The Electroencephalographic Effects of General Anaesthetics: A Suite of Clinical Studies and Theoretical Models.

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A thesis submitted for the degree of MD, The University of Auckland, 2000

Abstract

The primary object of this thesis was to investigate aspects of empirically-measured, anaesthesia-induced electroencephalographic (EEG) changes that could be explained by network models of cortical interactions.

The thesis consists of a collection of various theoretical and clinical papers in three sections:

(a) A background section summarizing previous relevant published works on the molecular actions of anaesthetic agents, and the origin and problems with the acquisition of the EEG.

(b) A second section dealing with the development of various **theoretical / computer** models of general anaesthetic action.

(c) A third section of various **clinical** and EEG studies of anaesthesia and sleep. These were done to confirm and clarify some of the theoretical results from the models. However there are many different ways of numerically capturing the information contained within the EEG. Because this problem needed to be overcome before the primary aim of the thesis could be accurately handled; the clinical studies tended to be diverted into this secondary "signal-acquisition" aspect of the EEG analysis in anaesthesia and sleep.

Because the thesis has a constellation of different interlocking threads of investigation, I have summarized the various themes in the following table.

Theme ⇒ **Chapter** ⇓	*Cortical / Subcortical influences*	*Processes of EEG generation*	*EEG signal acquisition / BIS*	*Phase-transition / Divergences*
1. Introduction				X
2. Cortical Anatomy	X			
3. EEG acquisition	X	X		
4.Mechanisms of GA	X	X	X	
5. Cellular Automata (1)		X		X
6. Cellular Automata (2)		X		X
7. Cellular Automata (3)	X	X		X
8. Continuum Models		X		X
9.BIS –SEF			X	X
10. Response / amnesia			X	X
11. Gamma rhythms		X	X	
12 & 13. Sleep		X	X	

(A) Background Section

The relevant conclusions from the background section were:

1) The transition from aesthesia to anaesthesia involved the whole animal, and thus may not be entirely measurable by the EEG. In contrast the transitions from consciousness to coma - and even more specifically - from mnesis to amnesis were predominantly observable by changes in the activity of the cortex and in the resultant EEG signal.

2) The EEG signal arose largely from the summation of coherent post-synaptic potentials in the cortical pyramidal cells. These were, in turn, mainly controlled by cortical layer-1 modulation – which was subject to ascending neuromodulatory systems.

3) The main artifacts in the EEG signal were eye-movements, blinks, and frontalis EMG.

4) The Bispectral index (BIS) consisted of three subcomponents. The first two (BetaRatio and SynchFastSlow) probably reflected the loss of high-frequency activity that is associated with the transition from consciousness to unconsciousness.

5) The state of the midbrain reticular formation projecting via the non-specific thalamo-cortical connections can profoundly alter the oscillatory state of the cortex and thence the EEG. Direct or indirect actions of general anaesthetic agents on these structures may be a major cause of the observed EEG changes. These changes are qualitatively similar to the changes observed during natural sleep.

6) Although there was variation between different agents, the most consistent action of commonly-used general anaesthetic agents was to prolong the fast inhibitory post-synaptic potential > 50% by GABAergic potentiation. This action was consonant with the observed EEG effects of anaesthesia - which are (1) an increase in EEG spectral power and frequency followed by, (2) a decrease in dominant frequency and overall power with increasing concentrations: the so-called "biphasic response". There were also a number of more specific features: namely loss of alpha band activity, an initial increase in relative beta activity, followed by a shift to lower frequencies, spindles - and in deep anaesthesia - burst suppression patterns. Other contributions to anaesthetic action may include: (1) inhibition of NMDA receptor function, (2) reduction of nicotinic acetyl-choline modulation, and (3) a direct hyperpolarizing action by opening potassium channels. Anaesthetic agents disrupted cortical function at lower doses than those required for inhibition of brain stem function.

(B) Theoretical Models

The fact that the cerebral cortex consisted of, effectively, a two-dimensional interconnecting neural network was of overriding importance. All the theoretical models were constrained by this topological fact, and showed a remarkable degree of similarity. Regardless of whether the model was continuous (appendix 2) or discrete (cellular automata), some robust and consistent features emerged:

1) Some form of abrupt decrease in information flow within the network occurred when the interaction between the network elements was interrupted greater than certain critical threshold amount – the order/disorder phase transition.

2) This critical point was manifest as (i) a large change in the simulated mean soma potential (the order parameter), (ii) divergence of the spectral power of the simulated pseudoEEG signal, and (iii) decrease in frequency content (in the cellular automaton models). Unfortunately the order parameter for the EEG is probably unmeasurable in clinical practice. The first derivative is measurable, but not completely reliable as a proxy order parameter.

3) All models required some form of noisy external (subcortical) input to drive them. Variations in this input could explain some of the anomalies observed in the clinical section of the thesis.

(C) Clinical Papers

The clinical papers were a series of papers recording the clinical data, which then influenced the development of the theoretical models. The single most popular clinical measure of anaesthetic depth in present practice is the Bispectral Index (BIS). Many of these studies explore the strengths and weaknesses of this index in various clinical situations. The main disadvantage of the BIS was that crucial aspects of its formulation are not in the public domain for commercial reasons. We attempted to separate out the changes in the various subcomponents of the BIS in patients under general anaesthesia, and natural sleep.

1) In the first paper we described how the EEG changed during induction and recovery from general anaesthesia with propofol and isoflurane. We compared EEG vs heart rate variability changes as monitors of anaesthetic depth. This study served to evaluate a clinically accepted measure of anaesthetic depth, as well as gaining practical EEG experience in collecting experimental data, both using the ASPECT EEG monitor, and in devising the best clinical methods of quantifying levels of consciousness. The main results were that the BIS was relatively reliable in steady-state conditions, and better than the raw 95% spectral edge frequency, and the approximate entropy of the EEG.

2) Auditory recall and response-to-command during recovery from propofol anaesthesia. In this paper we were able to collect data in a very controlled situation, somewhat different from that pertaining to clinical practice. From this we were able to identify separate components of consciousness and mnesis and how they correlated with EEG changes. We were also able to compare frontal and parietal EEG data. We established that there is a clear divergence of spectral power around the time of loss-of-consciousness when the propofol was administered as a slow infusion. This is good evidence supporting the basis of the theoretical models. This experiment also established that it is possible for a patient to be conscious, not paralyzed, but not responding to verbal command.

3) Electroencephalographic measures of depth of anaesthesia: the importance of the gamma band and the electromyogram signal. This study was concerned with different technical aspects of EEG signal acquisition and processing. It suggested that usually the EMG is not a significant problem, and that the gamma (40-60Hz) frequency band is important in distinguishing the awake from the anaesthetized state.

4) The Bispectral Index: A Measure of Depth of Sleep? Because the EEG changes of general anaesthesia are very similar to those of sleep, this study was a simple observational study collecting some information about changes in the BIS with natural sleep.

5) The Bispectral Index and Sleep Stage: A Polysomnographic study. In this study we formally compared the BIS with a full polysomnogramnographic sleep staging. It confirmed the results of the previous study, and demonstrated that the subcomponents of the BIS (the BetaRatio and the SynchFastSlow) changed in a manner very similar to those observed under general anaesthetic.

Conclusions

The observed changes in the EEG on induction of anaesthesia can be explained by changes in relatively simple theoretical network models. These changes can be reliably reduced to univariate parameters

Acknowledgements

I would like to acknowledge the help of Dr. Tim Short (Department of Anaesthesia, Auckland Hospital) and Dr. Blake Johnson (Department of Psychology, University of Auckland) for their advice and patient reading of the preliminary versions of the manuscript.

I would also acknowledge the efforts of a number of co-workers in the research for their diligence and expertise. These include Moira and Alistair Steyn-Ross from the Department of Physics University of Waikato, and members of the Anaesthetic Department of Waikato Hospital - John Andrzejowski, Jason Donovan, Murray Williams, and Peter Smith.

Table of Contents

Glossary / List of Abbreviations

CNS – Central nervous system

EEG – Electroencephalograph

ECoG – Electrocorticograph

EMG – Electromyogram

BIS – Bispectral index

SEF – 95% Spectral edge frequency

SE50 – 50% Spectral edge frequency or 'median' frequency

SE50d – 50% Spectral edge frequency or 'median' frequency of the first time-derivative of the signal

ApEn – Approximate entropy

HRV – Heart rate variability

GABA – Gamma amino butyric acid

Ach – Acetylcholine

NMDA – N-methyl D-aspartate

AMPA – alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionate

IPSP – Inhibitory postsynaptic potential

EPSP – Excitatory postsynaptic potential

IPSC – Inhibitory postsynaptic current

EPSC – Excitatory postsynaptic current

REM – Rapid eye movement sleep

FFT – Fast Fourier Transform

MAC – Minimum alveolar concentration for inhibition of movement in 50% of subjects

SEM – Standard error of the mean

CA – Cellular Automaton. A class of discrete model of the interactions between a network of elements.

Pb – Bond probability - the probability of successful transmission of information between neuronal assemblies

PseudoEEG – The output signal of a cellular automaton computer model of the cerebral cortex. It is the summed 'voltage' of all the elements of the cellular automaton at each time-step.

Aesthesia – The "animal-like" response of the organism to an external noxious stimulus.

Anaesthesia – The lack of response

Consciousness – The process by which we encode, or ascribe, or extract, meaning from our experience and environment.

Unconsciousness – The inability to conduct this process.

Mnesis – The formation in the CNS of a representation of past events.

Amnesis – The inability to form such a representation.

Phase transition – The sudden appearance of new qualitative properties in a system of interacting elements, brought on by a gradual change in a controlling parameter. (for example, water freezing as temperature is lowered)

Critical Point – the value of the parameter at which the phase transition occurs. It is usually marked by divergences to infinity of various thermodynamic quantities.

Order parameter – A parameter that is zero at one side of a phase transition, and takes a finite value as the critical point is crossed. It often reflects a symmetry-breaking

Mean Soma Potential – The mean potential across the cell membrane at the axon hillock of all the pyramidal neurons under consideration. (Usually about 100 000.)

1/f slope – the slope of the underlying power spectrum of the EEG (plotted on bilogarithmic scales), excluding harmonic spectral peaks. It is indicative of the underlying fractal structure of the EEG signal.

Publications

Work from this thesis has appeared in the following original peer-reviewed papers:

1). Sleigh JW, and Galletly D. A model of the electrocortical effects of general anaesthesia. British Journal of Anaesthesia 1997; 78(3): 260-263.

2). Sleigh JW, Steyn-Ross A, Steyn-Ross M. The first time-derivative of the EEG: A possible Proxy for the Order-parameter for the cerebral cortex. (Complexity International)- http://parallel.hpc.unsw.edu.au/complex/c98/proceedings.html

3). Sleigh JW, Andrzejowski J, Steyn-Ross A, Steyn-Ross M. The bispectral index: a measure of depth of sleep? Anesthesia and Analgesia. 1999 Mar; 88(3): 659-61.

4). Sleigh JW, Donovan J. Comparison of the Bispectral Index, 95% Spectral Edge Frequency, and Approximate Entropy of the EEG, with changes in Heart Rate Variability during induction and recovery from general anaesthesia. British Journal of Anaesthesia 1999; 82(5): 666-671.

5). Williams ML, Sleigh JW. Auditory recall and response to command during recovery from propofol anaesthesia. Anaesthesia and Intensive Care 1999 Jun; 27(3): 265-8

6). Steyn-Ross M, Steyn-Ross A, Sleigh JW, and Liley DTJ. Theoretical EEG stationary spectrum for a white-noise-driven cortex: Evidence for a general anesthetic-induced phase transition. . Phys Rev E. 1999; 60(6): 7299-7311.

Work from this thesis has been submitted to the following journals:

1). Sleigh JW, Steyn-Ross M, Steyn-Ross A, Wang P, and Patel J. The Bispectral Index and Sleep Stage: A Polysomnographic study, submitted to Sleep Medicine.

2) Sleigh JW, Steyn-Ross M, Steyn-Ross A, Williams M, and Smith P. Electroencephalographic measures during induction of general anaesthesia: the influence of the gamma frequency band, and the electromyogram signal. Submitted to British Journal of Anaesthesia.

Work from this thesis has been presented at the following scientific meetings:

1).European Congress of Anaesthesiology. Amsterdam May 1999. "Epinephrine has a stimulatory effect on the bispectral index and sedation". J Andrzejowski, J Sleigh, I Johnson, L Sikiotis. Published in British Journal of Anaesthesia 1999; (82) Suppl 1: A316.

2). "The First Time-Derivative of the EEG – A Possible Proxy for the Order-Parameter for the Cerebral Cortex". Complex Systems 99. Sydney, October 1998.

3). "The EEG Explained". ANZCA May 99

4). "Auditory recall and response to command during recovery from propofol anaesthesia". ANZCA May 1999

5). "EEG indices related to hypnosis and amnesia during propofol anaesthesia for cardioversion". ANZCA May 1999.

6). "The cortical effects of general anaesthesia modelled as an order/disorder phase transition". International Society for Brain Electromagnetic Topography (ISBET 99). October 1999, Adelaide.

7). "EEG measures of depth of anaesthesia: simple alternatives to the Bispectral Index". The 2nd Congress of the Asian Oceanic Society for Intravenous Anaesthesia. October 1999, Melbourne.