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ACTA UNIVERSITATIS OULUENSIS

Miika Koskinen

AUTOMATIC ASSESSMENT OF FUNCTIONAL SUPPRESSION OF THE CENTRAL NERVOUS SYSTEM DUE TO PROPOFOL ANESTHETIC INFUSION

FROM EEG PHENOMENA TO A QUANTITATIVE INDEX

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AUTOMATIC ASSESSMENT OF FUNCTIONAL SUPPRESSION OF THE CENTRAL NERVOUS SYSTEM DUE TO PROPOFOL ANESTHETIC INFUSION

From EEG phenomena to a quantitative index

Academic dissertation to be presented, with the assent of the Faculty of Technology of the University of Oulu, for public defence in Auditorium IT115, Linnanmaa, on September 29th, 2006, at 12 noon

OULUN YLIOPISTO, OULU 2006

Acta Univ. Oul. C 253, 2006

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ISBN 951-42-8174-8 (Paperback)
ISBN 951-42-8175-6 (PDF) http://herkules.oulu.fi/isbn9514281756/
ISSN 0355-3213 (Printed)
ISSN 1796-2226 (Online) http://herkules.oulu.fi/issn03553213/

Cover design
Raimo Ahonen

OULU UNIVERSITY PRESS
OULU 2006

Koskinen, Miika, Automatic assessment of functional suppression of the central nervous system due to propofol anesthetic infusion. From EEG phenomena to a quantitative index
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Acta Univ. Oul. C 253, 2006
Oulu, Finland

Abstract

The rationale for automatically monitoring anesthetic drug effects on the central nervous system (CNS) is to improve possibilities to gain objective information on a patient's state and to adjust the medication individually. Although monitors have shown their usefulness in practice, there are still a number of unclear issues, especially with respect to the scientific foundations and validity of CNS monitoring techniques, and in monitoring the light hypnotic levels. Current monitors are, for example, often based on heuristics and *ad hoc* solutions. However, a quantitative index for anesthetic drug effect should have a sound relationship with observations and with the selected control variable. The research objectives are: (1) to explore propofol anesthetic related neurophysiological phenomena that can be applied in the automatic assessment of CNS suppression; (2) to develop a valid control variable for this purpose; (3) by means of digital signal processing and mathematical modeling, to design and to evaluate the performance of an index that correlates with the control variable.

This dissertation introduces potentially useful neurophysiological phenomena, such as changes in phase synchronization between different EEG channels due to anesthesia, and painful stimulus evoked responses during the burst suppression. Furthermore, it refines the progression of the time-frequency patterns during the induction of anesthesia and shows their relation to the instant of unresponsiveness. The presented spontaneous and evoked EEG phenomena provide complementary information about the CNS functional suppression.

Most significantly, the dissertation proposes a continuous and observation based control variable (*r* scale) and the means to predict its values by using EEG data. The definition of the scale provides a basis for anticipating the instant of the loss of consciousness. Additionally, the phase synchronization index as an indicator of drug effect is introduced. The approximate entropy descriptor performance is evaluated and optimised with a non-stationary signal recorded during the induction of anesthesia.

The results open up opportunities to improve the preciseness, scientific validity and the interpretation of information on the anesthetic effects on CNS, and therefore, to increase the reliability of the anesthesia monitoring. Further work is needed to extend and verify the results in deep anesthesia.

Keywords: algorithms, brain, diagnosis, drug effects, intravenous anesthetics, physiological monitoring, signal processing

Preface

The original communications in this dissertation have been prepared during the years 1999-2006 at the Department of Electrical and Information Engineering, University of Oulu, Finland, the Department of Clinical Neurophysiology, Oulu University Hospital, and at the Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, USA.

My warmest gratitude goes to my supervisor, Professor Tapio Seppänen, for his unswerving support and for our numerous discussions, including those during coffee breaks. I also wish to thank Dr Ville Jäntti for all his support and for his comments on the manuscript of this dissertation. My interest in EEG and anesthesia originates from his studies and support in this field. I am also indebted to Professor Nitish Thakor for giving me the possibility to stay at Johns Hopkins University in the summer of 2003. The discussions we had and the experience will have a long-ranging influence on my work and my career.

I wish to thank Dr Seppo Mustola for our fruitful cross-disciplinary co-operation and for his comments on the manuscript. My co-authors Professor Seppo Alahuhta, Professor Arvi Yli-Hankala, Associate Professor Shanbao Tong, Dr Ari-Matti Huotari and Dr Johanna Tuukkanen also deserve my thanks and appreciation. I would like to thank Mr Kalervo Suominen and Mrs Raija Remes, not only as my co-authors, but also for all their technical support in data acquisition.

I am grateful to the official reviewers, Professor Pekka Meriläinen and Dr Mark van Gils, for their suggestions and constructive criticism.

Completing a dissertation is hard work, but it is made all the more bearable by being able to work in a research team with a warm team spirit. I am grateful to all my co-workers at the University of Oulu for this. Special thanks go to Dr Pertti Väyrynen for English language consulting. Last, but by no means least, I am grateful for the loving support of my wife Kirsi.

The research initially began at the Finnish Graduate School of Functional Studies in Medicine. This dissertation has been supported by the Infotech Oulu Graduate School, the Instrumentarium Science Foundation, TEKES and the Tauno Tönning Foundation.

Miika Koskinen

Job 9: 4-10

List of abbreviations

AAI	A-Line ARX index
AEP	Auditory evoked potential
ANFIS	Adaptive-network-based fuzzy inference system
ApEn	Approximate entropy
BAEP	Brainstem auditory evoked potential
BIS	Bispectral index
BSR	Burst suppression ratio
CNS	Central nervous system
EEG	Electroencephalography
EMG	Electromyography
EOG	Electro-oculography
EP	Evoked potential
ERP	Event-related potential
ERS	Event-related synchronization
ERD	Event-related desynchronization
FIR	Finite impulse response
FFT	Fast Fourier transform
ICA	Independent component analysis
ICU	Intensive care unit
IPG-FMH	In-place growing FIR-median hybrid filter
LLAEP	Long-latency auditory evoked potential
LMS	Least mean square adaptive filter
LOC	Loss of consciousness
LVC	Loss of response to verbal command
MAC	Minimal alveolar concentration
MLAEP	Middle-latency auditory evoked potential
MLR	Multiple linear regression model
MPF	Median power frequency
MSE	Mean square error
OAA/S	Observer's assessment of alertness/sedation scale
OR	Operating room

PACU	Postanesthetic care unit
PD	Pharmacodynamic modeling
PK	Pharmacokinetic modeling
PSI	Patient state index
QEEG	Quantitative EEG
RE	Response entropy
ROC	Return of consciousness
SCC	Semilinear canonical correlation
SD	Standard deviation
SE	State entropy
SEF95%	Spectral edge frequency 95%
SEP	Somatosensory evoked potential
TCI	Target controlled infusion
TIVA	Total intravenous anesthesia
VAS	Visual analogue scale

List of original communications

This dissertation is based on the following articles, which are referred to in the text by their Roman numerals:

I Koskinen M, Seppänen T, Tuukkanen J, Yli-Hankala A, Jäntti V (2001) Propofol anesthesia induces phase synchronization changes in EEG. Clin Neurophysiol 112: 386-392.

II Huotari AM, Koskinen M, Suominen K, Alahuhta S, Remes R, Hartikainen K, Jäntti V (2004) Evoked EEG patterns during burst suppression with propofol. Br J Anaesth 92: 18-24.

III Koskinen M, Mustola S, Seppänen T (2005) Relation of EEG spectrum progression to loss of responsiveness during induction of anesthesia with propofol. Clin Neurophysiol 116: 2069-2076.

IV Koskinen M, Seppänen T, Tong S, Mustola S, Thakor N (2006) Monotonicity of approximate entropy during transition from awareness to unresponsiveness due to propofol anesthetic induction. IEEE Trans Biomed Eng 53: 669-675.

V Koskinen M, Mustola S, Seppänen T (forthcoming) Forecasting the unresponsiveness to verbal command on the basis of EEG frequency progression during anesthetic induction with propofol. IEEE Trans Biomed Eng (accepted for publication).

Contents

1 Introduction

1.1 Background and motivation

In the management of sedation and general anesthesia, the function of the central nervous system (CNS) is intentionally suppressed (Spencer *et al.* 1994, Rampil 1998). However, with fixed dosing regimens, the physiological effect or potency of these drugs varies considerably between individuals (Avramov & White 1995, van Gils *et al.* 2002). Automatic assessment of CNS suppression would help to gain objective information on a patient's state and to steer the drug management individually and more effectively (Avramov & White 1995).

The rationale for monitoring the drug effects on the CNS comes from clinical practice. To begin with, the benefits of anesthesia to a patient must outweigh the risks (Senhadji *et al.* 2002). The motivation is to improve patient care and the quality and safety of anesthesia, to provide a more predictable intra- and postoperative course and better patient satisfaction, and to use the resources efficiently, gaining cost savings (Pomfrett 1999, Carrasco 2000, Rosow & Manberg 2001). During the last decade, considerable progress has been made in the operating room (OR) monitoring. Retrospective studies have shown, for instance, that intraoperative hypnosis monitoring reduces the risk of awareness and recall of events due to insufficient anesthesia (Ekman *et al.* 2004, Myles *et al.* 2004), and, additionally, helps to avoid unnecessary deep anesthesia, which could lead to prolonged recovery from anesthesia, hemodynamic problems, the need for postoperative respiratory assistance and increased post-anesthesia care unit stay (Yli-Hankala *et al*. 1999, Nelskylä *et al*. 2001, Senhadji *et al.* 2002, Kreuer *et al*. 2003). CNS monitoring has been shown to reduce the consumption of anesthetics (Yli-Hankala *et al*. 1999, Drover *et al*. 2002, Kreuer *et al*. 2003, Vakkuri *et al*. 2005), and to decrease post-operative vomiting (Nelskylä *et al*. 2001). Monitoring can also help in selecting more rationally between the need for hypnotic or analgesic drugs (Rosow & Manberg 2001, Vakkuri *et al*. 2004).

Many research efforts have focused on anesthetic effects in deep anesthesia. Reliable monitoring of light hypnosis or sedative levels, where a patient is conscious or easily arousable, still remains a challenge (see e.g. Yppärilä 2004). However, sedation is a primary objective in intensive care (Carrasco 2000). Sedation in the intensive care unit (ICU) is conventionally assessed by manual scoring systems. However, these have several known limitations. For example, some clinical signs may be absent due to medication (Jensen *et al*. 2004), or a bias can be introduced because of subjective assessment. Insufficient sedation may lead to myocardial ischemia or ventilator dysynchrony (De Jonghe *et al*. 2000). An unexpectedly prolonged sedation, in its turn, may cause diagnostic problems and lead to the use of expensive tests, such as computer tomography or magnetic resonance imaging (Avramov & White 1995), and it may increase the duration and the risks of mechanical ventilation (De Jonghe *et al*. 2000). Thus, similarly to monitoring in the OR, an automatic assessment of CNS suppression, and enabling a dosing-to-effect titration strategy (Avramov & White 1995) could bring considerable benefits for patient care in the ICU.

The degree of CNS depression is very difficult to measure with clinical signs (Stanski 1992). However, there is a need for a measure that is directly related to the state of consciousness, to hypnotic effect or to CNS depression (see e.g. Heier & Steen 1996, Rampil 1998). Recent progress in this field has been based on the utilization of electroencephalography (EEG). EEG is an important non-invasive tool for providing time-continuous measurements of the cerebral function. Rampil (1998) lists three applications of EEG in monitoring the drug effect. It can be used:

– as a quantitative tool for the pharmacological study of the CNS active agent;
– in burst suppression dose control (metabolic suppressive effect), and;
– in the assessment of CNS functional suppression.

EEG is a complex and often multi-channel signal, the interpretation of which requires training and depends on the experience of the investigator (Rampil 1998, Black *et al*. 2000). However, by means of mathematical signal processing and modeling techniques, it has been possible to extract clinically useful information related to drug effects, and to express this as an easily readable univariate index (also referred to as EEG descriptor or quantitative EEG (QEEG) variable). Such information processing may, for instance, reduce the clinician's workload, and enable automatic closed-loop titration of drugs (Rampil 1998, Zhang *et al*. 2002).

Today, there are a few commercially available indeces and monitoring systems to assess anesthetic depth, such as Bispectral Index (BIS; Aspect Medical Systems, Natick, MA, USA), Entropy indices (GE Healthcare Finland, Helsinki, Finland), Patient State Index (PSI; Hospira, Inc. Lake Forest, Il, USA) and Narcotrend (MonitorTechnik, Bad Bramstedt, Germany). Although these monitors have shown their usefulness in the OR, there are still a number of unclear issues, especially with respect to the scientific foundations and validity of CNS monitoring techniques, and in monitoring the light hypnotic levels. Current monitors are often based on heuristic and *ad hoc* solutions, as discussed in this dissertation. Moreover, it is likely that they cannot reliably indicate unconsciousness, but are more able to provide the trend or course of anesthetic effect on CNS (Heier & Steen 1996, Drummond 2000). These monitors provide only little, if any, insight into the underlying physiology (John *et al*. 2001, Jäntti 2005). Much research in this field has focused on evaluating the applicability of available monitors in clinical practice, while the very basis, the neurophysiological foundations, are still insufficiently understood (see e.g. Jäntti 2005).

This dissertation deals with questions related to the scientific and methodological validity of monitoring the functional suppression of CNS due to anesthic drugs. This implies that any given value of a mathematically derived quantity should have a sound relationship with measured observations and underlying physiological phenomena.

1.2 Research problems and hypothesis

The purpose of this dissertation is to develop a univariate index for quantifying the functional suppression of the CNS due to anesthetic drug infusion. To reach this goal, the following research objectives that outline the field of monitor design from EEG phenomena to a quantity are addressed:

1. exploring the neurophysiological phenomena which can be applied in automatic assessment of CNS suppression;
2. developing a valid control variable for this purpose;
3. designing and evaluating the performance of an index that correlates with the control variable.

As a starting point, it is assumed that an in-depth understanding of neurophysiological phenomena is essential for developing valid observation based methods for drug effect monitoring. EEG is the primary source signal in this dissertation. Both ongoing characteristics of EEG and reactivity to external stimuli can contain information on drug effect and the physiological state of the cortex. The purpose is to explore new ways of utilising the EEG signal in CNS monitoring.

The second research objective deals with an appropriate control variable for the functional suppression of CNS. Drug effects have been considered to form a continuum, which has been described with such terms, for example, as “light”, “moderate” and “deep” sedation or anesthesia. A continuum may form a scale or a control variable that a derived indicator should characterize. However, the concept of anesthesia, and thus the control variable for anesthetic state, is ill-defined (Stanski 2000, Zhang *et al.* 2002). Typically, clinical end-points, such as movement reactions to noxious stimuli, loss of consciousness or the occurrence of EEG burst suppression patterns, have been used as control measures. These events are dichotomous and sparsely manifested, however, although there is an intuitive assumption of the continuum. In contrast, the tendency of the current monitors is to exhibit the indicator value on a continuous scale (more specifically with an integer ranging from 100 to 0). Thus, the discrete characteristic of the control variable introduces definition problems. As a consequence, an index value may be related to the *probability* that a patient is awake or responsive (Glass *et al*. 1997, John & Prichep 2005) or the output can be derived with fuzzy-logic or other soft computing approaches (Zhang *et al*. 2002). Thus, an artificial continuum is introduced, in contrast to relating an indicator value directly with observation. The availability of a *continuous and observation based control variable* would therefore improve the scientific validity of the monitoring.

The third research objective deals with the development of an indicator to present accurately the values of the chosen control variable. When using discrete clinical end-points as control measures of anesthetic effect, the resulting control variable has at its best a rank-order level of measurement, in contrast to a ratio/interval level. In this respect, the functional relation between the control variable and the indicator ought to be monotonic (Smith *et al*. 1996) (the term monophasic has also been used in the relevant literature; see eg. Billard *et al*. 1997, Grouven *et al*. 2004, Schultz *et al*. 2004a). In contrast, the relation can be a biphasic function, i.e. an initial increase followed by a decrease of an index value on the scale. EEG derived variables, such as the spectral edge frequency 95% (SEF95%) or power in a passband, often show biphasic behavior as a function of concentration or dose (Heier & Steen 1996, Billard *et al*. 1997, Rosow & Manberg 2001), or as a function of time during anesthetic induction (Kuizenga *et al*. 2001, Schultz *et al*. 2004a). Biphasic behavior is often associated with light levels of sedation and an increase in beta range activity in the EEG. In such a situation, the descriptor gives an ambiguous estimate of anesthetic effect, because a certain index value is related to two different values of a control variable. Thus, an index should be constructed from EEG features in a unique and unambiguous manner, given the control variable.

1.3 Scope of the research

The current study belongs to the field of biomedical engineering, especially to that of bioelectrical signal processing and modeling. However, the advancement of monitoring technology requires a multidisciplinary approach. The field of research integrates the areas of signal processing, neurophysiology and anesthesiology. From the signal processing point of view, the dissertation deals with neuromonitoring, where the state and reactivity of CNS is studied during anesthesia by processing the EEG intelligently. The neurophysiological aspect concerns understanding and validating the EEG phenomena. From the anesthesiology viewpoint, the topic focuses on monitoring mostly the hypnotic effect of an anesthetic drug. It is in the interest of the anesthesiologist to have an easily understandable indicator to aid in drug administration.

The research problems are approached from the perspective of basic research, and as such, this work does not aim for a complete monitoring system. Moreover, comparison of commercially available monitoring systems in clinical settings is out of the scope of this study. The purpose is rather to introduce new ideas for further investigation, and to deepen an understanding of the related issues. The research has been carried out in ”laboratory conditions”, which implies limitations in the generalization of the results. Moreover, the limited number of subjects who participated and the narrow scope of anesthetic regimens allow the findings to be presented at a preliminary level only. The scope of research has been limited to reveal the EEG effects of a single anesthetic agent: propofol. Propofol, however, is a commonly used intravenously infused drug, providing hypnotic and amnesic effect (Reves *et al*. 2000). It is used for general anesthesia, as a sedative for local or regional anesthesia and in maintaining the sedation in ICU (see e.g. Sneyd *et al*. 1994). According to Sleigh & Bernard (2004), the development of the Bispectral Index or the Spectral Entropy monitors are largely based on using propofol or one of the halogenated ethers as the anesthetic drug.

Fig. 1 represents a schematic diagram of the assumed continuum of a hypnotic drug effect. The original communications can be categorized by means of this diagram. As indicated by the Roman numerals, three of the publications focus on the problems in the light levels of hypnosis, where the loss of consciousness is an important end-point. One study covers the level of hypnosis from the point where the ocular artifacts have ceased to the beginning of the EEG burst suppression, and one study concentrates on EEG phenomena during the burst suppression. The burst suppression study (II) is the only one that contains external controlled stimuli, while the rest of the papers study the characteristics of spontaneous EEG.

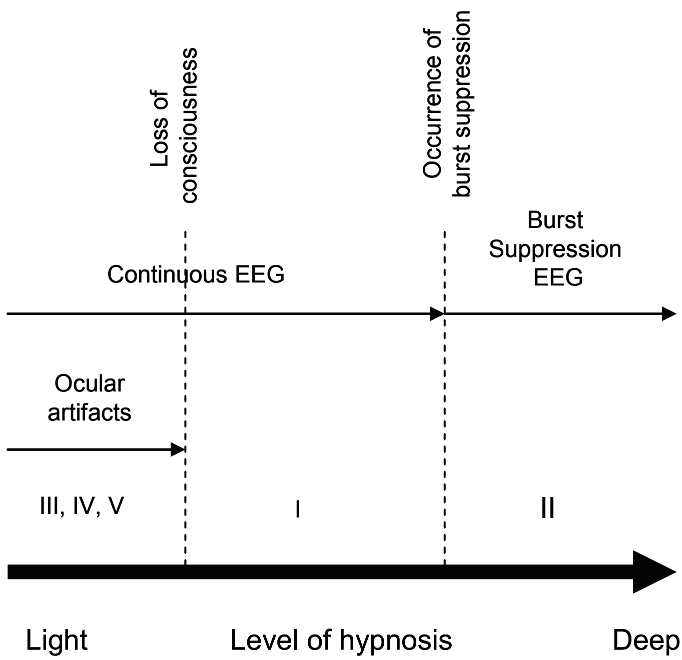

Fig. 1. Schematic presentation of the assumed continuum of the hypnotic drug effect. Two end-points, loss of consciousness, and the occurrence of burst suppression are marked. The Roman numerals I-V indicate the original communications related to certain levels of hypnosis.

1.4 Research methods

The original publications (I-V) are based on three patient materials. Depending on the place of data acquisition, the study plans were approved either by the institutional Ethics Committee of the University of Oulu, or by the Ethics Committee of the South Karelia Central Hospital, Lappeenranta. In addition, individual written consents of the volunteers were obtained.

The recorded data have been approached primarily in an explorative manner. In data processing and analysis, the principle of choosing methods that are justified and closely tied to neurophysiological observations or to anesthesiological foundations has been adhered to. The most important method is to study the recorded signal visually at first (see e.g. Jäntti *et al*. 2002). The EEG phenomena seen in the measurement signal may then help selecting useful signal processing methods. As the first phase of signal processing, artifacts in measurement signal originating from the electrical activity of muscles or blinks, for instance, are removed prior to further processing by means of filtering or independent component analysis (ICA). In the second phase, data is processed and analyzed by means of digital signal processing and modeling, data mining, or by means of visualization and statistical testing. EEG and its dynamics are studied in such dimensions as time, space (topographic aspect), frequency and complexity. Finally, the neurophysiological background of the phenomena, and signal processing methods are evaluated in relation to the relevant literature.

1.5 Author's involvement and contribution to the results

Study (I) is based on the readily recorded material. The author developed the idea of studying synchronization by examining the raw EEG patterns in deep anesthesia, designed the signal processing scheme, prepared the Matlab software, studied the neurophysiology behind synchronization and wrote the main part of the manuscript. Anesthesiologists Dr Johanna Tuukkanen and Professor Arvi Yli-Hankala offered an anesthesiological viewpoint and participated in the writing, especially with respect to the patient material and anesthesiological questions. Dr Ville Jäntti and Professor Tapio Seppänen provided support and helpful comments on the manuscript.

In study (II) the author was responsible for operating the EEG recordings in the operating room with help of Mrs Raija Remes and Mr Kalervo Suominen. The latter also wrote the computer program for controlling the electrical pulse stimulator. The author developed software for off-line analysis that included EEG filtering, evoked potential averaging, amplitude, latency and duration measurement tools, and graphical illustrations. The data analysis and the results were obtained together with anesthesiologist Dr Ari-Matti Huotari. The author prepared the text for the technical section of the manuscript. Dr Huotari along with Dr Jäntti, Professor Seppo Alahuhta and Dr Kaisa Hartikainen were mainly responsible for the prepartion of the manuscript.

Studies (III-V) were designed and carried out mainly by the author. Data recording was planned and executed in collaboration with anesthesiologist Dr Seppo Mustola, who also provided anesthesia protocols and patient population descriptions in the publications. Especially in IV, he carried out the pharmacokinetic simulations and reviewed the literature considering concentrations. Professor Seppänen gave advice regarding questions of engineering and useful comments on the text. With respect to study (III), Professor Nitish Thakor's advice was of the greatest importance. He was the one to initially draw the author's attention to the biphasic EEG effect at the beginning of the induction with propofol. Both he and Associate Professor Shanbao Tong discussed the important issues with the author and provided helpful comments.

2 Literature review

This chapter provides an overview of the EEG based assessment of functional suppression of the CNS due to anesthetics. The chapter is divided into four parts. Section 2.1 briefly describes some related terminology. Section 2.2 investigates the EEG, its neurophysiological basis and applicability in reflecting the effects of anesthesia. Section 2.3 deals with the problems related to choosing appropriate control variables for this purpose. Section 2.4 outlines the signal processing phases found in a typical CNS monitor.

2.1 Key terminology

To clarify the somewhat confusing terminology for the engineering community in this field of research, short explanations for some basic concepts follow. It should be noted that there is a great deal of controversy over these concepts, and thus the explanations are not unambiguous. A more extensive review of terminology has been provided by Ranta (2002).

By carrying out a literature review, Wansbrough & White (1993) investigated the use of the term *sedation*. Most commonly, sedation meant somnolence, drowsiness or hypnosis, although the term comes from Latin meaning ‘composed’ or ‘calm’. Sedation also refers to “a decrease in excitability”. Excitation, however, can be caused by pain, for instance. Wansbrough & White (1993) concluded that in the context of sedation, separate measurement scales should be used to assess pain or discomfort, drowsiness or somnolence and anxiety or excitation.

In an editorial by Sleigh & Bernard (2004), the concept of *consciousness* was divided into two subcomponents: alertness and awareness. Alertness was considered to represent a non-specific level of arousal, and it was associated to the metaphor “the TV is on”. Awareness, in turn, was considered to be “an ability to focus on and manipulate the information presented”, and using the TV example, it could be characterized by “the tuner is set and the program is running”. Consciousness is associated with the ability to recall (see section 2.3.3). Loss of consciousness has been investigated by means of specific surrogate measures or end-points, such as loss of response to verbal command (LVC).

According to Prys-Roberts (1987), the term *anesthesia* indicates a state where a patient is insensitive to the trauma of surgery. If the state of anesthesia is defined as a state where a patient does not recall or perceive noxious stimuli, anesthesia is basically an all-or-none phenomenon, because the loss of consciousness (LOC) is a threshold event. Thus, there cannot be different degrees or *depths of anesthesia*. However, Prys-Roberts (1987) indicates that three different objectives of anesthetic effect can be considered and their degree can be graded: hypnosis, analgesia and muscle relaxation. Hypnosis is related to the function of the cortex, analgesia is controlled on subcortical and spinal levels, and neuromuscular blocking is a peripheral phenomenon (van Gils *et al*. 2002). These general objectives can be controlled at least partly independently with different drugs. *Adequacy of anesthesia* is a common term indicating the lack of somatic or hemodynamic response to noxious stimuli (Thornton & Jones 1993) and complete amnesia (Ghoneim & Weiskopf 2000). Therefore, also this term implies the dichotomous nature of anesthesia.

Corresponding to the term *depth of anesthesia*, the notion *CNS functional suppression* (see e.g. Rampil 1998) or *CNS depression* (see e.g. Spencer *et al*. 1994) can be used. In this dissertation, these frequently used terms refer mainly to the hypnotic effects of anesthesia but also to altered CNS reactivity.

2.2 The EEG signal

2.2.1 The origins of EEG

The EEG signal reflects electrical potential differences between different locations on the scalp. Electrical potentials are caused by ionic currents that originate from pyramidal cells in the cerebral cortex. A pyramidal cell is the prevalent type of neuron, which has a long apical dendrite running through cortical layers towards the surface (Rampil 1998). The anatomical orientation of the layer of pyramidal cells is an important factor in the generation of the current (Schaul 1998). The dendrites of neighboring cells are roughly parallel. The postsynaptic potentials of the activated pyramidal cells are mainly responsible for creating a current flow in the extracellular fluid. Synchronized activation of numerous neurons may combine the flows additively, and thus, observable currents may emerge on the scalp (Rampil 1998, Schaul 1998).

Normally, the EEG signal has no obvious pattern. Higher cortical function is associated with desynchronized and relatively independent activity of neurons (Rampil 1998). However, in some mental and pathological states, in sleep, and in anesthesia, synchronized activity in cortical and thalamic neural structures may evoke distinguishable EEG patterns, such as waves, oscillations, spindles, spikes and bursts (Fig. 2; Lopes da Silva 1991, Steriade *et al*. 1993, Steriade *et al*. 1994, Schaul 1998). Different EEG phenomena may reflect different mechanisms of neuronal activity and synchronization between neural structures (see e.g. Steriade *et al*. 1993, Schaul 1998, Gugino *et al*. 2001). For example, the delta oscillation of 1-4 Hz during sleep originates from cortex-thalamus interaction, while the sleep related slow oscillation of <1 Hz has a cortical origin. Interestingly, this slow activity is a source for driving reticular and thalamocortical neurons, which may group sleep rhythms (spindle and delta oscillations) on higher frequencies (Steriade *et al*. 1993). Synchronized activity can extend from localized clusters of neurons to the entire neocortex. Generally, high frequencies are associated with small clusters, and low frequencies with larger clusters of synchronized cells (Steriade *et al*. 1993). Similarly, high frequencies tend to be lower in amplitude than low frequencies, while slow oscillations allow more time for cells to fire in relative synchrony (Schaul 1998).

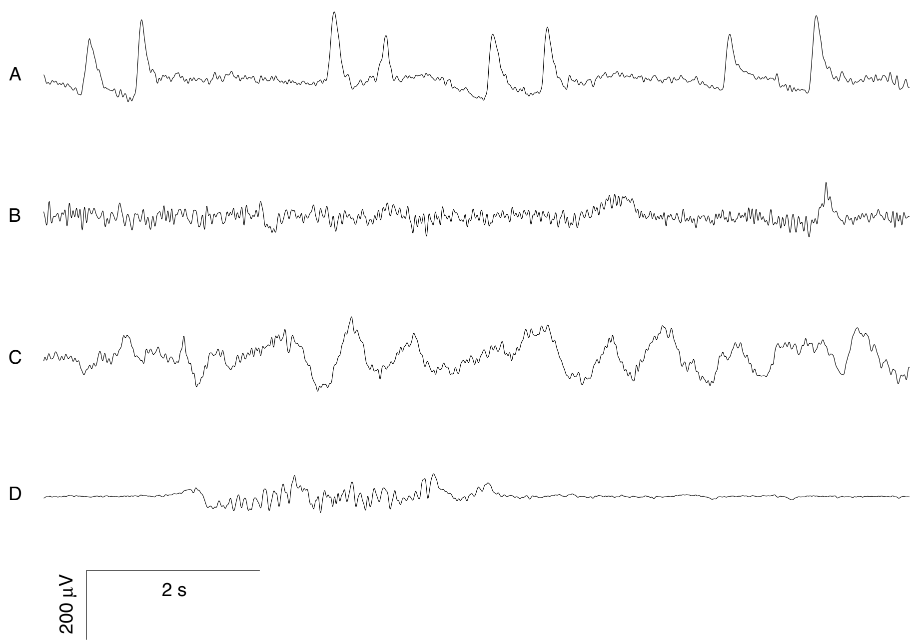

Fig. 2. An EEG recording presenting propofol effect at different levels of hypnosis. (A) Awake (desynchronized low-amplitude activity is contaminated by blink artifacts), (B) mixed α and β activity, (C) delta waves, and (D) burst suppression. (Fz referenced to the average of mastoid signals, passband 0.5-28 Hz.)

The distance of an electrode from a generator, volume conduction and anatomical structure have considerable effects on the observed signal (Nunez *et al*. 1997, Stegeman *et al*. 1997, Koles 1998, Schaul 1998). Electric currents must pass structures such as dura, skull and skin to be observable on scalp. As a consequence, the signal attenuates and spreads spatially (see e.g. Koles 1998). Thus, the signal picked up by a single electrode reflects activity in a wide area. In a simulation presented by Nunez *et al*. (1997), it was found that about 50% of the contribution originates from within a 3 cm radius of an electrode, and 95% within a 6 cm radius. Thus, closely spaced electrodes may pick up signals that are influenced by the same neural generator.

The EEG signal is usually recorded from multiple sites on the scalp with electrodes attached according to the international 10/20 system (Nuwer *et al.* 1998). As EEG is measured as a potential difference, the reference electrode placement has a considerable effect on the signal. In clinical work, reference electrodes are typically attached on mastoids or ear-lobes. However, modern commercial depth of anesthesia monitors may use only three or four electrodes placed on the forehead for reasons of ease of use (Vakkuri *et al.* 2004).

The amplitude of an artifact-free EEG signal is normally in the range of tens of microvolts. The main EEG power lies below 30 Hz, and thus, a sampling rate of a few hundred Hertz is enough to digitize the signal without aliasing effects. Evoked potential measurements can require a higher sampling rate due to rapid changes in signal waveforms. EEG characteristics are commonly described in terms of frequency contents and a power spectrum. Conventionally, EEG is divided into specific frequency ranges: δ (delta: 1-4 Hz), θ (theta: 4-8 Hz), α (alpha: 8-12 Hz), β (beta: 12-25) and γ (gamma: 25-50 Hz) bands. More specified ranges may also be defined, such as α_1 (8-10 Hz) and α_2 (10-12 Hz) (see e.g. Kishimoto *et al.* 1995). Today, EEG is mostly acquired in digital form allowing digital signal processing techniques to be utilized.

2.2.2 EEG during general anesthesia

The brain is the main target organ of anesthetic delivery (Senhadji *et al.* 2002). Anesthetic drugs markedly affect the EEG signal, generally in a dose related manner (Sloan 1998, Stanski 2000). Although clinical state can originate from diverse pharmacological mechanisms (Stanski 1992), some common characteristics can still be observed in the properties of the EEG. For example, a distinctive progression pattern of EEG activity can be seen with increasing concentrations of many anesthetic agents. With most anesthetics, the progression appears in the following order (Fig. 2; Clark & Rosner 1973, Sloan 1998, Guérit 1998, Black *et al.* 2000, Kuizenga *et al.* 2001, Gugino *et al.* 2001, John *et al.* 2001):

1. an initial decrease in posterior alpha rhythm, seen in an awake relaxed state with the eyes closed;
2. an increase in beta activity;
3. the progressive slowing to alpha, theta and to delta frequencies;
4. the burst suppression phenomenon.

Drug effects in the brain are anatomically widespread (John & Prichep 2005), which affects the topographic characteristics of EEG. Especially the frontal parts of brain are important. In the literature, the terms “anteriorization” or “frontal predominance” (Tinker *et al.* 1977) have been used to describe the anesthetic effects on frontal cortex. The increase of beta frequencies (12.75-20 Hz) in frontal and central parts of the brain with the use of propofol is considered to be associated with central nervous system depression and with impaired cognitive processing, such as learning and memorising (Veselis *et al.*

1992, John & Prichep 2005), the prolongation of reaction times and disappearance of the P300 auditory evoked response (Sneyd *et al*. 1994).

Gugino *et al*. (2001) investigated spectral changes in the EEG related to the loss and return of conscious awareness. The purpose was to identify features that contain information on sedation level and show similar changes during two different anesthesia protocols: in propofol/remifentanil and in sevoflurane/remifentanil anesthesia. Plasma and end-tidal concentrations were also measured. As induction progressed to the loss of consciousness (LOC, specified as the lack of response to verbal command accompanied by a painful stimulus), frontal predominance increased in terms of total absolute power. The predominance was most apparent in alpha and beta frequencies. At LOC, theta and delta power increased in anterior regions of the brain and spread to posterior parts.

Rundshagen *et al*. (2004) investigated the regional differences of anesthetic effects in EEG in discrete physiological states: in an awake state, after pre-medication, during induction, at LOC and after tracheal intubation. The most sensitive EEG measures for regional changes were the alpha and delta power.

John *et al*. (2001) studied power and coherence features in multichannel EEG common to isoflurane, desflurane, sevoflurane, propofol and to nitrous oxide/propofol anesthetics. With respect to suppression of the CNS function, the results showed a high heterogeneity of variance between different physiological states, but reversible changes with LOC (specified as the cessation of counting and the loss of the eyelash reflex) and return of consciousness (ROC, specified as the opening of eyes on a loud command) regardless of the anesthetic protocol. The power increase at LOC was found to be most significant with slow waves. They suggested that power increase is associated with more coherent activity within neuronal populations, indicating less differentiated and suppressed information processing. They also reported on hypercoupling in the anterior regions within each hemisphere, but uncoupling between anterior and posterior regions and between hemispheres.

Later in John & Prichep (2005), they implicated that functional uncoupling between the anterior and posterior regions happens at LOC. This uncoupled state remained present throughout the surgery. ROC, on the other hand, was suggested to be associated with the restoration of coupling between prefrontal cortex and sensory regions in beta and gamma bands. Interestingly, restoration was seen by means of the coherence estimate but not by power. In the gamma band, a coherence increase could be seen several minutes prior to ROC, while in the delta and alpha bands coherence was restored only after ROC. They suggested that the synchronization of anatomically dispersed neural structures is a critical factor in perceptual processing.

EEG changes during recovery from anesthesia are generally the opposite of those occurring during anesthetic induction. However, patients gain consciousness “at depressed levels of arousal” (Gugino *et al*. 2001), or are lethargic (John *et al*. 2001). At this state, brain function may have recovered enough to react to a specific stimulus, but a residual sedative effect can still exist (Vakkuri *et al*. 2004). Recovery from anesthesia is associated with decreased delta and theta power, followed by increased frontal beta power (Gugino *et al*. 2001, John *et al*. 2001). Coherence between anterior-posterior sites and between hemispheres is resumed (John *et al*. 2001). At ROC, frontal predominance remains in the beta band (Gugino *et al*. 2001).

Apart from the continuous EEG activity described above, burst suppression is often present in deep hypnosis. This is a non-stationary type of time-domain phenomenon, characterized by suppression periods when the EEG is of low amplitude and by the bursts of high amplitude activity that may begin abruptly and later return back to suppression. The occurrence of bursts decreases, and the periods of suppressions become longer with increasing doses of anesthetics. According to Steriade *et al*. (1994), at this state, a close correspondence exists between activities in EEG, cortex, thalamus and upper brain-stem. In their experiment, 95% of the studied cortical cells and 60-70% of the thalamic cells entered the burst-suppression state. They concluded that the most likely cause of this phenomenon is the disconnection of neural circuits related to the genesis of the EEG.

Although there are at least qualitative similarities in the effects different anesthetics have on the EEG, considerable differences also exist. The same EEG pattern with different drugs does not indicate the same clinical state (Clark & Rosner 1973). Guérit (1998) stated that differences can be seen particularly with low doses, while at higher doses the EEG commonly shows slowing and finally burst suppression. Gugino *et al*. (2001) reported similar findings stating that immediately before and at LOC frontal alpha predominance increased more with propofol than with sevoflurane. After LOC the differences disappeared. With respect to different drugs, the frontal beta activation at low doses can be seen with inhaled anesthetics, propofol, etomidate, barbiturates and benzodiazepines, but not with opioids (Seifert 1993, Black *et al*. 2000, Kishimoto *et al*. 1995). Opioids only slow down the EEG activity (Senhadji *et al*. 2002). Ketamine and nitrous oxide do not follow the common progression pattern (Black *et al*. 2000, Sleigh & Bernard 2004). Moreover, the burst suppression can be induced, for example, with propofol, fluranes and barbiturates, but not with opiates, ketamine or benzodiatzepines (Billard *et al*. 1997, Black *et al*. 2000, Senhadji *et al*. 2002). There are also differences in the appearance of burst waveforms with different anesthetics (Hartikainen *et al*. 1995, Akawi *et al*. 1996).

2.2.3 Event-related EEG changes and anesthesia

An important aspect in the assessment of the CNS functional suppression is to study the cortical reactivity to stimuli. Reactions to external stimuli may provide complementary information on neural structures. Moreover, the CNS is a dynamic system affected not only by drugs, but also by external stimuli. For example, noxious stimuli during surgery can modify EEG patterns and cause arousal reactions (see e.g. Kochs *et al*. 1994, Thornton & Sharpe 1998).

There are two types of categories of EEG responses which can be defined as responses to an external or internal stimulus (Pfurtscheller & Andrew 1999, Pfurtscheller & Lopes da Silva 1999). The first type comprises the event-related potentials (ERPs). ERPs are time and phase locked to an event, and can be considered transient changes in the postsynaptic activity of cortical neurons evoked by afferent activation. The second type of category includes both event-related desynchronization (ERD) and event-related synchronization (ERS), both of which, according to Pfurtscheller & Andrew (1999), reflect “changes in one or more parameters” in a system controlling oscillations in neural networks. ERS can be described as an occurrence of increased amplitude rhythmic activity (Pfurtscheller & Lopes da Silva 1999). ERD, on the other hand, reflects the activity of cells associated with amplitude decrease and less distinguishable EEG patterns. It should be noted, however, that synchronization in this concept does not refer to synchronized EEG activity in different channels, but rather to synchronized cell firing that may basically cause distinguishable patterns on a single EEG channel.

The category of ERPs include evoked potentials (EPs). EP waveforms are typically constructed by averaging tens or hundreds of EEG epochs triggered by a controlled stimulus. As EPs are very low in amplitude, lower than the spontaneous EEG, averaging is necessary to enhance the signal-to-noise ratio. EP waveforms consist of peaks, typically characterized by features such as amplitude, latency from stimulus and interpeak latencies (Black *et al*. 2000).

The EP waveform can provide information on the functional integrity of the sensory pathway from receptors to neural generators responsible for the evoked waveform (Stanski 2000). EPs can be used to identify neural structures and for the purpose of neurophysiological diagnostics (Stanski 2000). For example, latency describes the time for the encoded information to be transmitted in the sensory pathway (John & Prichep 2005). Abnormalities in latency or in amplitude may help to localize a functional defect in a pathway (Stanski 2000). Moreover, changes in waveforms may be applied in an indicator of anesthetic effect if the transmission velocities and latencies are considered to remain unchanged when a person is in a stable state (John & Prichep 2005).

Two of the most common types of EPs in anesthetic effect studies and in neuromonitoring are the auditory evoked potentials (AEPs) and somatosensory evoked potentials (SEPs). Interestingly, these responses represent the function of different neuronal pathways. AEPs are stimulated with repetitive clicks of 60-70 dB above the patient's click-hearing threshold to either ear (Black *et al*. 2000). Conventionally, AEPs are divided into three categories according to the latency times of the peaks in the EP waveform. The brainstem auditory evoked potentials (BAEP) occur within 10 ms after the stimulus, the middle-latency auditory evoked potential (MLAEP) appear with a latency of 10-100 ms, and the long-latency auditory evoked potentials (LLAEP) can be found up to 1000 ms from stimulus (van Gils *et al*. 2002). As pointed out by Drummond (2000), these components arise in a sequence from the brain stem, the auditory radiation, the auditory cortex, and the association areas. BAEP is relatively resistant to anesthetics, while MLAEP and LLAEP are sensitive. MLAEP peaks Pa and Nb show consistent and dose-dependent changes (Drummond 2000, van Gils *et al*. 2002). These peaks occur between 20 to 80 ms and reflect the activation of the temporal lobe and the primary auditory cortex (Thornton & Sharpe 1998). Characteristically, due to anesthetics the amplitudes of the peaks decrease and the latencies increase (Drummond 2000). It has been considered that changes in latency can be related to the hypnotic component, whereas amplitude is more associated with the analgesic component of anesthetic action (van Gils *et al*. 2002). LLAEPs are especially sensitive to anesthetics and surgical actions, claimed to be even too sensitive to be used in monitoring (Thornton & Sharpe 1998, van Gils *et al*. 2002). However, LLAEPs have been used to monitor the low-dose sedative effects of drugs (Yppärilä 2004).

SEPs are evoked with electrical spikes applied to a peripheral nerve, most commonly to the median or ulnar nerve. The peaks in the median nerve SEP waveform originate in a sequence from nucleus cuneatus, to median lemniscus, thalamus, primary somatosensory cortex, frontal cortex and association cortices (Thornton & Sharpe 1998). Analogically to AEPs, latencies generally increase and amplitudes decrease with deepening anesthesia (Black *et al*. 2000). However, amplitudes vary considerably from one patient to another (Thornton & Sharpe 1998). Rundshagen *et al*. (2000) reported that anesthetic effects were most apparent with components occurring at 35 ms and later after median nerve stimulus. Latencies were prolonged and amplitudes, except for N20/P25, were reduced. During the recovery from anesthesia, the effects were partly reversed right after anesthesia when the patient was able to name an object. The peak-to-peak amplitude of this N20/P25 has been found to increase during intense surgical stimulation (Rundshagen *et al*. 1995). It has been shown that, at the level of burst suppression with sevoflurane anesthesia, the P40 wave to tibial stimulation can be seen even without averaging due to a good signal-to-noise ratio (Rytky *et al*. 1999). This wave showed habituation to a repeated stimulus by an amplitude decrease. Later peaks were missing. In intraoperative monitoring, SEPs have been utilized during surgical procedures, involving the pathway at risk, such as in the correction of scoliosis (Black *et al*. 2000).

An ERD type of response is, for example, the disappearance of the occipital alpha rhythm in the awake state when the eyes are opened (Pfurtscheller & Andrew 1999). During anesthesia, sensory stimulation can elicit an arousal reaction of the ERD type, i.e. an increase of the fast-wave activity, a pattern correspondent with emergence from anesthesia (Kochs *et al*. 1994, Rundshagen *et al*. 2004). Alternatively, stimulation may evoke an ERS type of response: a shift towards low-frequency, high amplitude activity. This kind of phenomenon is typically related to deep anesthesia. With respect to arousal, this response has been called "reverse" or "paradoxical" arousal (Bimar & Bellville 1977, Kochs *et al*. 1994, Litscher & Schwarz 1999). Kochs *et al*. (1994) suggested that a type of response is related to the central nervous system depression in a dose-dependent manner: an ERD type of response is most prominent when low doses are applied, while ERS is more related with deep anesthesia.

Burst suppression patterns have similarities with ERS characteristics. Bursts can be evoked, for example, with a chain of visual, auditory, and somatosensory stimulation (Hartikainen 1996), as well as with vibration (Yli-Hankala *et al*. 1993). The onset of burst waveform is dependent on stimulus modality (Hartikainen 1996). It has been suggested that evoked bursts might be associated with different central pathways than those with SEPs, and that they could be used to monitor nerves that are not involved in the generation of a SEP (Hartikainen *et al.* 1996).

2.3 Control variables representing the CNS functional suppression

2.3.1 The rationale for using a control variable

Clinicians require tools to assess the effectiveness of a drug for an individual patient in relation to the objectives of medication (De Jonghe *et al*. 2000). Anesthesiologists or an automatic closed-loop control system use information for the purpose of steering the drug delivery. However, making an explicit and detailed characterization of these objectives is challenging. Anesthetic drugs modulate the physiological processes in the CNS in multiple ways (Kissin 1993). There is no generally accepted definition or "golden standard" for drug effect. The purpose of a control variable is to provide meaningful grounds and a quantitative scale in this framework for the development of an index. A control variable:

- steers the generation and selection of the appropriate signal features utilized by a mathematical model behind an index value;
- is a reference against which an index performance is evaluated;
- is the basis that determines the choice and the scope of modeling which is used to map EEG activity into a single variable.

The scientific validity and interpretation of an indicator value is a three-level problem:

- an indicator should be in a direct relation with observed EEG patterns (see e.g. Jäntti *et al.* 2002);
- the relation between the EEG patterns and the control variable selected ought to be understood;
- an indicator should present accurately the values of the control variable.

This implies that when the indicator is supposed to reflect the level of consciousness, for instance, the relation between consciousness and EEG patterns and the relation between EEG patterns and an index value should be clear. This particular relation, consciousness versus EEG, is still inadequately understood. One of the recent studies shedding light on this important relation has been published by John & Prichep (2005).

A control variable for a drug effect is analogous, for example, to a temperature scale. On the Celsius scale, two particular physical phenomena are selected as fixed points: the freezing point and boiling point of water. These fixed points anchor an observable temperature continuum meaningfully. The Celsius scale has an interval level of measurement, i.e. differences between any two amounts of the attribute equal the difference between measurements at these points. The Kelvin scale reflects similar temperature intervals as the Celsius scale, but also has a physically meaningful zero point, which enables making meaningful attribute/variable ratio statements (see e.g. Sheskin 2004). In our opinion, an ideal scale for CNS depression quantification would be continuous and quantified at the interval or the ratio level of measurement.

The candidate scale or control variable can reflect basically one of the three different aspects (Thornton & Jones 1993): the adequacy of anesthesia (see section 2.1), the dose of the anesthetic agent, or level of cognitive function. The dose expresses the amount of anesthetic agent given. It is also related to the concentration of an agent and to the concepts of pharmacokinetics and pharmacodynamics. Cognitive function can be studied by means of assessment of memory impairment or observation of loss and regain of consciousness (see e.g. Rampil 1998, John *et al.* 2001).

2.3.2 The continuum of anesthetic drug effect

The increasing concentration of a general anesthetic agent in the brain induces changes in the patient's physiological and cognitive state. An anesthetic effect is typically considered to be a continuum, a sequence, or a cascade, where certain states occur in a predictive order (Clark & Rosner 1973, Rosner & Clark 1973, Wansbrough & White 1993, Smith 1996, Pomfrett 1999, John & Prichep 2005). This consistent transition can be observed in cognitive functions in general, in EEG activity and in clinical signs. However, as indicated in section 2.1.2, there are exceptions in the progression pattern depending on the anesthetic used.

As noted by Smith *et al*. (1996), anesthetic depth is typically defined with a response-to-stimulus test. They distinguished three different factors in the assessment of drug effect: the "underlying anesthetic depth", "observed anesthetic depth" and "an anesthetic depth indicator". The "underlying anesthetic depth" is presumed to be a continuum, whereas the level of measurement of the observation, "observed anesthetic depth" (i.e. control measure or end-point), is only rank ordered. For example, a response can have three coarse categories: "response to weak stimulus", "response to strong but not to weak stimulus", or "no response" (Smith *et al*. 1996). Clinical end-points can even be dichotomous. Consciousness, for example, is considered to disappear in 10-20 ms (John & Prichep 2005). However, "anesthetic depth indicator" or an index can be based on EEG signal processing and, once again, considered to be finely graded (see sections 2.3.3-2.3.6). When using a relatively sparsely sampled rank-ordered control variable there seems to be a lack of continuity with the control variable both in time and in the level of measurement. Thus, no corresponding observations for the drug effect are available for the development of an interval/ratio level indicator. Unlike discrete clinical end-points, the continuous nature of both EEG and anesthetic concentrations may provide the means for the development of a continuous control variable. In fact, EEG has been used to describe the potency of medication with pharmacodynamic models.

It has been argued that the concepts depth of anesthesia or depth of hypnosis are obsolete notions, because anesthetics have widespread actions in CNS (Kissin 1993, Jäntti 2005). However, the common assumption of the continuum and the evident progression pattern of observable phenomena support the postulation that there still could be a quantitative measurement scale for the drug effect.

2.3.3 The continuum as manifested in clinical signs

Traditionally, clinical signs or end-points and physiological measures have been used as surrogate measures of the drug effect and as guidelines to adjust medication. These include somatic signs, such as the movement reaction to surgical stimulus, change in breathing pattern, grimacing, tearing, eye opening, and coughing. Hemodynamic signs include heart rate and blood pressure measures, such as hypertension or hypotension, and bradycardia or tachycardia (Thornton & Jones 1993, Drover *et al*. 2002, Senhadji *et al*. 2002, van Gils *et al*. 2002). Clinical end-points, such as loss of eyelash reflex, loss of pupillary light reflex, loss of counting and loss of obeying verbal commands (Mustola

2004), as well as signs of sedation, loss of consciousness, lack of awareness, explicit and implicit recall and EEG burst suppression pattern are related to cognitive function. These can be considered to represent hypnotic effect and to be related to the function of the cortex (Witte *et al*. 1999, Drummond 2000, Rosow & Manberg 2001, Mustola 2004).

Various end-points can occur independently. Thus, a monitoring system that is able to predict one end-point can be inefficient in predicting others (Drummond 2000). Moreover, due to multiple sites of drug action, all possible end-points are not part of the same one-dimensional continuum. However, it can be argued that different concepts of a continuum, and correspondingly, different control variables, can be utilized with different aspects of assessment. Reflex responses, for example, can be considered to form a continuum in the sense that the more intense the stimuli, the higher doses of an anesthetic are needed to prevent the reactions (Clark & Rosner 1973). Likewise, by increasing the dose, the amnesic effect is achieved first, then suppression of consciousness, and finally the immobility during surgical stimuli (John & Prichep 2005).

With respect to cognitive function, four sequential stages of anesthetic drug action can be identified (Thornton & Jones 1993, Heier & Steen 1996, Ghoneim 2000):

1. conscious awareness with explicit memory;
2. conscious awareness without explicit memory;
3. unconscious awareness without explicit but with implicit memory, and;
4. no awareness.

A similar conclusion was made by John & Prichep (2005), but they also suggested a more detailed description of suppression of awareness and linked certain oscillatory frequencies with certain states. In particular, perceptual processing was considered to be enabled by the synchronization of anatomically dispersed neural structures (John & Prichep 2005).

Somatic and hemodynamic reflex responses are controlled below the level of the cortex in CNS. Thus, they are not directly related to consciousness (Glass *et al*. 1997, Rampil 1998). For example, suppression of movement has been related to actions of anesthetics on the spinal cord, which is not well correlated with actions of higher brain centers with most non-volatile agents (Rosow & Manberg 2001). Cortical measures are poor predictors of autonomic or motor responses (van Gils *et al*. 2002), however, but they are more likely to be applicable in monitoring the hypnotic effect of anesthesia and the level of consciousness, memory or other cortex related neural functions (Rampil 1998, van Gils *et al*. 2002). Indeed, in the literature in recent years, the control measures used for anesthetic effect have turned from autonomic or somatic reflexes to the phenomena of cortical origin (Glass *et al*. 1997, Rosow & Manberg 2001, Jäntti 2005).

In the assessment of hypnosis, loss of counting and syringe dropping (where the patient has been instructed to hold a syringe for as long as possible) occur at a lower level than eyelash reflex. However, the LVC, loss of pupillary light reflex, and loss of the eyelash reflex represent an equal level when estimating the LOC during induction of anesthesia (Mustola 2004). The transition from consciousness to unconsciousness has been seen as the only “golden standard” of hypnotic effect along with the burst suppression pattern (van Gils *et al*. 2002). Burst suppression has been recommended to be used as an end-point for barbiturate coma therapy (Rampil 1998).

Table 1. The modified OAA/S scale as presented in Glass et al. (1997).

Response	Score
Responds readily to name spoken in normal tone	5 (Alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to noxious stimulus	0

2.3.4 Manual scoring systems

Clinical signs have been employed in manual scoring systems to grade the effects of the anesthetic and sedative drugs. These scaling systems can provide a rank-ordered multi-level control variable. At least 25 such measures that categorize the state of a patient by using signs such as consciousness, agitation, ventilator synchrony, pain, responsiveness, ocular appearance, facial expression, speech, anxiousness or tranquility and movement reaction have been proposed for evaluation of neurological state in ICU (Avramov & White 1995, Carrasco 2000, De Jonghe *et al*. 2000). One of the most commonly used scoring systems is the Observer's Assessment of Alertness/Sedation (OAA/S) scale, often presented in a modified form (Table 1). Levels 3-5 of this scale represent graded responses to verbal commands, and levels 0-2 are responses to tactile or noxious stimuli (Jensen *et al*. 2004), also indicating unconsciousness (Glass *et al*. 1997). However, there are a number of concerns related to these scales. In relation to the OAA/S score, Jensen *et al*. (2004) stated that the score can be assessed with intervals of 10 seconds at the shortest. Thus, the rating cannot be time-continuous. Stimuli can also lighten the sedation. Moreover, the OAA/S scale may deviate from the real hypnotic level. For example, although awake, patients may not respond to verbal or tactile stimuli due to certain drugs such as opioids, diseases such as Parkinson's, or just because of ignorance (Jensen *et al.* 2004). Especially the use of neuro muscular blocking agents makes the traditional signs and related scoring systems useless (Thornton & Sharpe 1998).

2.3.5 Anesthetic drug concentration

Changes in the EEG are causally connected with the infusion of a drug to plasma. Plasma concentration and the effect may not be linearly related (Olkkola 1999). The main target organ or the effect-site of general anesthetics is the brain, which is typically assumed to represent a different compartment from the plasma. The effect-site concentration as a function of time t can be described with a pharmacokinetic (PK) model, such as

$$\frac{dC_e(t)}{dt} = k_{e0}(C_p(t) - C_e(t)) \,, \tag{1}$$

where $C_e(t)$ and $C_p(t)$ are the time-dependent effect-site and plasma concentrations, respectively, and k_{e0} is a rate constant expressing the elimination of drug from the effect site (Shafer & Schwinn 2005).

Although each drug has its own characteristic effect, considerable similarities between drugs can be found, and further described by means of pharmacodynamics (Olkkola 1999, Senhadji *et al.* 2002). A pharmacodynamic (PD) model characterizes the relation between the effect-site concentration and the anesthetic effect. An example of an equation representing such a model is:

$$E(t) = E_0 + (E_{\max} - E_0)\frac{C_e(t)^\alpha}{C_e(t)^\alpha + EC_{50}{}^\alpha} + \varepsilon(t) \,. \tag{2}$$

Eq. (2) is called the Hill function. EEG effects are related to effect-site concentration via the effect variable E in eq. (2). For example, $E(t)$ can represent the value of a QEEG variable as a function of time. Such quantities are, for example, MPF, SEF95%, signal power, approximate entropy (ApEn) or BIS (Gregg *et al.* 1992, Gambus *et al.* 1995, Schnider *et al.* 1996, Bruhn *et al.* 2003). Variables $E_{\max}$ and E_0 are the maximal possible effect and effect without a drug, respectively. The exponent α is a shape parameter to be experimentally adjusted. EC_{50} is the steady-state effect compartment concentration that influences the effect halfway between $E_{\max}$ and E_0. Variable ε denotes the random error.

Eq. (2) suggests that effect-site concentration can be used as a time-continuous control variable. In accordance with eq. (1), EEG effect can be related to plasma concentration. However, using effect-site concentration or plasma concentration as a control variable is problematic. There is a wide variation in pharmacokinetic and pharmacodynamic responses between individuals (Levy 1986, Avramov & White 1995, Heier & Steen 1996, van Gils *et al.* 2002), and parameters in the models are typically adjusted for every individual. Unlike plasma concentration, the effect-site concentration is a theoretical notion that cannot be directly observed. Plasma concentration, however, can be recorded simultaneously with EEG (see e.g. Stanski 1992). The use of multiple drugs (Heier & Steen 1996) and the biphasic behavior of effect variables can cause difficulties in pharmacodynamic modeling (Billard *et al.* 1997).

Pharmacokinetic modeling can be helpful in targeting the appropriate plasma concentration or effect. For example, the so called target controlled infusion (TCI) scheme can help the anesthesiologist to automatically adjust the plasma concentration to the desired level (Glen 1998). Pharmacodynamic modeling has been applied, for example, in the semilinear canonical correlation method (SCC). This method has been used to develop a QEEG index that is optimally correlated with the effect-site concentration (see e.g. Gregg *et al.* 1992, Gambus *et al.* 1995, Schnider *et al.* 1996, Bruhn *et al.* 2002).

Levy (1986) distinguished two advantages in the utilization of “mental state or specific level of autonomic function” in the development of an indicator in contrast to using anesthetic concentration as a control variable. First, it helps to get rid of inter-individual variability in responses to an anesthetic agent. Secondly, transient conditions can be studied, for example during the induction of anesthesia when end-tidal and brain concentrations of an inhalation anesthetic are not in equilibrium. This argument of Levy (1986) can be extended to cover also plasma concentration with intravenous anesthetics.

2.3.6 Time as a control variable

As seen in eq. (1) and (2), QEEG and concentration are basically time-continuous measures. In non-steady state conditions where plasma concentration and drug effect are in a non-equilibrium state, time t can be understood as a control variable in pharmacokinetic and pharmacodynamic models. In the simplest form, drug effect E is a function of time. For midazolam, for example, recovery time after infusion is proportional to the dose (the rate of recovery is still constant) (Stanski 1992).

Time is a commonly used control variable. Billard *et al*. (1997) studied alfentanil, propofol and midazolam drug effects as indicated by SEF95%, delta power and BIS indices. Time courses were investigated to estimate the potency (EC_{50}), and the equilibration rate constant k_{e0} for each drug. Kuizenga *et al*. (2001) studied the time-course of the EEG amplitude in the 2-5 Hz band, 11-20 Hz band, and SEF95% and BIS during induction of anesthesia with thiopental, propofol, etomidate, midazolam or sevoflurane anesthesia. They described biphasic curves of amplitudes and SEF95% for all drugs but midazolam. Interestingly, correlation of the biphasic peak time and LOC was investigated. No relation was found, however. Naguib *et al*. (2003) used bolus injection of melatonin, thiopental or propofol and studied the time courses of EEG indicators including total power, MPF and SEF95%. Powers of delta, alpha and beta (>13 Hz) bands were studied in relation to total power, as was ApEn in relation to its baseline value. Only relative total power, relative SEF95% and relative ApEn showed consistent time-series due to bolus injection of these drugs. Mustola *et al*. (2005) studied the EEG effects of combined propofol and remifentanil anesthesia. During fixed rate infusion, BIS values, times to different end-points and cumulative dosage of propofol were collected at each end-point.

Time has also been used as a measure of clinical usefulness of commercial anesthesia monitors. Typically, it has been studied whether a QEEG guided anesthesia delivery can accelerate emergence from anesthesia compared to the delivery without monitoring. Drug consumption and index time-courses may also have been investigated. Such a procedure has been applied, for example, to PSI (Drover *et al*. 2002), Narcotrend index (Kreuer *et al*. 2003), Entropy Index (Vanluchene *et al*. 2004, Vakkuri *et al*. 2005) and BIS index (Yli-Hankala *et al*. 1999).

2.4 Monitoring systems

This section overviews monitoring systems and the control variables applied. The choice of describing mostly commercial monitors is based on the fact that they are the most widely validated both in scientific literature and in practice.

2.4.1 General aspects

The purpose of a typical monitoring system is to provide a reliable and reproducible univariate measure, an index that quantifies the functional suppression of CNS as indicated by a relevant control variable chosen (see e.g. Rampil 1998, Senhadji *et al.* 2002). Moreover, the independency of the measure from an anesthesia protocol is required (see e.g. Billard *et al.* 1997). Independency can be achieved by taking advantage of the observed similarities of drug effects.

When using a univariate index, a multidimensional information space is projected onto a single dimension. A multidimensional and characteristically complex EEG signal can be projected to a univariate index basically in an arbitrary manner (see e.g. Jäntti *et al.* 2002). This is done with a mathematical model that, compared to the real-world situation, makes simplifications and assumptions. Reduction of dimensions means that available information is utilized selectively, and thus some information will be lost. There is a possibility that a univariate presentation may not be sufficient enough to express the multifaceted state of a patient, however. This can lead to a loss of important clinical information and introduce a systematic or random measurement error (De Jonghe *et al.* 2000). Such a model can work well normally, but may behave misleadingly under unexpected situations or pathological conditions if not covered by modeling or controlled by internal validation in a monitor. Such deviating situations can be, for example, the presence of epileptiform activity, ischemia, hypothermia, mechanical damage or paradoxical arousal reactions (Guerit 1998, Kochs *et al.* 1994, Rundshagen *et al.* 2004, Rosow & Manberg 1998). It is to be noted that EEG patterns seen during anesthesia from a healthy subject can be similar to those of a subject with a pathological condition while awake (Senhadji *et al.* 2002). The combination of two or more agents, for example hypnotics and opiates, can also complicate the monitoring task, because pharmacological mechanisms may differ greatly (Stanski 1992, Sleigh & Bernard 2004) and EEG effects may not be cumulative (Senhadji *et al.* 2002). Other factors related to EEG activity are the subject's age (Schultz *et al.* 2004b), cerebral blood flow and cerebral metabolism in general (Stanski 2000).

Spontaneous EEG is not a deterministic signal, but rather stochastic. Future signal values cannot be anticipated exactly, but nevertheless some predictable statistical characteristics exist (Rampil 1998). EEG is not a strictly stationary signal, but more likely quasistationary when EEG is studied in short time frames, for instance, up to 10 seconds. Stationarity is challenged, for example, by artifacts, amplitude and frequency changes due to medication, burst suppression pattern and transient responses to stimuli. Moreover, EEG and its features seldom have a Gaussian probability distribution (Rampil 1998).

2.4.2 System components

Although there are great differences between different monitors in the features they use, the algorithms applied and the control variables selected, a general signal processing scheme as presented in Fig. 3 can be outlined (see e.g. Rampil 1998, Drover *et al*. 2002, Schultz *et al*. 2004). In the preprocessing phase, the signal is prepared for utilization. This phase may include artifact processing, filtering, segmentation, baseline identification and data normalization. Artifacts are common in EEG recordings and can hamper the analysis substantially. Artifacts arise from biological sources (eye movements and blinks, muscle activity (electromyogram; EMG), cardiac activity (electrocardiogram; ECG)), recording devices (saturation of amplifiers, movement of electrodes, power line interference), and from recording conditions (train-of-four stimulation, electro-surgical instruments, diathermy knife) (Rampil 1998, Senhadji *et al*. 2002). The feature generation phase produces the quantitative measures calculated from the preprocessed EEG signal. Typical features include spectral or complexity measures (discussed in the next section) and burst suppression quantifications. In some situations, such as with the Fourier transform or with bispectrum calculation, numerous features are generated. Possibly only a subset of these is useful from the control variable point of view, and thus further utilized. The choice of the feature subset is carried out in the feature selection phase. In the implication phase, selected features are embedded in a mathematical model, such as a regression model, neural network, fuzzy rulebase, classification algorithm, etc. to provide a univariate index. An index value may also be further normalized. The last component in the scheme presents internal validation. A monitor can, for example, refrain from presenting an output value due to uncertainty in the decision made.

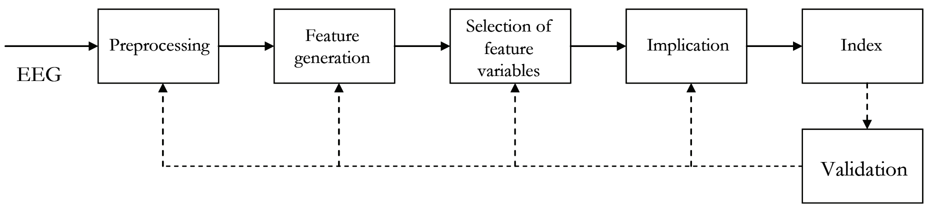

Fig. 3. Schematic diagram of signal flow in a typical monitoring system.

2.4.3 Some common EEG features

In the following, some commonly used EEG features are listed:

Signal power. The most frequently investigated characteristic in anesthetic EEG is the signal power as a function of frequency

$$P(\omega) = |X(\omega)|^2 . \tag{3}$$

This is called a power spectrum. The $X(\omega)$ is the Fourier transform of a recorded signal and ω is the frequency. The equation allows calculating the signal power in a selected frequency range.

SEF and MPF. Spectral edge frequency (SEF) is a frequency in the power spectrum that indicates the upper limit below which some percentual amount of power lies (Rampil *et al*. 1980, Rampil 1998). For example, SEF95% is the frequency below which 95% of power in the spectrum resides. Median power frequency (MPF) is the same as SEF50%.

Bispectrum is mathematically defined as (Sigl & Chamoun 1994, Muthuswamy *et al*. 1999, Thakor & Tong 2004)

$$B(\omega_1, \omega_2) = X(\omega_1) X(\omega_2) X^*(\omega_1 + \omega_2) . \tag{4}$$

The notation (*) indicates the complex conjugate. The bispectrum can be used to suppress Gaussian noise of unknown spectral origin, to reconstruct phase and magnitude response and to characterize quadratic nonlinearities in time series, and also to quantify phase coupling between two different frequency components (Proakis *et al*. 1992, Muthuswamy *et al*. 1999).

Bicoherence is a derivative of the bispectrum and defined as (Sigl & Chamoun 1994, Muthuswamy *et al*. 1999)

$$bic(\omega_1, \omega_2) = \frac{|B(\omega_1, \omega_2)|}{\sqrt{P(\omega_1) P(\omega_2) P(\omega_1 + \omega_2)}} . \tag{5}$$

The amplitude of the bispectrum is influenced both by the amplitude of the signal and the phase coupling, whereas bicoherence is a measure only of quadratic phase coupling (Sigl & Chamoun 1994).

Entropy is a large-scale macroscopic measure of a system state that is generated by properties and interactions of microscopic particles (Sleigh *et al*. 2004). When applied to signals, entropy can be considered to reflect irregularity, complexity, uncertainty or the unpredictability of a signal (Sleigh *et al*. 2004, Viertiö-Oja *et al*. 2004). The use of entropy in anesthesia monitoring is based on the characteristic EEG change from complex multi-frequency activity in an awake state to simpler and more regular low-frequency activity with deepening anesthesia (Sleigh *et al*. 2004). In contrast to frequency or amplitude of the signal, entropy is independent of an absolute measurement scale (Viertiö-Oja *et al*. 2004). Three commonly used entropy descriptors are the Shannon entropy, spectral entropy and the approximate entropy (ApEn). ApEn is described in publication (IV) of this dissertation.

Shannon entropy is defined as (see e.g. Sleigh *et al*. 2004)

$$H_{Shannon} = -\sum_{i=1}^{N} p_i \ln(p_i) , \tag{6}$$

where p is the probability of the system being in the discrete state i of N possible states.

Spectral entropy is calculated correspondingly, but utilizing an intermediate power spectrum such as (see e.g. Sleigh *et al*. 2004)

$$H_{Spectral} = -\frac{1}{\ln(N)}\sum_{i=1}^{N} p_i \ln(p_i)\,, \tag{7}$$

where p is now the power of the frequency bin i. It should be noted that $\sum p_i = 1$ in eq. (6) and in (7). Variable N is the number of bins in the frequency range studied. The term $1/\ln(N)$ is used to normalize the scale into the range [0, 1]. Correspondingly, spectral entropy gets the value zero when all the spectral energy is found in a single bin and the value one when the frequency distribution is completely flat. The equation allows limiting the analysis to a specific passband.

Burst suppression ratio (BSR). BSR is a fraction of the time covered by suppression periods in a relatively long time window. BSR calculation requires the segmentation of the signal into suppression periods and bursts (Rampil 1998, Särkelä *et al*. 2002).

2.4.4 Bispectral Index

The bispectral Index (BIS; Aspect Medical Systems, Natick, MA, USA) is the most common monitor of the hypnotic effect of anesthesia. According to the manufacturer, BIS has been considered in more than 2000 publications. One indication of its popularity is that BIS has been used as a control variable or as a reference in comparisons between different methods. However, only a few reports give any information on the proprietary algorithm itself. The BIS index is a univariate descriptor varying from 100 to 0, representing the range from complete awareness to flat EEG, correspondingly. Kelley (2003) discussed the practical aspects of BIS application. Values above 70 may indicate "adequate level of sedation", but also greater probability of consciousness and recall. Free or cued recall was stated to be lost with the index values 70-75. Values below 60 indicate the probability of the response to verbal command to be low (Rosow & Manberg 2001). An adequate hypnosis level is stated to be between 40 and 60 (Kelley 2003).

The index values have no explicit definition, however. BIS has been created statistically by utilizing measures such as the OAA/S scale, loss of recall, or EEG effects with different drug concentrations (Liu *et al*. 1996, Billard *et al*. 1997, Glass *et al*. 1997, Flaishon *et al*. 1997, Rampil 1998). The work of Glass *et al*. (1997) presented logistic regression curves for the probability of loss of consciousness (stated by OAA/S level 0-2) and the probability of recall as a function of BIS values. BIS is considered to be a measure of a state of the brain, not of a drug concentration (Rosow & Manberg 2001). Early versions of BIS were correlated with responses to surgical stimulation (Sigl & Chamoun 1994). It was shown that BIS correlates with movement to skin incision (Kearse *et al*. 1994a, Vernon *et al*. 1995), or with blood pressure responses to endotracheal intubation (Kearse *et al.* 1994b).

Rampil (1998) has provided the most thorough presentation published of the BIS algorithm. EEG is first filtered to exclude high and low-frequency artifacts and then partitioned into 2 second epochs. Next, artifact detection is carried out by cross-correlating the EEG epochs with a template of an ECG waveform. When detected, ECG is removed and the missing data are replaced by interpolation. Eye blinks are searched for by matching (cross-correlation) a template waveform with data. Epochs containing blinks are rejected. Furthermore, data is tested for wandering baseline, originating from low-frequency electrode noise, and filtered if required. As a final step of artifact removal, variance of an epoch of raw EEG is checked. The epoch is marked "noisy" if the deviation is considerable in relation to the mean variance of the previous epochs.

For the surviving epochs, a number of parameters are calculated. Fast Fourier Transform (FFT) and bispectrum is calculated, using Blackman window weighted epochs. Estimates are smoothed, using a running average over the previous minute. Then, signal features are further processed. The so called *BetaRatio* parameter is defined by the logarithm of the power relation of two bands, 30-47 Hz and 11-20 Hz, as $\log(P_{30\text{-}47}/P_{11\text{-}20})$. The *SynchFastSlow* parameter is correspondingly defined as the logarithm of the ratio of the sum of the bispectrum peaks between 0.5-47 Hz and the sum of the bispectrum in 40-47 Hz: $\log(B_{0.5\text{-}47}/B_{40\text{-}47})$. Furthermore, two parameters to determine the degree of the burst suppression are derived. *BSR* is the burst suppression ratio, calculated from a time window at least 60 seconds long. Suppression with *BSR* algorithm is detected if EEG voltage is within ±5 μV for more than half a second. Another burst suppression parameter, *QUAZI*, detects suppressions from a signal with a wandering baseline, thus incorporating spectral information from below 1 Hz.

The BIS index is a combination of these parameters (Glass *et al*. 1997, Rampil 1998). As the EEG characteristics change, *BetaRatio* has the most weight when EEG has the characteristics of light sedation. *SynchFastSlow* predominates in surgical levels, but also at the initial excitement phase. *BSR* and *QUAZI* are weighted in deep anesthesia. The presentation of Glass *et al*. (1997) suggests that a combination of terms is achieved with multiple regression.

It has been reported that biphasic behavior in the initial excitement phase during anesthetic induction has been taken care of in the BIS algorithm (Glass *et al*. 1997, Kuizenga *et al*. 2001). However, Vakkuri *et al*. (2004) reported occurrence of flat periods, in contrast to monotonical progression of the index value, at the transition point from continuous EEG to burst suppression EEG. They speculated that at this point, the algorithm changes the feature set it uses.

2.4.5 Response and state entropy

The *M-ENTROPY* module (GE Healthcare Finland, Helsinki, Finland) calculates the spectral entropy of EEG. Sleigh *et al*. (2004) suggested that spectral entropy is an indicator of changes in cortical neuronal interactions, or more specifically, it is "a logarithmic measure of the rate of synaptic interaction." Three descriptors are calculated in the algorithm of the M-ENTROPY module: the so called state entropy (SE), response entropy (RE) and BSR. The BSR algorithm applied is explained in Särkelä *et al*. (2002). The difference between SE and RE is mainly in frequency ranges: with SE 0.8-32 Hz and with RE 0.8-47 Hz. SE basically utilizes the EEG range, while RE also employs forehead

EMG activity (Viertiö-Oja *et al*. 2004). An increased frontal EMG activity can be related to recovery from anesthesia, to nociception or inadequate anesthesia. Facial muscles are characteristically resistant to neuromuscular blocking agents and, although suppressed, they preserve their ability to respond at clinically practical amounts (Vakkuri *et al*. 2004). EMG activation before emergence can be seen as a difference between RE and SE (Vakkuri *et al*. 2004). RE-SE difference may also uncover nociception and the need for analgesic medication (Vanluchene *et al*. 2004, Vakkuri *et al*. 2005). RE and SE are *ad hoc* methods, not explicitly associated with any control variable, but rather they describe signal characteristics as such. However, in a study by Maksimow *et al*. (2005), it was retrospectively shown that spectral entropy in the 0.8-32 Hz band correlates with individual cortical and global regional cerebral blood flow values.

The algorithm has been described by Viertiö-Oja *et al*. (2004). EEG is recorded with a frontal-temporal montage of three electrodes and sampling frequency of 400 Hz. In the preprocessing phase, the EEG signal is divided into 256 sample (0.64 sec) epochs for artifact detection. Electrocautery artifacts are detected by the hardware in the 200 kHz - 1000 kHz range and in the recorded EEG signal in the 66-86 Hz range. Corresponding epochs are rejected if artifacts are found. Furthermore, ECG and pacer waveforms are subtracted from the EEG signal. The choice to accept or reject an epoch is made with a rule-based classifier. This choice is based on the assessment of stationarity of EEG, detected in a time window of 24 epochs, and on the basis of a set of signal features (unspecified) that are calculated for each epoch.

Viertiö-Oja *et al*. (2004) call the entropy method used time-frequency balanced spectral entropy, meaning that entropy measures are calculated from time windows the lengths of which are dependent on frequency. The shortest time window applied is 768 samples (1.94 sec) and used for the frequencies between 32 Hz and 47 Hz. The longest window is 24064 samples (60.16 sec), and used for frequencies below 2 Hz. Short time-windows enable rapid response to increased high-frequency activity. The RE index utilizes data in these windows, covering the range 0.8-47 Hz. RE can be written as eq. (7). SE is the spectral entropy in the 0.8-32 Hz but scaled in such a way that these two descriptors are equal when no EMG activity is present on 32-47 Hz band, i.e. by the term c that can be written as

$$c = \frac{\ln(N_{0.8-32})}{\ln(N_{0.8-47})} . \tag{8}$$

N is now the number of frequency bins in the frequency range marked with the subscript. The calculated entropy values are then scaled from the 0-1 range to a 0-100 scale. This is done with an *ad hoc* non-linear spline function to enhance the entropy values between 0.5 and 1, which are stated to be relatively more interesting than those values that indicate very deep anesthesia (Viertiö-Oja *et al*. 2004). The final RE descriptor values vary between 100 to 0 and 91 to 0 for RE and SE respectively.

2.4.6 Narcotrend

The Narcotrend Index (MonitorTechnik, Bad Bramstedt, Germany) is a pattern recognition based indicator. The EEG is classified into fourteen categories on the basis of the visual categorization of typical EEG patterns observable at different states of hypnosis: A, $B_{0\text{-}2}$, $C_{0\text{-}2}$, $D_{0\text{-}2}$, $E_{0\text{-}1}$ and $F_{0\text{-}1}$. The idea originates from sleep studies (Schultz *et al*. 2004). Category A represents the awake state. Its recognition utilizes the typical artifacts, such as blinking, eye movements and muscle activity (Schultz *et al*. 2003). Category F indicates burst suppression. There is also stage "E_2" representing transition from continuous activity to burst suppression (Schultz *et al*. 2004). Late version of the algorithm (4.0) shows the anesthetic effects with a dimensionless numeric scale from 100 to 0. It is notable that Narcotrend incorporates age-related changes in EEG activity (Schultz *et al*. 2003, Schultz *et al*. 2004). Narcotrend has been shown to correlate (rank-order level of correlation) with the OAA/S scale, with the target propofol concentration (Bauerle *et al*. 2004), and with simulated effect-site concentration (Schultz *et al*. 2004a). Moreover, a monophasic trend has been demonstrated during anesthetic induction (Schultz *et al*. 2004a).

The algorithm is described in the articles of Schultz *et al*. (2003), Kreuer *et al*. (2003) and Schultz *et al*. (2004). EEG is acquired with a sampling frequency of 128 Hz, 12 bit amplitude resolution, and 0.5-45 Hz passband. An additional notch filtering for 50 Hz or 60 Hz is applied. The bipolar electrode montage C_3-P_3 is used. The electrode impedances are automatically tested at certain time intervals. EEG is analyzed in 20 second epochs every five seconds. No published documentation of artifact detection algorithms is available. However, EMG artifacts, eye movements and electrocautery are reported to be handled (Kreuer *et al*. 2003). Narcotrend rejects more EEG epochs than BIS does (Ellerkmann *et al*. 2004). Several parameters are calculated from the EEG epoch. Schultz *et al*. (2003) bring up FFT based spectral parameters, such as portions of delta, theta, alpha and beta power, MPF, SEF95% and spectral entropy. Time-domain features are also implemented such as amplitude measure and autoregressive model parameters. There are unspecified algorithms for detecting suppression periods, pattern recognition and classification. However, it has been stated that the classification function assigns probabilities for a sample epoch to match with the trained categories (Schultz *et al*. 2003). Classified epochs undergo an additional validity check to confirm that the sample EEG is sufficiently similar to a trained category and to avoid misclassification and uncertainty. For this purpose, the so called background parameters are computed from EEG and they help to identify untypical waveforms of anesthesia EEG, such as epileptic patterns or K-complexes. Finally, the classification result is a weighted average of the current and preceding classifications. The weighting is dependent on the calculated background parameters.

2.4.7 Patient State Index

The *Patient State Index* (PSI) is a descriptor produced by the PSA 4000 monitor (Hospira, Inc. Lake Forest, Il, USA). Similarly to BIS, response entropy, and Narcotrend, PSI is expressed by a number ranging from 100 to 0. PSI represents the probability that a patient is awake (John & Prichep 2005). PSI combines a set of processed EEG features. The goal has been to maximize the electrophysiological variance of the process of loss and return of consciousness, to minimize redundancy and to maximize sensitivity to hypnotic state changes (John *et al*. 2001, Drover *et al*. 2002, Prichep *et al*. 2004). PSI is based on the measurements of EEG in different states in a standard clinical protocol (Drover *et al*. 2002). In the work of Prichep *et al*. (2004), such states were pre-operative state (a day before surgery), baseline recorded outside the OR, induction when a patient can count numbers, loss of consciousness (after cessation of counting, loss of eyelash reflex and loss of response to painful stimuli), uneventful period during surgery, state prior to unexpected somatic events, emergence approximately 10 minutes and 5 minutes prior to eye opening, and return of consciousness (eye opening).

An overview of the PSI algorithm and PSA 4000 monitor is provided in Drover *et al*. (2002). EEG is recorded from FP_1, FPz, Cz, and Pz sites, and referenced to linked ears. The sampling frequency is 2500 Hz. The signal is passband filtered to 0.5-70 Hz, but downsampled to 250 Hz. The purpose of the original oversampling is to minimize the electromagnetic interference in the OR. Electrode impedances are continuously monitored. In the preprocessing phase, the artifact handling includes notch filtering, checking the non-linearity of the measured signal, EOG artifacts, signal magnitude, stationarity, and electrocautery artifacts. Preprocessing also contains burst suppression detection.

The artifact-free epochs of 1.25 seconds are then transformed into the frequency domain. A number of features from the spectrum are calculated, such as power in typical EEG bands, total power (0.5-50 Hz), power gradients, and covariances among regions and bispectral features (Drover *et al*. 2002, Prichep *et al*. 2004). A subset of features that show reversible and invariant changes during deepening hypnosis and LOC are selected, such as (Drover *et al*. 2002):

- absolute power gradient between frontopolar and vertex regions in the gamma band;
- absolute power changes between midline frontal and central regions in the beta and between the midline frontal and parietal regions in the alpha band;
- total spectral power in the frontopolar region;
- mean frequency of the total spectrum in the midline frontal region;
- absolute power in delta at the vertex;
- posterior relative power in the slow delta band.

The applied features are transformed into the metric of probability of the deviation from a specific reference state. This is achieved by first expressing the features as standard deviation units from the mean value of the distribution (z-score) and then extracting the probabilities from the thus estimated Gaussian distribution (Drover *et al*. 2002, John & Prichep 2005). The PSI utilizes a method called neurometrics that considers age-related changes in the power spectrum in the applied distributions. The PSI value is calculated with a proprietary discriminant algorithm.

2.4.8 Other approaches

In technical literature there are many sophisticated signal processing and modeling techniques presented that automatically assess anesthetic effects. However, their relevance from the neurophysiological point of view or from the point of view of control variables is seldom discussed. An extensive literature review of methods is provided by Zhang *et al*. (2002). Other helpful reviews are provided by Senhadji *et al*. (2002) and van Gils *et al*. (2002).

Soft computing based approaches can also be useful in anesthesia monitoring. They can handle noisy data and may be able to make reasonable implications in the presence of uncertainty. In their review, Zhang *et al*. (2002) bring up artificial neural networks, fuzzy logic models and combined neuro-fuzzy techniques. The advantage of neural networks is their ability to be trained to a specific task and to handle non-linear and multidimensional data. The use of fuzzy logic has the advantage that anesthetic state variables can be described in terms of natural language. Moreover, the expert knowledge of an anesthesiologist can be modeled as fuzzy rules to estimate and control the anesthesia management. Neuro-fuzzy methods can be useful for creating and refining a fuzzy inference system when expert knowledge is not directly available. Soft computing methods are typically used as “black box” methods, i.e. the aim is not to obtain a precise system model or understand the problem, it is rather to achieve practical usefulness.

Muthuswamy and Roy (1999), for example, presented the design of a monitor that utilizes fuzzy logic and neural networks to predict a movement response to tail clamping (noxious stimulus) of a canine under isoflurane/N_2O anesthesia. The input signals used were two channels of EEG, MAC values, heart rate and systolic/diastolic blood pressure. Both channels of EEG were modeled as a summation of two autoregressive based linear systems, one driven by Gaussian white noise (autocorrelation), other by non-Gaussian white noise (third order cumulants). Signal features were processed first by four parallel multilayer feed-forward neural networks, whose outputs were further integrated by a fuzzy logic system. Three fuzzy membership functions were defined on a depth of anesthesia scale from zero to one: awake state, intermediate and sleep state. This continuous scale was based on discrete state definitions: awake state was defined as the presence of movement reaction to tail clamping, sleep state was defined as no movement and no significant hemodynamic response, and intermediate state was defined as no movement but a significant hemodynamic and/or respiratory response.

Zhang and Roy (2001) presented a method that used the Lempel-Ziv complexity measure C(n), ApEn and spectral entropy of EEG as inputs to an adaptive-network-based fuzzy inference system (ANFIS). With this system, the depth of anesthesia measure, i.e. a number between 0 and 1, was calculated with a regression type of summation of the weighted input parameters. Weighting coefficients, however, were dependent on a fuzzy if-then rule set. The scale was defined by two extremes: awake state if movement, eye blinking, shivering, etc. occurred as a response to tail clamping of a dog; and asleep state if there was no response. The fuzzy system created the artificial continuum in between these end-points. The authors state that the assessment of anesthetic effect and adjusting the dosage is based on heuristic decisions of anesthesiologists.

ERPs, and especially AEPs, have been used in the assessment of hypnotic drug effect (see e.g. Thornton & Jones 1993, Kochs *et al*. 1999, Zhang *et al*. 2001, van Gils *et al*. 2002, Yppärilä *et al*. 2002, 2004a, 2004b, Haenggi *et al*. 2004). For example, Yppärilä *et al*. (2004b) studied the discontinuation of propofol sedation in auditory N100 and mismatch negativity waveforms. Most clearly, amplitude of N100 differed between sedation levels. Huang *et al*. (1999) used wavelet transformation coefficients of MLAEPs with an artificial neural network to predict the depth of anesthesia for an automated closed-loop anesthetic drug delivery system. Analysis of MLAEPs is also adapted in a commercial system; the A-Line ARX Index (AAI) (Danmeter, Odense, Denmark). It is a monitor based on estimating the AEP waveform from 15 sweeps using an ARX model (Litvan *et al*. 2002). The unitless index values 0-99 are constructed from calculating the sum of absolute amplitude differences in the latency range 20-80 ms.

2.5 Summary

The key observations from the literature review are:

- EEG has been proven to be an essential tool for assessing the functional suppression of the CNS during anesthesia.
- Both the spontaneous cortical activity and EEG reactivity to external stimuli can offer information on drug effects on CNS.
- Recent progress has turned the attention to control measures related to CNS activity, especially to cortical function.
- Topographic aspects and synchronization of brain areas may offer complementary information in addition to spectral and entropy features.
- Many anesthetics have similarities in their effects on EEG, such as frequency decrease and amplitude increase due to deepening anesthesia, which could be beneficial in designing of an anesthetic agent independent monitor.
- The connection between EEG patterns and consciousness is still inadequately understood.
- A major challenge in anesthesia monitoring has been the lack of definition of the drug effect or depth of anesthesia. This problem is reflected in the literature and in commercial monitors that adopt dissimilar interpretations and control measures for the drug effect.
- The existence of an anesthetic continuum is often presumed by grading the anesthetic effect, although observed clinical end-points are nominal or rank-order level measurements, both of which are assessed relatively infrequently.
- The problem of defining a control variable for the degree of CNS depression appears to be one of seeking EEG signal characteristics that:
  - show consistent change in the population studied, when the level of hypnosis is changed;
  - provide unambiguous physiological interpretation for a given value on the scale (i.e monotonic progression with the control variable, in contrast to biphasic behavior);
  - can act as fixed points where a scale can be anchored.

3 Research contributions

This chapter discusses the methodological contributions and neurophysiological findings described in detail in the original publications I-V. Study I utilizes the idea of quantifying functional synchronization between different cortical areas and the changes to it due to anesthesia. Study II describes four distinct event-related EEG phenomena seen in deep propofol anesthesia that may be useful in neuromonitoring. Studies III-V focus on the EEG effects during the transition period from an awake state to unconsciousness. These three studies are based on the same patient material. Study III describes in detail the transition by means of the progression of the EEG frequency contents and, by introducing a novel normalized time-scale *r*, suggests a relationship between the frequency progression and the occurrence of LVC. Study IV investigates the applicability of the approximate entropy (ApEn) descriptor in revealing this transition period monotonically. In study V, the *r* scale is further used as a continuous control variable for anesthetic effect. Moreover, it is shown that the definition of the *r* scale enables forecasting the time of LVC.

3.1 Anesthetic effects on functional synchronization of cortical areas

Study I investigated the effects of propofol anesthesia on functional interactions between spatially distinct cortical sites. The key problem was to study, whether there are systematic changes in phase coupling between EEG signals in different channels in association with changes in a patient's physiological state during induction and recovery of propofol anesthesia.

EEG was recorded with Neuroscan SynAmp (NeuroScan Inc., Serling, VA, USA) from nasion, Fp1', Fp2' (about 1 cm down from the corresponding sites in the 10/20 system), Fz, F7, F8, Cz, Pz, Oz and left mastoid. A reference electrode was placed on the right mastoid. The sampling rate was 10 kHz and was off-line downsampled to 250 Hz. The original bandwidth of 0.05 Hz - 2 kHz was reduced correspondingly. The analysis of the recordings of 23 of the participating patients (aged 28-52 years) focused on the induction and recovery phases of propofol anesthesia, administered with a Target

Controlled Infusion (TCI) pump. In the end, the recordings from 21 induction and 18 recovery periods were approved for analysis.

Artifacts were handled by rejecting contaminated recording periods. Furthermore, analysis was limited to the induction periods after the ocular artifacts had disappeared, and recovery periods before the appearance of the relatively rapid increase of EMG artifacts. Burst suppression periods were discarded. Then, a filter bank was applied to the EEG signal to provide <1 Hz range and the consecutive passbands 1-4 Hz, 4-8 Hz, and so on, up to 16 Hz. The time series of the instantaneous phases was derived for all EEG channels and passbands by means of the complex valued analytic signal and the Hilbert transform. A phase synchronization index, ranging from zero to one, was constructed by the statistical comparisons of two phase time-series at a time in a sliding time window of 10-20 seconds (Tass *et al*. 1998, Rosenblum *et al*. 2001). It should be noted that synchronization is not equivalent to correlation or coherence (Rosenblum *et al*. 2001). Coherence, for instance, does not necessarily indicate the existence of synchronization. Rosenblum *et al*. (2001) demonstrated experimentally that the tremor activity of the flexor muscle (EMG signal) can be more specifically localized to the sensimotor and premotor cortices (magnetoencephalographic signals) by means of synchronization than by coherence analysis.

The existence of systematic changes in functional interactions was evaluated by fitting the first order polynomials (straight lines) to the phase synchronization index time series. The choice of the first order polynomial was based on the assumption that such a simple linear model can reveal consistent trend changes by its slope parameter. As the intention was to investigate whether phase synchronization changes exist or not, the non-parametric Sign Test statistic was used. The hypothesis that the median of the distribution of slope values is zero was tested for all pairs of channels and for all passbands, and was rejected when $p \leq 0.05$.

Statistically significant changes that were specific to the scalp location and the passband were observed. In the 0.05-1 Hz band, the phase synchronization generally decreased during induction and increased during emergence from anesthesia. The indications of desynchronization in this band at a deep sedative level could be observed even visually with an unprocessed signal. On the alpha band, the changes in synchronization were opposite, and on the other bands, the directions of changes, whether existing, were diverse and dependent on the scalp location. The observed changes in the phase coupling of the measured signals reflect the effect of anesthesia on CNS, especially on the cortex. It is likely that the changes arise from modifications of functional interaction of distinct neural sites. The passband specific changes in phase coupling suggest that different neural mechanisms are affected differently by the anesthetic agent.

Study I introduces the use of the phase synchronization index in the context of drug effect monitoring. Synchronization and topographic aspects of EEG can provide useful information of anesthetic drug effect. Phase synchronization index is a measure that processes the EEG phenomena directly into an intuitively interpretable index. It may also contain information complementary to the typical amplitude, spectral or coherence features.

3.2 Evoked EEG patterns during burst suppression

In study II, the reactivity of the CNS, especially the cerebral cortex, was investigated at the burst suppression level. The question addressed was whether noxious somatosensory stimuli can elicit EEG responses that could be useful in assessing the cortical information processing and thus potentially applicable in neuromonitoring.

Eight adult patients, 35-53 years of age, participated the study. Propofol was administered manually to maintain EEG burst suppression, guided by online EEG visualization. EEG was recorded with a NeuroScan Synamp amplifier (Neuroscan, El Paso, TX, USA) with a sampling rate of 5000 Hz and the bandwidth of 0.05-1000 Hz. Ag/AgCl electrodes were placed on Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, CPz, CP3, CP4, T3, T4, T5, T6, Pz, P3, P4, O1 and O2 according to the international 10/20 system. There were also electrodes on the nose, spinal C7, on the left and right zygoma and left and right mastoids. The reference electrode for this unipolar montage was placed on FCz. Constant current pulses of 100 mA and 0.1 ms duration were given manually to stimulate the medianus nerve in the wrist with surface electrodes. The stimulator was a Medelec ST-10 (Medelec, Old Woking, UK).

The recorded multichannel EEG was lowpass filtered to smooth data for illustrations. No further artifact rejection was applied, however. The SEP responses elicited by single electrical stimuli, and evoked potential waveforms formed by the averaging paradigm were analyzed. In addition to amplitude time-series, latency time from stimulus and the duration of patterns were determined. The study was primarily descriptive, i.e. measurements were compared with findings reported in the literature.

As a result, four separate EEG phenomena which are signs of the information processing capability of CNS in deep anesthesia could be elicited. These included (1) the somatosensory responses N20 and P22 with peaks between 22 and 27 ms. The N20 and P22 originate from the primary somatosensory cortex, and are not likely related to pain but rather to other modalities of perception. (2) A negative sharp wave with a peak latency from 180 ms to 1 s appeared next with the maximum amplitude in the central and occipital areas. This wave is probably related to information processing of noxious stimulation. Thereafter, (3) bursts were initialized from 200 ms on; they had the form of a slow wave with superimposed 10 Hz oscillation. The amplitude was greatest at parietal and occipital midline leads with ear reference. The burst is considered to be a phenomenon of the ERS type and to reflect arousal mechanism. (4) Finally, 13-15 Hz spindle activity, approximately 1 s in duration, was evoked with a latency of 1-7 s after stimulus. The spindle is similar to those seen during physiological sleep, where they are related to blocking of information flow from thalamus to cortex. These different EEG phenomena occurred partly independenly and may reflect the activation of at least partly different cerebral mechanisms. Spindle activity, for example, could be seen in complete suppression where bursts had ceased, or the negative sharp wave could be elicited on a spontaneous burst wave or already before the burst suppression period.

In the light of monitoring, study II introduces four evoked responses in propofol anesthesia that can offer complementary information on the CNS reactivity and functional suppression. In particular, the relation between the negative sharp wave and the state of analgesia is an interesting prospect. In contrast, current monitors typically utilize only the BSR at the level of burst suppression. As seen in this study, external stimulus can also affect this ratio. However, more studies and more controlled anesthetic regimen are needed to study the relation of these responses with particular pain modalities and at different levels of hypnosis. In general, the paper points out the importance and potentiality of studying the multitude of neurophysiological phenomena as a foundation of CNS monitoring.

3.3 Relation between EEG spectral progression and LVC

The purpose of study III was to investigate whether two cortical function related measures, EEG and loss of consciousness (as defined by LVC), are mutually related during the period of induction of anesthesia. Initially 20 patients participated in the study, but 16 patients, 20-59 years of age, were accepted for further analysis on the basis of successful recording procedure in the OR. EEG was recorded with an Embla polygraphic recorder (Medcare, Reykjavik, Iceland) with a sampling rate of 200 Hz and bandwidth 0.5-90 Hz. EEG montages Fz referenced to the average of mastoid signals (EEG), and Fp1 referenced to a cheekbone (electro-oculography (EOG) signal) were formed off-line and used in the analysis. The recordings focused on the induction period of anesthesia with a fixed rate propofol infusion (30 mg/kg/h). During the induction, patients were asked loudly “squeeze my hand” every 15 seconds to determine the time for the LVC end-point. BIS values were recorded with a Datex-Ohmeda S/5 anesthesia monitor (GE Healthcare, Espoo, Finland). It should be noted that studies III-V are based on the same patient material. For the purposes of comparison, the effect-site propofol concentrations were also simulated for the patients with TIVAtrainer software (GuttaBV, Aerdenhout, The Netherlands).

In the preprocessing phase, the recorded signals were first lowpass filtered (34 Hz cut-off frequency), then visually inspected in order to remove interfering artifacts manually. Finally, using the separate EOG channel and independent component analysis (ICA), the EOG artifacts were removed from the EEG signal. The independent component representing purified EEG was used in further analysis. ICA has been effectively applied in a similar task (Vigário 1997, Tong *et al*. 2001).

Preprocessed EEG was filtered with a finite impulse response (FIR) filter bank into subbands 0.5-4 Hz, 4-8 Hz, and so on, up to 28 Hz. The 0.5-28 Hz band was also studied. Passband signals were investigated by finding the magnitude trend with an in-place growing FIR-median hybrid filter (IPG-FMH) (Fig. 4; Wichman *et al.* 1990). The choice of IPG-FMH was based on its robust nature and capability to effectively remove transient waveforms. It can also react rapidly to sharp changes in the trend. Formed time-series were further smoothened with Savitzky-Golay filtering (Press *et al*. 1992, Orfanidis 1996). The idea of Savitzky-Golay filtering is to approximate the signal by means of fitting a polynomial function in a moving window. Filtering is performed by replacing a signal sample with the corresponding polynomial fit. The study was based on the visual inspection of the processed amplitude trends of the passbands and their time-related properties during the induction of anesthesia. For an approach like this a filter bank might be a more appropriate tool than a spectrogram, because it may enable the visualization of the data more readily. With a filter bank the data of a large population can be drawn onto one two-dimensional graph and are thus easily comparable.

The relation between the EEG frequency progression and the moment of the LVC was studied by means of a novel normalized time scale r

$$r = \frac{t}{t_{LVC}}. \tag{9}$$

In eq. (9), the elapsed time of induction t is normalized in such a way that the beginning of the anesthetic infusion is marked as zero and the moment of the LVC (t_{LVC}) is marked as one. If a relation between EEG frequency progression and the LVC exists, the trends of the population studied should show a grouping on this normalized time scale. If these two factors were independent, no consistent pattern should occur.

Signal envelope time-series showed passband specific biphasic progression patterns. A biphasic peak in trend time-series shifted systematically from high frequencies towards delta frequencies in time. Dissimilar behaviour in the narrow 4 Hz passbands suggest that the typical beta range is too wide to express this shift accurately. Moreover, by presenting the individual amplitude envelope time-series of the study population as a function of r, consistent grouping of the waveforms could be observed, irrespective of interindividual variability in response to the dosage. In contrast, no such clustering occurred as a function of the conventional time scale t, or when BIS or simulated effect-site concentration were used as control variables. EEG changes could be seen after r=0.35 at the earliest.

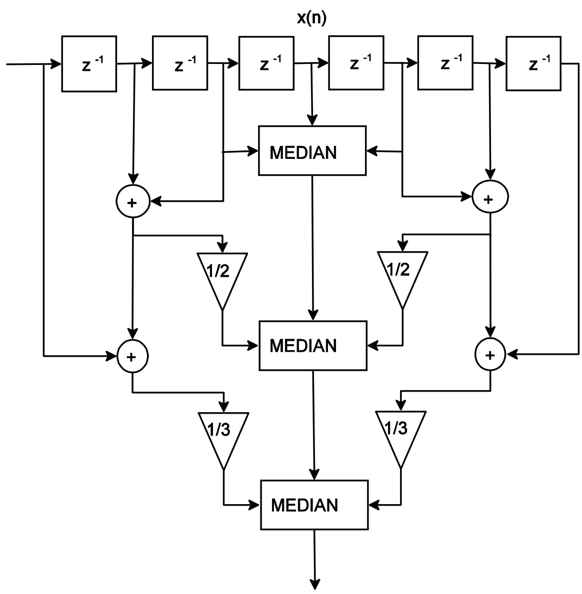

Fig. 4. A 3-level IPG-FMH filter.

The results favor the hypothesis that the pattern of spectral progression is related to the instant of the LVC. From the monitoring point of view, the significance of the finding is that the *r* scale provides a common basis in the study population for grading the hypnotic effect of propofol between the awake state and the LVC. However, further studies are needed to verify its potential as a continuous and observation based control variable. Later in study V, the *r* values are predicted by mathematical models, potentially applicable in a monitoring system.

3.4 ApEn during induction of anesthesia

ApEn is an *ad hoc* method proposed for quantifying the anesthetic drug effects on EEG. Paper IV focuses on the performance of ApEn during the induction of anesthesia, where the signal is relatively nonstationary. The objective of the study was to test whether the ApEn index of an EEG signal and the underlying depth of hypnosis are related in a monotonic manner during anesthetic induction with propofol. In contrast, biphasic progression is typical, for example, for spectral features in a corresponding situation. In the study, the parameters of the ApEn algorithm are optimized for this task, and the dependency of ApEn on underlying amplitude variations is investigated.

Section 3.3 above describes the EEG recordings and anesthesia protocol. Fourteen patients were approved for the analysis on the basis of successful recordings and annotations. Analysis was carried out for two partly overlapping periods: from the start of propofol induction to LVC or to the ending of induction. EEG was preprocessed likewise by lowpass filtering, manual artifact rejection and ICA. In this study, EOG related independent components were set to zero and by using inverse mapping, the original physical units (µV) were reconstructed. ApEn was calculated with data in sliding time windows of 5, 10 or 15 seconds. The effect of the filter level parameter *r* in the algorithm was also examined with different ratios of the standard deviation (SD) of the signal (the notation *r* as used in the original ApEn publication by Pincus (1991) is not equal to the *r* scale variable in eq. (9)). SD was calculated by using data in a time window or by using data covering the whole period of analysis. Moreover, white noise signal with linearly increasing amplitude was simulated in order to study the dependency of ApEn on underlying amplitude.

It was assumed that both the underlying depth of anesthesia and the elapsed induction time progresses monotonically during the induction period. This assumption allowed studying the progression of the indicator in relation to the continuous control variable of the anesthetic effect (i.e. time) instead of sparsely assessed clinical end-points. The monotonicity was quantified by the prediction probability (P_K) statistic (Smith *et al.* 1996). The P_K statistic is a commonly used method in evaluations of anesthetic depth indicators, because it suits ordinal data and allows performance comparisons independently of the scales used.

It was found that the performance of ApEn is highly influenced by the choice of the algorithm parameter values. ApEn time-series had very different shapes, from the biphasic form to monotonic, depending on the parameters. The shapes were typically sigmoidal, a plateau in the beginning, and the changes occurring in a relative short time-period. The median P_K values of the individual curves ranged from 0.527 to 0.886. Those setups that were non-adaptive, i.e. where the parameter *r* values were fixed for a patient, were greatly influenced by the variation in signal amplitude. It should be noted that this fixed *r* approach has been used in some studies, as reviewed in IV. This can be an advantage, however, from the P_K statistic point of view. Adaptive *r* setups, in contrast, were not affected by amplitude trend. Thus, with the adaptive approach, ApEn can be interpreted more reliably as a measure of regularity. In general, ApEn time-series show a nonlinear response to anesthetic induction. In respect to the P_K statistic, the study demonstrates that care must be taken when interpreting P_K values and in the choice of the data sample. For example, when data do not behave strictly monotonically, a small subset of data can yield larger P_K values than the data as a whole. This effect should also be taken into account when comparing the performance of indices with different control variables. Taking time as a control variable, as has been done in this study, provides much finer sampling than clinical end-points. Denser sampling may reveal deflections from monotonicity better than sparse sampling.

The study highlights the importance of studying the progression of an indicator during the induction of anesthesia with propofol, where EEG shows nonstationary characteristics. With the proper choice of ApEn algorithm parameters, biphasic response can be avoided.

3.5 Forecasting the LVC on the basis of EEG spectral progression

In study III (summarized in section 3.3 above), the theoretical and neurophysiological basis was introduced for a continuous and observation based control variable *r*. The purpose of study V is to further validate the association between the EEG spectral features and the *r* scale. A mathematical model is proposed and a trained model is applied in predicting the unknown *r* values. Furthermore, on the basis of the definition of the *r* scale, a trained model is applied in forecasting the time of the upcoming LVC end-points of individual patients using the data from the induction of anesthesia.

The same EEG recordings, electrode montage and anesthesia protocol were used, as described in section 3.3. Sixteen recordings were selected for analysis. In the signal preprocessing phase, no manual assessment of artifacts was performed. Unlike in studies III and IV, EOG artifacts were removed by means of the adaptive Least Mean Square (LMS) filter, because methods suitable for on-line monitoring were preferred. The filter took advantage of a separate EOG signal. No manual artifact markings were made. The filtered EEG was divided into consecutive 4 Hz subbands with the filter bank and the signal envelope was constructed with the IPG-FMH and Savitzky-Golay filtering, similarly to study III. The amplitude trend time-series of different passbands served as the first order polynomial input data to multiple linear regression (MLR) models. The second order data was also constructed. The model parameters were estimated with the least squares method. The MLR type was chosen in order to find the simplest possible model construction. The range of modeling was limited to $r \in [0.4, 1]$, the range where propofol showed clear changes in the EEG.

The performance of the MLR was assessed by comparing n predictions $\hat{r}$ of the trained model with the corresponding known values of r at the time sample i by calculating the mean square error (MSE) value and the R^2 statistic (see e.g. Bruhn *et al.* 2002)

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(r_i - \hat{r}_i)^2}{\sum_{i=1}^{n}(r_i - \bar{r})^2}. \tag{10}$$

Cross-validated results were also derived by training the models with the data of all patients except one, which was used for testing. This procedure was repeated for all subjects. The predictions with the testing data were used for performance evaluation. Furthermore, a subset of available features was selected to optimize the embedding dimension and the performance of the models by using the MSE as an optimization criterion and by using an exhaustive search or sequential forward floating selection algorithm (Pudil *et al.* 1994).

According to eq. (9), the time of the LVC can be anticipated when the induction time t and the value of r are known. In practice, the predictions $\hat{r}$ were used. The error in forecasting was measured and compared with a reference method, i.e. by using the median value of the measured LVC times in the training population as a predictor.

The analysis covered the induction period from the point where changes in EEG began to be seen to the point of the LVC. The performance of the models that were trained and tested with data of an individual yielded the R^2 statistic value 0.983. By pooling the data of the training population and by using the cross-validation procedure, R^2 value was 0.775. The difference between these two numbers was greatly dependent on the signal preprocessing techniques applied (data normalization). The progression of the predicted r values was monotonic, approximately linear as a function of time and as a function of the trained values of r. In forecasting, the median error was 10-13 seconds (at the LVC) indicating that the error was smaller than the 15-seconds assessment interval. In comparison, forecasting the t_{LVC} only by using the median value of the training population gave the median error of 26 seconds.

The results support the notion that an r value can be explicitly predicted, given a set of spectral features in the range studied. The progression of the predicted r values was monotonic in contrast to biphasic. Moreover, a small prediction error suggests that there is practically a unique set of feature values for each r value in the range studied. The paper introduces a novel concept for forecasting a future event during the induction of anesthesia. It is notable that the methods presented can be applied in on-line signal processing. The developed r scale and the possibility to forecast may be helpful in grading the state of a patient, in assessing whether hypnosis (or sedation) is going to be too deep, or whether unconsciousness is likely to occur soon. They may both also help to prepare beforehand for intervening when unconsciousness is anticipated.

4 Discussion

4.1 Potentially applicable EEG phenomena

With respect to the first research problem of this dissertation, neurophysiological phenomena reflected in EEG signal were studied from the perspective of monitoring the functional suppression of CNS due to anesthetic drug effect. The original communications cover basically the whole continuum of propofol effect from full awareness of a patient to long lasting EEG suppression, as illustrated in Fig 1. In the transition phase from wakefulness and drowsiness to unconsciousness, an initial increase in EEG beta activity following the shift to delta frequencies was investigated. The signal in this period is considerably non-stationary and can induce biphasic behaviour in some EEG indicators. Although this initial activation phenomenon has been generally known, study III presented this shift in greater detail than before and showed its relation to the LVC end-point. The utilization of advanced signal processing methods as presented, especially the use of a filter bank, was the key to revealing this progression. These initial EEG phenomena were studied and utilized in studies III-V.

Study I investigated the period approximately from the point of unconsciousness to the beginning of the burst suppression. This is the first publication utilizing the phase synchronization measure to study drug effects. Changes in phase synchronization, assumed to originate from changes in functional interaction between cortical sites, were found to be dependent both on spatial location and on the frequency band. It is likely that the results reflect drug effects in different neural mechanisms.

Study II investigated the EEG during burst suppression level. At this level, only the ratio between bursts and suppressions is typically detected with monitors. This study presented four separate noxious stimulus elicited EEG phenomena: N20/P22 SEP waveforms, a pain-related negative sharp wave occurring between 180 ms and 1 s after stimulus, bursts and spindles. These phenomena reflect reactivity and activation of different neural mechanisms related to cortical function, and can thus provide more in-depth information on the state of the cortex.

4.2 The development of a continuous control variable

The second research question in this dissertation deals with a valid control variable for the assessment of the functional suppression of the CNS. A proposition for a continuous and observation based control variable is provided. The key factor in the development of such a control variable has been time, more specifically elapsed time of anesthetic induction. Time as a control variable requires an assumption of the physiological system being under constant transition. This requirement is considered to be met by using data recorded during anesthetic induction or during recovery. In study I, the time-series of the phase synchronization index was investigated. An analogy was drawn between the elapsed time during induction or recovery and changes in a patient's physiological state. However, time as a control variable was not discussed any further. In study IV, a similar analogy was explicitly proposed. With this idea, it was possible to study the monotonicity of the ApEn indicator time-series in relation to anesthetic effect in much finer steps than the typical clinical end-points would allow. In study III, the analogy was confirmed by simulating the effect site concentration time-series with PK/PD modeling and by measuring the BIS index.

Utilization of time as a control variable led to the development of the *r* scale. Time provided the continuum needed. The beginning of the induction and the LVC were used as fixed points to anchor this continuum meaningfully. Empirical support for this theoretical definition came up by utilizing EEG recordings. In study III it was shown that EEG patterns clustered on the *r* scale. No such clustering occurred on other continuous scales or control variables used: as a function of induction time, BIS or effect site concentration. The relation between EEG patterns and the *r* scale was further verified in study V. The changing characteristic of EEG patterns in these periods favors the notion that an anesthetic continuum can exist. By means of EEG this continuum was able to be *observed* in finer steps than by using the clinical end-points.

4.3 Quantitative measures of functional suppression of cortex

The third research problem in this dissertation concerned the scientific and methodological validity of a univariate index in quantifying the CNS depression. In this perspective the most significant contribution is the derived *r* index, an indicator predicting the instant values of the *r* scale as presented in study V. The *r* index has some useful properties:

- the underlying *r* scale values for an individual can be determined with a mathematical model that has been trained with pooled data of a study population;
- the definition of the *r* scale along with a trained mathematical model can be applied to anticipate the forecoming instant of the LVC during induction of anesthesia with propofol;
- moreover, the selected signal processing methods and ready trained model can be implemented in an on-line processing environment.

Additionally, two other univariate descriptors were applied in this dissertation, namely the phase synchronization index (I) and ApEn (IV). These two are *ad hoc* methods, i.e. they quantify the feature set as such and do not explicitly predict a value of a certain control variable. However, changes in phase synchronization are related to changes in functional relations between brain areas, and thus, an intuitive physiological explanation can be found. ApEn is based on information theory and its interpretation from the physiological point of view is more abstract. ApEn measures regularity or repetitiveness of patterns in a signal.

The fulfillment of the requirement of an indicator to progress monotonically during the induction of anesthesia was considered with ApEn and the r index. With ApEn, monotonic behavior was confirmed by the P_K statistic. Monotonicity of the r index was not explicitly tested but this requirement is fulfilled by the definition of the r scale.

4.4 Scientific and technological significance

On the one hand, the development of technology in this field of research is inextricably related to neurophysiology and anesthesiology. This dissertation introduces or provides a refinement of descriptions of neurophysiological phenomena, such as

- changes in phase synchronization between different EEG channels due to anesthesia;
- painful stimulus evoked responses during the burst suppression;
- the consistent progression of the EEG frequency patterns during the induction of anesthesia and their relation to LVC.

On the other hand, to reveal these phenomena, appropriate signal processing methods were required. The results of this dissertation benefit most directly the field of anesthesiology.

From the technological point of view, this dissertation:

- introduces a continuous and observation based control variable (r scale);
- suggests means to predict the r values using EEG data;
- describes the basis for forecasting the instant of the LVC;
- introduces the phase synchronization index as an indicator of drug effect;
- evaluates and optimizes the ApEn descriptor performance with non-stationary induction of anesthesia signal;
- sheds light on the problematics of designing an observation based monitor.

The original communications are published in peer-reviewed international scientific journals. Three of these in clinically oriented journals and two in a technically oriented journal. By the time of writing (March 2006), study (I) has been cited in four articles, of which three are review papers. Study (II) has also been cited in four papers.

4.5 Limitations and future work

The starting point in this research has been to carry out experiments in controlled situations, with a limited number of subjects, with exclusion criteria explained, and with the narrow scope of anesthetic regimens. Thus, the original articles present the results basically at a preliminary level. Studies I and III-V consider EEG changes during induction and/or recovery periods. To verify practical usefulness of the techniques, prolonged or steady-state periods in anesthesia protocol should also be investigated. In studies I and II, the depth of anesthesia or the state of CNS depression where EEG was analyzed was not well controlled. In future work, it could be beneficial to study EEG activity also in relation to other clinical end-points, especially those related to cortical function.

Multichannel EEG was analyzed in studies I and II, but not in III-V. In these three studies, only one montage, Fz referenced to average mastoids, was used. Thus, the montage was not explicitly optimized. In the literature, however, the importance of frontal cortex as a site of drug effect has been clearly reported (discussed in section 2.2.2). EEG waveforms are dependent on cortical site. Thus, another choice of electrode montage could lead to different results. This could provide more insights into the phenomenona studied. EEG in the patient group of studies III-V was acquired with two separate Embla recorders, because the first one broke. However, a possible effect of this incident has been to increase inter-patient differences and variability in results.

Preprocessing the signal is necessary, for example, for dealing with artifacts. In study I, light levels of sedation where ocular or blinking artifacts occurred were not analyzed. These artifacts were taken care of in studies III-V, but study V was the only one that used a technique that is applicable in on-line monitoring. The artifact processing by means of ICA or LMS both worked sufficiently in respective studies, but their performance was not explicitly compared. Study V also showed that signal amplitude normalization as a preprocessing phase is crucial. Interpatient variance in amplitude affected the results considerably. Further investigation is needed into the development of normalization techniques applicable for on-line processing.

In study I, the changes of the phase synchronization index were investigated by using the first order polynomial model fitted to the index time-series. Statistically significant deviation from zero in the slope parameters, however, does not guarantee practical usefulness. It is suggested that changes in absolute index values be studied in future work. Another area that needs further investigation is index values in relation to other control variables than time. The results showed that phase synchronization is affected by an anesthetic drug. The neurophysiological origin of this change could be further verified by comparing the phase synchronization with coherence analysis and the power spectrum, for example.

Identification of neurophysiological origin could be carried out also with the ApEn (IV). ApEn has been successfully used as a quantitative EEG descriptor, but there are no studies investigating its relation to the underlying EEG phenomena. Study III focused only on its relation to amplitude changes. ApEn describes the regularity characteristics that may be at least partly related to frequency contents of a signal. With respect to the r scale in studies III and V, the EEG changes could be seen after r=0.35 at the earliest. Due to this limitation, the *r* scale cannot be considered to be a truly interval or ratio level scale at this point of development. This restriction should be taken into consideration in future research. It is possible that r=0.35 could be used as a fixed point. To verify this, predictions of *r* should be investigated during steady state situations. Moreover, the *r* scale was defined and studied up to the point of LVC and no further.

The EEG phenomena presented in study II were not utilized further in developing a univariate index in this dissertation; this might be an area for future work. More studies with controlled anesthesia regimen are needed to reveal the range of functional suppression of CNS where these different phenomena occur, and to gain more understanding of their origin.

Finally, to gain clinical acceptance, the phase synchronization index, *r* scale and LVC forecasting should be evaluated with variable clinical settings, such as with variant infusion rates, different anesthetic drugs and with a more extensive study population.

5 Summary and conclusions

In this dissertation EEG phenomena that can be utilized in monitoring during anesthesia were explored. These potential phenomena include the phase synchronization alterations between cortical areas that might provide insight into changes of functional bindings due to drug effects. The spectral progression pattern during the induction of the anesthesia period was shown to be very consistent and have a relation to the moment of occurrence of LVC. This phenomenon was utilized in the development of a continuous EEG based control variable, the *r* scale. Noxious stimuli evoked EEG patterns at burst suppression level were described. These patterns showed partly independent behavior, and thus present anesthetic effects on different neural mechanisms. The presented spontaneous and evoked EEG phenomena provide complementary information about the CNS functional suppression.

Secondly, QEEG indicators and control variables for drug effect were studied. As a main result, the novel *r* scale was proposed for a control variable of sedative levels. The *r* scale has some advantageous properties from the methodological and neurophysiological point of view:

- it is based on cortical function and observable neurophysiological phenomena;
- it is continuous;
- it has an intuitive explanation as a phase of induction between the two fixed points;
- although not experimentally tested, its practical usefulness is not basically restricted only to the state transition period (induction of anesthesia) by definition.

The *r* values could also have been explicitly predicted by means of a trained mathematical model, utilizing EEG frequency characteristics.

In general, a mathematically derived quantitative index for anesthetic drug effect should have a sound relationship with observations and with a selected control variable. This approach affects the whole process of index design, as well as preciseness, validity and interpretation of the gained information about a patient's physiological state, and therefore, the reliability of the adjustment of medication.

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ISBN 951-42-8174-8 (Paperback)
ISBN 951-42-8175-6 (PDF)
ISSN 0355-3213 (Print)
ISSN 1796-2226 (Online)