the model used in this thesis the concentration of anaesthesia present after surgery is the same as that used during surgery – and judged as sufficient to keep the infant anaesthetised. Effective analgesia is crucial in controlling responses to pain during anaesthesia and the anaesthetist used their judgment also to make sure analgesia was sufficient to prevent pain responses. If there are no pain responses (theoretical and undefined), either due to absence of pain or due to effective analgesia, the measurement of the effect of varying steady state concentrations of anaesthesia becomes meaningful. Future studies need to test the effect of clinically used concentrations of sevoflurane on EEG and HRV in infants and such a study will require cooperative parents.

Pain, however, is a feature of the typical clinical situation and therefore it could be argued that steady state is not relevant. The counter argument is that pain can be effectively removed by regional local anaesthesia and potent opioids such as remifentanil. A combination of local anaesthesia and remifentanil has been used to test awakening in women undergoing surgery in which the concentration of

anaesthesia was gradually reduced until communication was possible[173-175]. In these circumstances tracheal intubation and controlled ventilation are essential to manage respiratory depression causes by opioids.

Other factors may be relevant to the definition of steady state because they affect conscious level, and drug dynamics and kinetics. Body temperature may alter drug receptor interaction or change the kinetics, for example by changes in blood flow. All infants presented in this thesis had their body temperature maintained above 35.5^{o}C.

Muscle relaxation prevents afferent signals from muscle spindles that can provoke arousal. Residual effects of muscle relaxation were unlikely and were not apparent when awakening occurred because movements were always vigorous.

9.2.2 Stimulation as a test of consciousness rather than pain

Infants respond to painful stimuli but this is influenced by analgesia as well as anaesthesia. A stimulus to test consciousness should therefore not be painful. Yet is such a separation of painless from painful stimuli practicable? A noise stimulus can be described in terms of loudness, pitch and timing, but the presence of hearing impairment, the infant's perception and learning make any response variable. Noise was not effective in an early pilot study in this thesis. Stimulation by *mothers voice* could be effective but has problems of calibration (making mothers voices similar). Skin stimulation was effective however but is difficult to describe. Pressure and timing of skin stimulation were not measured. Nevertheless tickling the foot was easy to perform and did not cause parental anxiety.

9.2.3 Do EEG and HRV characteristics predict awakening?

This thesis has tested only a narrow or limited stimulus. A more intense stimulus could have caused awakening earlier. The stronger stimulus such as suctioning the pharynx or the trachea could have been used however any stimulus would need to be repeated in an infant – or used once per infant as used in the *Up and Down method*. Consequently, the EEG and HRV changes only relate to tickling the foot and not to any stronger stimuli. Testing infants with various types of clinically relevant stimuli is

needed to prove that EEG and HRV characteristic predict awakening or rousability. More intense stimuli could be applied, ethically, if they were going to be used as part of the surgical or anaesthetic management.

9.3 EEG changes during awakening

9.3.1 Limited to before awakening began

EMG interference obscures EEG signals during movement, and movement was almost always a constant feature of awakening. The EEG findings were therefore limited to those before awakening began and cannot be considered to represent the EEG of the awake state. It is possible that the infant was not truly awake at the time of the beginning of awakening and that they were lightly anesthetised or sedated. Nevertheless, they did respond to skin tickling. In the typical situation of an infants under sevoflurane anaesthesia the following periods of EEG activity take place when sevoflurane levels decrease: oscillation, quiet, and awakening. Awakening has not been tested in this work.

The same EEG progression may also take place during anaesthesia when there is stimulation that breaks through and in these circumstance, intraoperative awareness and distress may occur.

Many LOC studies have been unable to show that any EEG characteristic distinguishes sleep and awake states. Perhaps this is because they were looking at the point of transition from sleep to awake. In this work there were changes before this transition and such changes could be more useful because they warn of potential awakening rather than true awakening.

9.3.2 Limited to a single drug and to a dose range

Other investigators have investigated the EEG effects due to isoflurane and combinations of analgesics and anaesthetic agents.[143] Their findings may therefore not be comparable with this work. In particular Lo and colleagues have studied the EEG effects of sevoflurane in infants and have used a higher dose.[159] They found that EEG power increased as sevoflurane was reduced after surgery and this may be

explained if higher doses sevoflurane caused EEG suppression. Constant and colleagues found that higher doses reduce total power.[144] The findings of this thesis are limited to end-tidal sevoflurane dose range of less than 2.5% which is close to one MAC in infants older than 6m[94] but appreciably less than one MAC in younger infants (MAC in infant <6m = 3.2%[94]).

9.3.3 Evoked responses of skin stimulation

The stimulation of skin in this work could have caused evoked changes on the EEG. This was not tested but is unlikely because the EEG characteristics before and after surgery, and before and during skin stimulation were similar. Nevertheless, evoked potentials have been detected in awake preterm infants in response to heel lancing and skin stimulation and may be present during anaesthesia.[66] The EEG in infants of this age, and infants less than 52 weeks PMA has little activity and evoked potentials maybe easier to identify than in older infants.

9.3.4 EEG changes with sevoflurane concentration and pain

The association of EEG power to sevoflurane concentration in older infants was shown clearly but may be related to the scenario and not necessarily repeatable in others situations. For example it is possible that once awakening occurs the EEG power characteristics may not return. This was not seen in the case reported in chapter 8. EEG characteristics, seen before sevoflurane was turned off, returned quickly when sevoflurane is restored. More evidence of this nature can be obtained with parental consent or by observing clinical situations.

EEG characteristics can change however even under steady state sevoflurane concentrations showing that it is the balance of stimulation and anaesthesia dose that create the EEG characteristics. This was also shown in the case described in chapter 8 and this kind of situation is commonplace in clinical anaesthesia and can be obtained relatively easily. Further clinical trials could follow from these observations to determine the doses of analgesics and anaesthetics required to prevent EEG or HRV changes. Extradural analgesia in children over 2 years old has been shown to reduce the dose of sevoflurane required to maintain a constant BIS[306] In infants under 2 years

old however BIS was not reduced by caudal anaesthesia.[307] This may be because either caudal anaesthesia has less cortical effects or the BIS algorithm does not match conscious level in small children.

9.3.5 Power spectrum and band power

The dominance of low frequency signal power is crucial when describing the EEG power spectrum. Whereas log transformation can reduce this dominance, problems of interpretation remain when TP, MF and SEF are used because MF and SEF are dependent on TP. Visual inspection of the spectra show that signal power within the 5-20 Hz range are potentially valuable and should be considered in isolation from signal power in other frequency ranges. Low frequency power is also affected by changes in baseline. These can be removed by filters but slow changes in baseline signal may be important. No consistent changes were seen in low frequency power in this thesis.

High frequency power (less than 70 Hz) was always low and usually less than 5 μV^2. Signals in this range maybe markers of consciousness but were not tested.

9.3.6 P5-20Hz

This work found that P5-20Hz band power was a potentially useful of depth of anaesthesia and anaesthesia concentration in infants older than 52 weeks PMA. As anaesthesia dose increases it is likely that the EEG will be suppressed and P5-20Hz will decrease – which could be misinterpreted as increasing conscious level. The combined use of HRV may prevent this because HRV LF suppression is a feature of effective anaesthesia. In contrast, HRV LF power increases in burst with increasing consciousness and in response to pain.

In younger infants there was low band power in this range. In one young infant there were sleep spindles that seemed to come together as sevoflurane concentration decreased. In normal development sleep spindles appear by 4 weeks of age and become established by 3m. It is speculation but possible that the P5-20Hz signal is a

continuous sleep spindle. If true this suggests that anaesthesia and natural sleep share some EEG characteristics that develop by 3m (52 weeks PMA).

The power within the alpha range has been used in testing of sedative drugs in sheep because this band power was found to be associated with sedation.[300]

9.4 HRV changes during awakening

The finding that LF band power has a burst like pattern could change much of the interpretation of HRV data reported previously. Moreover there are difficulties with LF power because it incorporates the power caused by trend in the heart rate. Trend needs to be removed from the RR sequence either by subtracting the mean, using the detrend Matlab algorithm or by applying a high pass filter. None of the publications state what method they used and this may explain why some authors have avoided LF band power altogether.[302]

The plotting of the progression of band power over time shows an interesting variation. The plots shown have used percentage change band power that may exaggerate or obscure meaningful changes. Nevertheless there are no simple power units other than s^2 – some authors have chosen to use beats-per-minute^2 which makes comparison between data awkward.[212]

9.5 Association of age to EEG power

The relationship of EEG band power has been described before by Davidson and colleagues[143] but their data has included the low frequency components of the EEG power spectrum. Data from their unit has been reprocessed to add strength to the age relationship of P5-20Hz in this thesis. Many more data sets from steady state conditions are required to confirm this initial finding. Such data should not be difficult to obtain if EEG monitoring in infants and children becomes routine. However steady, defined conditions (eg absence of surgery) at various concentrations of anaesthesia are needed and this will involve ethical and parental approval

There are some interesting possible explanations for why there should be a power versus age relationship. Care should be drawn however to the important problem of

steady signal that is crucial in the calculation of power by FFT. EEG with transients or *tracé alternant* or *tracé discontinu* may be common in young infants and this makes interpretation of signal power difficult.

The frequency of an EEG oscillation may be related to the synaptic neurotransmitter activity. GABA may be the main neurotransmitter involved in causing unconsciousness since its receptors are present at the anatomical sites that affect consciousness and most anaesthetics, including vapour anaesthetics, barbiturates and propofol, are GABA-ergic. There are GABA receptor changes related to age in infants. From human cadaver studies the cerebellum of neonates contains only one-third of the number of $GABA_A$ receptors found in an adult and the receptor subunits themselves have reduced binding affinity for benzodiazepines.[308] The concentration of $GABA_A$ receptors identified by positron emission tomography is much higher in children aged 2 y than in adults[309] and these changes are consistent with age-related concentration effects of inhalational anaesthetics.

9.6 Direction of future investigation

The EEG and HRV patterns in infants and children of all ages should be tested during routine clinical anaesthesia in which a reliable surgical painful stimulus can be observed. Such a study should not, initially, need to alter the conduct of the anaesthetic, but as confidence in the observation increase, it will become necessary to test various doses of anaesthetic drugs in the presence of effective analgesia. Remifentanil infusions and local anaesthesia make low dose anaesthesia feasible and what is required is a method of showing that the dose of anaesthetic (and analgesia) is sufficient to prevent evidence of arousal or awakening. The EEG P5-20Hz and HRV LF band power are contender variables to monitor in infants older than 52 weeks PMA.

In younger infants EEG band power is unlikely to help monitor conscious level or dose of sevoflurane. In these infants evoked potential need investigating at light levels of anaesthesia. These infants are potentially more vulnerable than older infants to the toxic effects of anaesthesia and therefore, if parents could be contacted early enough, and given sufficient time to consider the research, they may consent to allow their

infants to enter a randomised clinical trail comparing the suppression of EEG evoked responses by anaesthesia. A pilot study to show the absence of evoked responses and their return as anaesthesia wanes may be acceptable to some parents. A difficulty to overcome will be the choice of stimulus which will need to be sufficiently intense to evoke a response.

10 Appendices

10.1 Details of ethics approvals, correspondence references, dates of studies and numbers of patients studied

A summary of ethics committee approvals, amendments, correspondence, dates of studies and numbers of patients studied are presented in Table 10-1. The studies were approved by the Ethics committee and Research and Development Department of the Institute of Child Health and Great Ormond Street Hospital NHS Trust. The Project R&D number was 03AR16

Table 10-1. Summary of protocols and ethics committee approvals

Title	Protocol version	Process & dates of letters/ approvals	Details and key questions (Q)	Patients allowed	Patients studied
Development of a reliable auditory stimulus for infants during anaesthesia	1	Initial R&D registration August – Dec 2003	Advice of ethics chairman sought. Q: Can response to noise be used to stimulate infants during?		
Arousal of infants to noise during recovery from anaesthesia	2	Ethics approval obtained 10th Dec 2003	NB: change of title Q: What is the arousal response of infants to noise during recovery from anaesthesia?	30	2
Arousal of infants to noise during recovery from anaesthesia	3	Non-substantial amendments requested Approved by	Noise was not effective Amendments: change of noise		18

		Ethics committee chairman 13th May 2004	harmless stimulation observations during natural sleep		
EEG changes during anaesthesia and awakening in infants	4	Non-substantial amendments requested and approved by Ethics committee chairman 21st Feb 2008	NB: change of title Amendments: noise no longer used extra EEG channels Q: What are the EEG and HRV changes during anaesthesia and awakening in infants?	30	9
EEG changes during anaesthesia and awakening in infants	5	Substantial amendments requested and approved by Ethics sub-committee 15 Jan 2009	Addition of multiple trivial stimuli blood pressure cuff inflation foot tickling		21
EEG changes during anaesthesia and awakening in infants	6	Amendments declined 17 March 2009 Full ethics approval obtained 15th June 2009	Does the EEG signal reappear if anaesthesia is re-established after recovery has begun?	10	Nil

10.2 Abstracts of presentations

10.2.1 ESPA Warsaw 2009

The following abstract was presented at the Annual Scientific Meeting of the European Society of Paediatric Anaesthesiology in Warsaw on 10th September 2009

THE EEG DURING AWAKENING FROM ANAESTHESIA IN INFANTS

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Introduction Processed EEG monitoring of consciousness, developed in adults, may not be reliable in infants.(1) The normal EEG of infants is different to that in adults and EEG data from infants during anaesthesia are sparse. Are there characteristics of the EEG that could be used as a monitor of anaesthesia depth and to indicate whether or not an infant will awaken? Davidson and colleagues found that mean EEG power decreased before awakening in children older than 6m anaesthetised with various drug combinations.(2) This study analyses EEG data from infants awakening from sevoflurane anaesthesia and searches for characteristic patterns.

Methods The study was approved by the local ethics committee and parents gave written informed consent. All infants were anaesthetised with sevoflurane in oxygenated air and mechanically ventilated. Analgesia was appropriate for the surgery. Silver cup scalp electrodes were applied to record EEG from frontal and centro-parietal montages. Recording began after surgery had ended. Sevoflurane administration was continued at surgical levels for one minute and then turned off. Infants were unstimulated except for tickling a foot continuously until awake. EEG was recorded using a Grass Telefactor “Aura 10-20” system connected to a PC. Analogue filters limited data to between 0.3 and 70 Hz. The input range was +2 to -2 millivolts, digitisation was 400 Hz and signal resolution was 0.06 µV. Off-line, raw signals were visually inspected for obvious oscillations, patterns and non-EEG artefacts and analysed with discrete Fourier transformation using Matlab signal processing software. Signal power was calculated for epochs of 6s; frequency band

resolution was 1Hz. Events were recorded by a video time-linked to the EEG. Data capture ended when infants were awake for one minute. Criteria for awakening had been developed in a previous study by consensus with 30 consultant anaesthetists.
Results Fourteen infants were studied. Visual inspection showed two obvious phases. After awakening started there were large changes in the baseline, bursts of EMG activity and other non-physiological artefacts. Before awakening signals were constant and 2 patterns were obvious that were associated with age. The youngest infants had low amplitude signals (<10 μV) whereas the oldest infants had appreciable amplitude (>50 μV) in mixed frequencies between 3 and 20 Hz; this pattern was prominent during anaesthesia but decreased after sevoflurane had been turned off. Visualisation of power spectrum arrays confirmed these observations. In 8 infants older than 52 w (postmenstrual age (PMA)) the power within 5-20Hz frequency bands decreased after sevoflurane was turned off and almost disappeared approximately one minute before awakening began.
Discussion In infants older than 52 w PMA, there were characteristic power spectrum changes before awakening from sevoflurane anaesthesia that may be a useful warning of awakening. These findings are similar, but in reverse, to those described during induction of propofol anaesthesia in adults.(3)

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(2) Davidson AJ, Sale SM, Wong C, McKeever S, Sheppard S, Chan Z, et al. The electroencephalograph during anesthesia and emergence in infants and children. Paediatr Anaesth 2008 Jan;18(1):60-70.
(3) Koskinen M, Mustola S, Seppainen T. Relation of EEG spectrum progression to loss of responsiveness during induction of anesthesia with propofol. Clinical Neurophysiology 2005 Sep;116(9):2069-76.

This research was supported by funding from the Portex Unit ICH UCL.

10.2.2 ARS London 2009

The following abstract was presented at Anesthesia Research Society in London on 4th December 2009

EEG CHARACTERISTICS IN INFANTS DURING AWAKENING FROM ANAESTHESIA

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Processed EEG monitoring of consciousness, developed in adults, may not be reliable in infants.(1) The normal EEG of infants is different to that in adults and EEG data from infants during anaesthesia are sparse. Are there characteristics of the EEG that could be used to indicate whether or not an infant will awaken? Davidson and colleagues found that EEG power decreased before awakening in anaesthetised children older than 6m (2) whereas Lo and colleagues found that EEG power increased(4). This study analyses EEG data from infants awakening from sevoflurane anaesthesia and searches for characteristic patterns.

The study was approved by the local ethics committee and parents gave written informed consent. All infants were anaesthetised with sevoflurane in oxygenated air and mechanically ventilated. Analgesia was appropriate for the surgery. Silver cup scalp electrodes were applied to record EEG from frontal and centro-parietal montages. Recording began after surgery had ended. Sevoflurane administration was continued at surgical levels for one minute and then turned off. EEG was recorded using a Grass Telefactor “Aura 10-20” system. Analogue filters limited data to between 0.3 and 70 Hz. The input range was +2 to -2 millivolts, digitisation was 400 Hz and signal resolution was 0.06 µV. Off-line, raw signals were visually inspected for obvious oscillations, patterns and non-EEG artefacts and analysed with discrete Fourier transformation using Matlab signal processing software. Signal power was calculated for epochs of 6s; frequency band resolution was 1Hz. Events were recorded

by a video time-linked to the EEG. Data capture ended when infants were awake for one minute. Criteria for awakening had been developed in a previous consensus study.

20 infants were studied. Visual inspection showed two obvious phases. After awakening started there were large changes in the baseline, bursts of EMG activity and non-physiological artefacts, whereas before awakening few epochs had interference. Before awakening there were 2 patterns confirmed by power spectra. In infants <52w post menstrual age (PMA) summated power within 5-20Hz remained <100 µV2 until awakening began. Older infants however had power >100 µV2 during anaesthesia which decreased to <50 µV2 at least 1 min before awakening began. In addition older infants had appreciable power in a prominent frequency usually between 8 and 16 Hz during anaesthesia that blended with background EEG before awakening began.

In infants older than 52 w PMA, there were characteristic power spectrum changes before awakening from sevoflurane anaesthesia that may be a useful warning of awakening. These findings are similar, but in reverse, to those described during induction of propofol anaesthesia in adults.(4)

(1) Davidson AJ. Paediatr Anaesth 2006 Apr;16(4):374-87

(2) Davidson AJ, Sale SM, Wong C et al. Paediatr Anaesth 2008; 18(1):60-70

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(4) Koskinen M, Mustola S, nen T. Clinical Neurophysiology 2005; 116(9):2069-76.

This research was supported by funding from the Portex Unit ICH UCL and the Trustees of Great Ormond Street Hospital.

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