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*Jukka Kortelainen*

# EEG-BASED DEPTH OF ANESTHESIA MEASUREMENT

## *SEPARATING THE EFFECTS OF PROPOFOL AND REMIFENTANIL*

*UNIVERSITY OF OULU,*
*FACULTY OF TECHNOLOGY,*
*DEPARTMENT OF COMPUTER SCIENCE AND ENGINEERING;*
*INFOTECH OULU*

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# EEG-BASED DEPTH OF ANESTHESIA MEASUREMENT

Separating the effects of propofol and remifentanil

Academic dissertation to be presented with the assent of the Faculty of Technology of the University of Oulu for public defence in OP-sali (Auditorium L10), Linnanmaa, on 26 August 2011, at 12 noon

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***Abstract***

Within the last few decades, electroencephalogram (EEG) has become a widely used tool for the automatic assessment of depth of anesthesia. The EEG-based depth of anesthesia measurement has been associated with several advantages, such as a decreased incidence of intraoperative awareness and recall, faster recovery, and reduced consumption of anesthetics. However, the measurement is challenged by simultaneous administration of different types of anesthetics, which is the common practice in the operating rooms today. Especially, the assessment of depth of anesthesia induced by supplementing the primary anesthetic drug, i.e. the hypnotic agent, with an opioid has been raised as one of the major problems in the field.

In this thesis, the EEG-based depth of anesthesia measurement during multidrug infusion with propofol (hypnotic agent) and remifentanil (opioid) is addressed. The problem is approached by first giving a quantitative description for the EEG changes occurring during propofol infusion. Two different methods, both utilizing the spectral properties of EEG, for this are presented. Next, the effects of remifentanil on the clinical signs and EEG changes during propofol infusion are investigated by applying the first one of the presented methods. Coadministration of opioid is shown to significantly modify the mutual relations of the EEG changes and the clinical signs of the patient. Furthermore, remifentanil is found to significantly affect the EEG itself, more specifically, the power spectrum and derived quantitative parameters during propofol infusion. This effect is strongly dependent on the level of anesthesia. Finally, by utilizing the results on the effects of remifentanil, a technology is developed for the assessment of depth of propofol-remifentanil anesthesia. The technology is based on improving the determination of the anesthetic state of the patient by EEG-based separation of the effects of propofol and remifentanil.

The thesis provides a framework for the depth of anesthesia measurement during multidrug administration with propofol and remifentanil. Due to the similar mechanisms of action, the results are likely to be generalizable to other hypnotic-opioid drug combinations. The study thus offers potential for the development of more advanced systems for automatic monitoring of depth of anesthesia.

*Keywords:* hypnotic, monitoring, opioid, pattern recognition, signal processing

**Kortelainen, Jukka, EEG-pohjainen anestesian syvyyden mittaus. Propofolin ja remifentaniilin vaikutusten erottelu**
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### *Tiivistelmä*

Viime vuosikymmeninä elektroenkefalogrammista (EEG) on tullut suosittu apuväline anestesian syvyyden automaattisessa seurannassa. EEG-pohjaisella anestesian syvyyden mittauksella on saavutettu useita hyötyjä: sillä on pystytty esimerkiksi vähentämään leikkauksen aikaista hereillä oloa, pienentämään anesteettien kulutusta sekä nopeuttamaan anestesiasta palautumista. Mittaus on kuitenkin haasteellista yhdistelmäanestesiassa, jossa useampaa erityyppistä anesteettia käytetään samanaikaisesti. Erityisesti nykyisin yleisesti käytössä oleva tapa täydentää pääasiallista anesteettia eli hypnoottia opioidilla on nostettu yhdeksi merkittävimmistä haasteista automaattisessa anestesian syvyyden mittauksessa.

Väitöskirja käsittelee EEG-pohjaista anestesian syvyyden mittausta käytettäessä propofolin (hypnootti) ja remifentaniilin (opioidi) yhdistelmää. Ongelmaa lähestytään antamalla aluksi kvantitatiivinen kuvaus propofoli-induktion aikana ilmeneville EEG-muutoksille. Tähän tarkoitukseen esitetään kaksi menetelmää, joista molemmat hyödyntävät EEG:n taajuussisältöä. Seuraavaksi remifentaniilin vaikutusta potilaan kliinisiin merkkeihin sekä EEG-muutoksiin propofoli-infuusion aikana tutkitaan soveltamalla ensimmäistä esitetyistä menetelmistä. Opioidin osoitetaan vaikuttavan merkittävästi EEG-muutosten ja kliinisten merkkien väliseen yhteyteen. Lisäksi remifentaniilin todetaan vaikuttavan merkittävästi myös propofoli-infuusion aikana ilmeneviin EEG-muutoksiin. Vaikutus heijastuu signaalin tehotiheysspektriin sekä siitä johdettuihin kvantitatiivisiin parametreihin ja on vahvasti riippuvainen anestesian syvyydestä. Lopuksi, hyödyntämällä tuloksia remifentaniilin vaikutuksista, esitetään teknologia propofoli-remifentanilli-yhdistelmäanestesian syvyyden mittaukseen. Teknologia perustuu propofolin ja remifentaniilin vaikutusten EEG-pohjaiseen erotteluun ja tätä hyödyntäen potilaan anestesian syvyyden tarkempaan määrittämiseen.

Väitöskirja tarjoaa tarvittavan tutkimustiedon sekä teknologian propofoli-remifentanilli-yhdistelmäanestesian syvyyden mittaukseen. Samankaltaisten vaikutusmekanismien vuoksi tulokset on mahdollista yleistää myös muille hypnootti-opioidi-lääkeyhdistelmille. Tutkimus avaa näin uusia mahdollisuuksia kehittää edistyneempiä anestesian syvyyttä automaattisesti seuraavia järjestelmiä.

*Asiasanat:* hahmontunnistus, hypnootti, monitorointi, opioidi, signaalinkäsittely

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Jukka Kortelainen
Oulu, 2011

# Abbreviations

| | |
|---|---|
| AP | *Action potential* |
| AEP | *Auditory evoked potential* |
| AU | *Arbitrary units* |
| BIS | *Bispectral Index* |
| BSP | *Burst suppression pattern* |
| BSR | *Burst suppression ratio* |
| CNS | *Central nervous system* |
| EEG | *Electroencephalogram* |
| EMG | *Electromyogram* |
| EP | *Evoked potential* |
| EOG | *Electro-oculogram* |
| FPP | *Frequency progression pattern* |
| GABA | *Gamma-aminobutyric acid* |
| GRNN | *Generalized regression neural network* |
| IV | *Intravenous* |
| LC | *Loss of counting* |
| LRT | *Loss of reaction to tetanic stimulation* |
| LVC | *Loss of obeying verbal command* |
| MAC | *Minimum alveolar concentration* |
| MPF | *Median power frequency* |
| NMDA | *N-methyl-D-aspartate* |
| NMBA | *Neuromuscular blocking agent* |
| OAA/S | *Observer's Assessment of Alertness/Sedation* |
| PSD | *Power spectral density* |
| PSP | *Postsynaptic potential* |
| RDP | *Relative delta power* |
| RE | *Response entropy* |
| SE | *State entropy* |
| SEF95% | *Spectral edge frequency 95%* |
| SpEn | *Spectral entropy* |

# List of original articles

This thesis is based on the following five publications, which are referred to in the text by their Roman numerals (I–V):

I Kortelainen J, Koskinen M, Mustola S & Seppänen T (2007) EEG frequency progression during induction of anesthesia: from start of infusion to onset of burst suppression pattern. Proceedings of the 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Lyon, France: 1570–1573.

II Kortelainen J, Koskinen M, Mustola S & Seppänen T (2008) Remifentanil modifies the relation of electroencephalographic spectral changes and clinical endpoints in propofol anesthesia. Anesthesiology 109: 198–205.

III Kortelainen J, Koskinen M, Mustola S & Seppänen T (2009) Effects of remifentanil on the spectrum and quantitative parameters of electroencephalogram in propofol anesthesia. Anesthesiology 111: 574–583.

IV Kortelainen J, Väyrynen E & Seppänen T (2011) Depth of anesthesia during multidrug infusion: separating the effects of propofol and remifentanil using the spectral features of EEG. IEEE Transactions on Biomedical Engineering 58: 1216–1223.

V Kortelainen J, Väyrynen E & Seppänen T (2011) Isomap approach to EEG-based assessment of neurophysiological changes during anesthesia. IEEE Transactions on Neural Systems and Rehabilitation Engineering 19: 113–120.

# Contents

# 1 Introduction

## 1.1 Background

The invention of general anesthesia in the 19th century undoubtedly represents a quantum leap in the history of medicine. Before this, surgery had remained a treatment of last resort largely because of the unwillingness of the patients to undergo an operation. The operations themselves, when performed, were done in a hurry to minimize the agony of the patient but compromising the quality of the procedure. The unawareness and unresponsiveness provided by anesthetics fundamentally changed this arrangement. It is therefore justifiable to say that general anesthesia has made the transition to modern surgery possible.

While the exact definition of general anesthesia varies to some extent, it is mostly agreed that this drug-induced reversible condition comprises of multiple behavioral states originating from different neural mechanisms. The states are generally associated with different anesthetic components, most commonly either hypnosis or analgesia. Hypnosis represents the state of consciousness, whereas analgesia relates to management of pain. High quality anesthesia requires a careful balance of these components. In today's clinical practice, this is usually attained by supplementing a hypnotic drug with an opioid, a centrally acting analgesic drug.

Ever since the invention of general anesthesia, the measurement of its depth has provided a challenge for the clinicians. While too deep anesthesia leads to numerous complications, such as hemodynamic instability and prolonged recovery, too light anesthesia has catastrophic consequences from the patient's point of view as well. The classic approach to assess the anesthetic state has been to observe the patient's clinical signs (e.g. a response to verbal command or reaction to a painful stimulation). Later, the estimation of drug concentration in the exhaled gas and in the blood using mathematical models has provided an alternative way to approximate the effect of anesthetic drugs.

Already in the early 20th century, electroencephalogram (EEG), the measure of the electrical activity of the brain, was shown to react to the administration of anesthetic drugs (Berger 1931, 1933). The findings spawned a whole branch of research investigating the relation of EEG changes and depth of anesthesia. The advantage of this

approach is that, unlike the above-presented methods, it is a direct measurement from the main effect-site of anesthetics, the brain. However, it was not before the late 1990s that the technological development made the automatic assessment of depth of anesthesia possible. The first commercial monitor, Bispectral Index (BIS), for this purpose was introduced in 1996 by Aspect Medical Systems. Soon after the introduction of BIS, several other commercial indices were launched. The EEG-based depth of anesthesia measurement has been associated with a decreased incidence of intraoperative awareness and recall (Ekman *et al.* 2004, Myles *et al.* 2004), faster recovery (Gan *et al.* 1997, Yli-Hankala *et al.* 1999, Johansen & Sebel 2000, Drover *et al.* 2002, Vakkuri *et al.* 2005), and reduced postoperative vomiting (Nelskylä *et al.* 2001). In addition, the monitoring reduces the consumption of anesthetics (Yli-Hankala *et al.* 1999, Guignard *et al.* 2001, Kreuer *et al.* 2003a, Vakkuri *et al.* 2005, Aimé *et al.* 2006).

The EEG-based depth of anesthesia measurement has faced, however, some significant challenges. One of these is that many different classes of anesthetic drugs, all of which affect EEG, are used nowadays simultaneously in the operating rooms. Especially, the assessment of depth of multidrug anesthesia induced by combining an opioid to a hypnotic agent has been raised as one of the major problems in the field. The mechanisms of action of these drugs are different resulting in distinct neurophysiological changes and thereby challenging the EEG-based depth of anesthesia indices generally developed to measure the effect of a single hypnotic agent. Even though a large body of literature addresses this problem, the results presented are somewhat controversial and cannot be used to draw clear-cut conclusions about the reliability of the indices during hypnotic-opioid anesthesia.

## 1.2 Research problem and objectives

This thesis concentrates on investigating the effect of coadministration of opioids on the EEG-based depth of anesthesia measurement. Thus far, the papers published on this topic represent a heterogeneous group of studies, in which the application of different drug combinations, EEG measures, and clinical protocols fundamentally complicate the interpretation of results. It therefore remains unclear, how supplementing the hypnotic drug with an opioid affects the EEG-based depth of anesthesia measurement. The main objective of the thesis is to answer this question. Furthermore, the aim is to develop a technology for a more reliable measurement of depth of anesthesia during hypnotic-opioid anesthesia.

## 1.3 Research scope and approach

The objectives of the thesis are approached by investigating the EEG changes and depth of anesthesia in terms of clinical signs during induction of multidrug anesthesia with propofol and remifentanil. Both drugs, representing a hypnotic agent and an opioid, respectively, are widely used in the clinical practice and have typical mechanisms of action making the results generalizable to some extent to other anesthetics. The analysis is restricted to the induction of anesthesia excluding the emergence phase.

The original publications are all based on one data set recorded in 2000 and 2001. The data originally included 45 patients, but due to variation in the technical details related to EEG measurement protocol, only 27 were approved to the studies. Furthermore, the data of one more patient were later excluded because of the measurement artifact. The patients were randomly assigned to one of three groups: R0 (9 patients), R1 (8 patients), and R2 (9 patients). Depending on the group, patients received either saline (R0), low-dose remifentanil (R1, 7.5 $\mu g \times kg^{-1} \times h^{-1}$) or high-dose remifentanil (R2, 30 $\mu g \times kg^{-1} \times h^{-1}$) during the induction of anesthesia with propofol (30 $mg \times kg^{-1} \times h^{-1}$). Both drugs were infused at a fixed rate until the burst suppression pattern (BSP) was detected in an EEG monitor. During the induction, different clinical signs were observed. During the induction process, EEG was recorded from 17 different electrode locations. However, the analysis was performed using only one frontal montage (Fz) with a common average reference.

The work can be divided into three separate tasks. The first is the quantification of EEG phenomenon during induction of anesthesia. Two different methods are developed to describe the continuum of EEG changes related to propofol infusion. In these methods, spectral features are used to delineate the EEG changes due to their intuitive interpretation and computational simplicity. The commercial indices are intentionally not used as they present the depth of anesthesia usually with only one variable, whose algorithm is often not revealed, and therefore do not sufficiently give information about the changes in the EEG itself. The second task is to describe the effect of coadministration of remifentanil on the EEG-based depth of anesthesia measurement during propofol infusion. The first of the methods developed in task one is utilized to attain this goal. The effects of remifentanil on both the clinical signs and the EEG changes are investigated separately. The third and final task is to develop a technology for depth of anesthesia measurement during multidrug infusion with propofol and remifentanil. The technology is based on improving the determination of the anesthetic state of the patient

by EEG-based separation of the effects of propofol and remifentanil. Also in this task, the same method developed for quantification of EEG changes during propofol infusion is utilized.

## 1.4 Original publications and authors' contributions

Publications I and V focus on a quantitative description of the EEG changes during induction of anesthesia with propofol. In Publications II and III, the effects of coadministration of remifentanil on the EEG-based depth of anesthesia measurement during propofol infusion are investigated. A technology for depth of anesthesia measurement during multidrug infusion with propofol and remifentanil using EEG is presented in Paper IV. Papers II–V utilize the method presented in Publication I.

In all five original publications, the author was primarily responsible for the study design, development and implementation of algorithms, analysis of results, and manuscript's production. Professor Tapio Seppänen contributed to all publications as a supervisor providing valuable ideas and comments, as well as revision of the manuscripts. In Papers I–III, Dr. Miika Koskinen participated in the study design and preparation of the manuscripts, whereas, in Papers IV and V, a similar contribution was given by M.Sc. Eero Väyrynen. Dr. Seppo Mustola participated to the revision of Papers I–III. The study data, whose collection the author did not attend, were also provided by Dr. Seppo Mustola.

# 2 Literature review

The chapter provides an overview of the literature related to the topic of the study. It comprises three parts. Whereas Section 2.1 and Section 2.2 concentrate on giving fundamental background information pertaining to general anesthesia and EEG, respectively, Section 2.3 deals with the EEG-based depth of anesthesia measurement focusing on multidrug administration.

## 2.1 General anesthesia

*"The state should, I think, be called "Anesthesia". This signifies insensibility."*
*Oliver W. Holmes*

### *2.1.1 Definition of anesthesia*

General anesthesia is a drug-induced reversible condition that can be defined with five behavioral states: unconsciousness, amnesia, antinociception, immobility, and hemodynamic stability (Evers & Crowder 2006). Even though some anesthetic drugs may induce most of the states, usually a combination of hypnotic agent, analgesic agent, and neuromuscular blocking agent (NMBA) is nowadays used to improve the quality of anesthesia (van Gils *et al.* 2002). With these drugs, the anesthesia is attained by affecting the neural transmission in brain, spinal cord, and peripheral neuromuscular junctions. Fig. 1 illustrates the relationship between the different types of drugs and behavioral states during general anesthesia.

#### Hypnosis

Hypnosis is a crucial component of general anesthesia guaranteeing the patient to be unaware of the ongoing events and have no memories of the intraoperative period. It can be induced by affecting the neural activity of the brain using either intravenous (IV) anesthetics, such as propofol, or inhaled anesthetics like isoflurane, sevoflurane, and desflurane. Most of the hypnotic agents act in the central nervous system (CNS) by either increasing the transmission of the primary inhibitory neurotransmitter gamma-aminobutyric acid (GABA) or by decreasing the activity of the glutamate-driven pri-

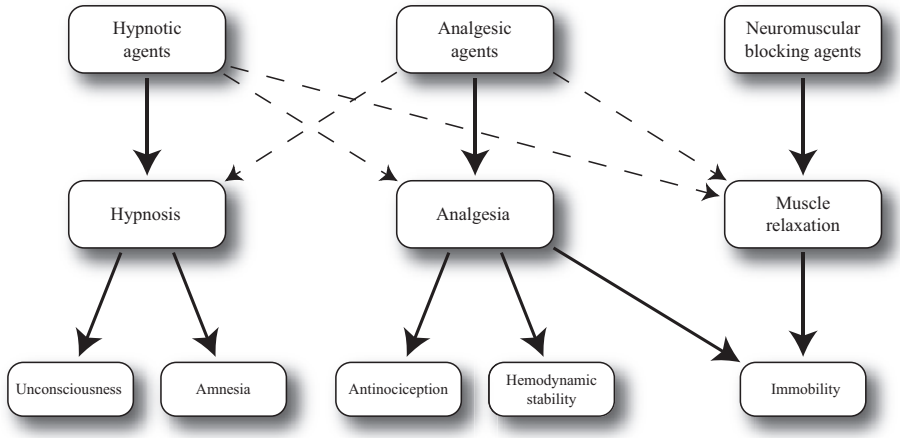


**Fig. 1. A schematic representation of the relationship between the different types of drugs and behavioral states during general anesthesia. The figure is constructed from van Gils *et al.* (2002) and Evers & Crowder (2006).**

mary excitatory N-methyl-D-aspartate (NMDA) receptors (Århem *et al.* 2003). According to the current opinion, this is done by affecting the ligand- and voltage-gated ion channel proteins of neurons (Campagna *et al.* 2003). However, whether the hypnosis is induced by drug effects on the cerebral cortex, thalamus, or thalamocortical interactions is still under debate (Alkire & Miller 2005, John & Prichep 2005, Velly *et al.* 2007). Many of the centrally acting analgesic agents also affect the hypnotic component of anesthesia (Mehta *et al.* 1991, Mustola *et al.* 2005).

## Analgesia

The purpose of analgesia is to suppress the perception of pain and hemodynamic responses to noxious stimulation. As many of the hypnotic drugs have poor analgesic properties (Vuyk *et al.* 1995), a separate drug for this purpose is often coadministered. Nowadays, a common practice is to combine an opioid with the hypnotic agent to improve the quality of anesthesia (Lichtenbelt *et al.* 2004). Opioids, such as morphine, fentanyl, and remifentanil act through specific receptors located in the brain and spinal cord (Mansour *et al.* 1995). These G protein-coupled receptors, in which opioids act as ligands, can be divided into four subtypes: $\mu$, $\kappa$, $\delta$, and nociceptin receptors (Fukuda 2005). The majority of the opioids used for analgesia activate $\mu$ receptors which are con-

sidered to produce analgesia via GABAergic neural transmission (Christie *et al.* 2000). The analgesic effects of opioids arise from their ability to inhibit the transmission of nociceptive information from the spinal cord to the brain, as well as their direct influence on the pain perception in the brain (Fukuda 2005). Numerous reports have demonstrated that a major benefit of opioids is also the hemodynamic stability they provide during anesthesia (Bovill *et al.* 1984). This results from the attenuated nociception, but also from the direct effects of opioids on the neurologic and cardiac mechanisms regulating the blood pressure and heart contraction (Fukuda 2005). Due to the suppression of pain perception, a well-produced analgesia also induces immobility.

### Muscle relaxation

Intraoperative muscle relaxation is necessary for several reasons. It facilitates endotracheal intubation in the beginning of anesthesia (Kaur & Heard 2008, Naguib & Lien 2005). Adequate muscle relaxation also contributes to the anesthesia by guaranteeing immobility during the operation, which is beneficial to the surgeon (van Gils *et al.* 2002). Even though a sufficient combination of hypnotic and analgesic drug often provides satisfactory muscle relaxation (Merk & Goudsouzian 1995), a separate drug dedicated to this purpose is often used to assure optimal conditions for the operation (Naguib & Lien 2005). There exist two major groups of muscle relaxants: NMBAs and spasmolytics (i.e. centrally acting muscle relaxants). In practice, the effective intraoperative muscle relaxation is restricted to the usage of NMBAs (Erkola & Rautoma 1999). NMBAs, such as succinylcholine and rocuronium, block neuromuscular transmission at the peripheral neuromuscular junctions by binding to the acetylcholine receptors located postsynaptically in the membrane of skeletal muscle cells (Erkola & Rautoma 1999). Because of this peripheral mechanism of action, NMBAs do not contribute to the other behavioral states of anesthesia besides immobility. Therefore, to avoid unintentional awareness during operation, they should be administered only to appropriately anesthetized individuals. NMBAs are nowadays routinely used in combination with hypnotic and analgesic drugs to facilitate endotracheal intubation and to maintain immobility through different surgical procedures (Naguib & Lien 2005).

### 2.1.2 Propofol

Propofol is the most frequently used IV anesthetic today (Reves *et al.* 2005). It is utilized in the operating room and intensive care unit (ICU) for both induction and maintenance of anesthesia. These are carried out using either repeated boluses or continuous drug infusion. When delivered to the circulation, propofol is rapidly metabolized in the liver to water-soluble compounds, which are then excreted in the kidneys (Simons *et al.* 1985). Propofol is primarily a hypnotic agent resulting in unconsciousness and amnesia swiftly after beginning of administration. Evidence suggests that a significant portion of propofol's hypnotic action is mediated by potentiation of the GABAergic neural transmission (Krasowski *et al.* 2001, Jurd *et al.* 2003). The drug also results in widespread inhibition of NMDA receptors, which may contribute to its CNS effects (Lingamaneni *et al.* 2001). Even though propofol's main effect-site is the brain, studies have demonstrated its direct depressant effect on the neurons of the spinal cord (Antognini *et al.* 2000). Despite this, propofol has poor analgetic properties as the concentration suppressing the reactions to surgical stimulation is much higher than the one needed in the hypnotic point of view (Scheinin & Valtonen 1999). The major disadvantage of propofol is the decrease of blood pressure it induces (Scheinin & Valtonen 1999). To avoid high concentrations of propofol during an operation, an analgesic drug is often combined with it (Lichtenbelt *et al.* 2004).

### 2.1.3 Remifentanil

Remifentanil is an opioid increasingly used in the operating room and intensive care (Fodale *et al.* 2008). Intraoperatively, it is given to patients as a supplement to hypnotic drug, or alone in high-dose opioid anesthesia (Servin 2003, Coda 2009). The pharmacodynamic properties of remifentanil are similar to all opioids representing strong $\mu$ receptor agonism (James *et al.* 1991). By this mechanism, it selectively decreases the amount of pain and discomfort during surgical procedure (Laitinen & Salomäki 1999). When compared with propofol, remifentanil provides significantly better analgesia (Coda 2009). The drug also has hypnotic effects. However, clinical investigations have found that loss of consciousness is not reliably achieved with remifentanil alone (Coda 2009, Jhaveri *et al.* 1997). The real advantage of remifentanil is in its pharmacokinetic properties. After administration, the drug is rapidly distributed throughout the body (Battershill & Keating 2006). Unlike other intraoperative opioids, remifen-

tanil is metabolized via blood- and tissue-nonspecific esterases (Beers & Camporesi 2004, Fukuda 2005). This organ-independent elimination guarantees rapid metabolism leading to the lack of accumulation and rapid emergence even after long infusion time (Hoffman *et al.* 1993, Battershill & Keating 2006). Remifentanil thus constitutes the first "ultra-short"-acting opioid for general anesthesia (Fukuda 2005). Due to the rapid metabolism, remifentanil is usually administered using continuous drug infusion. The favorable pharmacodynamic and pharmacokinetic properties of remifentanil have made it a popular supplement to propofol for total IV anesthesia (TIVA) (Coda 2009, Grundmann *et al.* 1998). This kind of multidrug infusion decreases the amount of propofol needed to reach a certain depth of anesthesia when defined using clinical signs (Mustola *et al.* 2005).

### 2.1.4 Measuring depth of anesthesia

Literature presents several ways to measure the depth of anesthesia. In this subsection, the most common approaches will be introduced. The EEG-based depth of anesthesia measurement is not discussed here, as it is explained in detail in Section 2.3.

#### Clinical signs

Clinical signs can be defined as the physiological signals readily measured by observing the patient (van Gils *et al.* 2002). These provide a gold standard for the assessment of depth of anesthesia. For example, the breathing pattern, muscle tone, heart rate, and ocular signs of the patient have traditionally been used to give information about the adequacy of anesthesia. Commonly, the state of the patient is determined by observing the occurrence of different endpoints representing the beginning or ending of a certain clinical sign. This approach is exceptionally favorable from the research point of view, as the occurrence of such a clinical endpoint provides a discrete moment that can be associated with a particular depth of anesthesia. The endpoints are roughly divided into hypnotic and analgesic, depending on whether they reflect more the patient's awareness or reaction to painful stimulation, respectively.

The hypnotic endpoints give information about the patient's state in terms of consciousness and memory formation. Historically, the ocular signs, such as pupillary light reflex (Belani *et al.* 1993) and eyelash reflex (Cruccu *et al.* 1991, Mourisse *et al.* 2003), have provided a popular approach to assess the hypnosis of the patient. However, the

ocular signs are driven by spinal reflexes and are thus considered to reflect also the analgesic state of the patient. Therefore, the endpoints like loss of counting (LC) and loss of obeying a verbal command (LVC) involving higher central areas are thought to be more adequate for the measurement of the hypnotic component of anesthesia. In LC, the patient is asked to count slowly as long as he/she can from the beginning of infusion of anesthetic drug and the moment the patient stops counting defines the endpoint. The LVC is defined as the moment the patient stops obeying a verbal command like "squeeze my hand" or "open your eyes". The command is given continuously every 10-20 seconds from the beginning of drug infusion. LVC has been shown to represent a deeper level of anesthesia than LC (Dunnet *et al.* 1994, de Grood *et al.* 1985).

The analgesic endpoints are used to assess the patient's response (movement or hemodynamic changes) to painful stimulation. Traditionally, reactions to skin incision, laryngoscopy and intubation have been used for this purpose. However, the trapezius squeeze and tetanic stimulation provide good alternatives to those stimulations (Zbinden *et al.* 1994a,b). The advantages of the latter ones are that they are reproducible and noninvasive. The electrical tetanic stimulation may nowadays be the most commonly used pain stimulus (Mustola 2004). It is applied by conducting a current via self-adhesive or needle electrodes to the upper or lower limb. The moment the purposeful somatic movement ceases defines the endpoint, i.e. the loss of reaction to tetanic stimulation (LRT).

Even though the clinical signs provide a traditional and intuitive approach to depth of anesthesia measurement, they have several shortcomings. Firstly, using a single endpoint only two anesthetic states can be distinguished: "before endpoint" and "after endpoint". In order to overcome this problem, scoring systems utilizing more than one endpoint have been developed. One of the most commonly used is the Observer's Assessment of Alertness/Sedation (OAA/S) scale (Table 1, Chernik *et al.* 1990). It combines hypnotic and analgesic endpoints to form a six-level rank order scoring system for the depth of anesthesia, five and zero representing the lightest and deepest anesthetic levels, respectively. However, the clinical scoring systems still have major disadvantages. They are laborious requiring continuous effort from the observer. The interpretation of clinical signs may also vary between observers leading to different scoring. Since the clinical signs can be assessed only with certain intervals, the measurement is discontinuous (Jensen *et al.* 2004). In addition, the usage of NMBAs makes the scoring systems derived from clinical signs useless (Thornton & Sharpe 1998).

**Table 1. The Observer's Assessment of Alertness/Sedation Scale.**

| Score | Responsiveness |
|---|---|
| 5 | Responds readily to a name spoken in normal tone |
| 4 | Lethargic response to a name spoken in normal tone |
| 3 | Responds only after a name is called loudly and/or repeatedly |
| 2 | Responds only after mild prodding or shaking |
| 1 | Responds only after a painful trapezius squeeze |
| 0 | No response after a painful trapezius squeeze |

### Drug concentration

At population level, the effect of anesthetic drugs can be predicted from their concentration in the blood. For examples, concentrations required for loss of consciousness, amnesia, and unresponsiveness to painful stimulation have been reported for propofol (Reves *et al.* 2005). The pharmacologic effect and blood concentration of the anesthetic are, however, usually not linearly related (Olkkola 1999). Therefore, different nonlinear pharmacodynamic models have been developed to give a mathematical description of the relationship between the drug concentration and its pharmacologic effects (Shafer & Schwinn 2005).

When using inhaled anesthetics, the estimation of drug concentration in the blood is rather easy. Modern patient monitors are able to measure the concentration of anesthetic drug in both inhaled and exhaled gases. Exhaled drug concentration in the end of expirium represents the alveolar concentration, which is an adequate estimate for the concentration of anesthetic in the blood and brain (i.e. effect-site) during the steady state (van Gils *et al.* 2002). Minimum alveolar concentration (MAC) is a value developed to measure the potency of different anesthetic drugs (Koblin 2005). It is defined as the alveolar concentration producing immobility in 50% of subjects exposed to a noxious stimulus (Quasha *et al.* 1980). The MAC values for all commonly used inhaled anesthetics have been presented (Nickalls & Mapleson 2003). The MAC concept can also be used with other endpoints like LVC (MAC awake) and lack of response to endotracheal intubation (MAC intubation) (Koblin 2005).

With IV anesthetics, the determination of drug concentration in real time is more complicated. Today, the measurement of the concentration in exhaled gas is not yet possible, even though the recently published results on this are promising (Perl *et al.* 2009,

Gong *et al.* 2009, Miekisch *et al.* 2008). As a solution, pharmacokinetic models have been developed to mathematically describe the relationship between a given dose of the IV anesthetic and the resulting drug concentration (Shafer & Schwinn 2005). Such models for both propofol and remifentanil, for example, have been proposed (Adam *et al.* 1983, Westmoreland *et al.* 1993). The introduction of pharmacokinetic models has led to the development of target controlled infusion (TCI) systems, in which the administration of the anesthetic is automatically adjusted to achieve and maintain certain drug concentration (Glass *et al.* 2005).

Despite the extensive use of drug concentration in the estimation of depth of anesthesia, this approach has some major disadvantages. There is a wide variation in the pharmacokinetic and pharmacodynamic responses between individuals (Avramov & White 1995, Heier & Steen 1996, Høymork *et al.* 2000, van Gils *et al.* 2002). This means that the same amount of drug given to a different patient may not lead to the same drug concentration in the blood or effect-site and, on the other hand, certain drug concentration does not induce the same effect in all patients. For example, age and gender have been shown to affect these properties significantly (Reves *et al.* 2005, Shafer & Schwinn 2005). Hence, the models, even though suitable for studying the behavior of the drug in a subject, cannot be reliably used for the depth of anesthesia monitoring (van Gils *et al.* 2002).

## 2.2 EEG

*"If the brain were simple enough for us to understand it, we would be too simple to understand it."*
*Ken Hill*

### *2.2.1 Origin of EEG*

The CNS generally consists of neural cells, or neurons and glia cells, which surround neurons providing support for them and insulation between them (Sanei & Chambers 2007). Neurons are electrically excitable cells processing and transmitting information by electrical and chemical signaling (Pocock & Richards 1999). Each neuron has a cell body, an axon, and at least one dendrite. The cell body contains a nucleus and is responsible for the most of the cell's metabolism. In the surface of human brain, the neuronal cell bodies have been aligned into horizontal layers constituting the cerebral

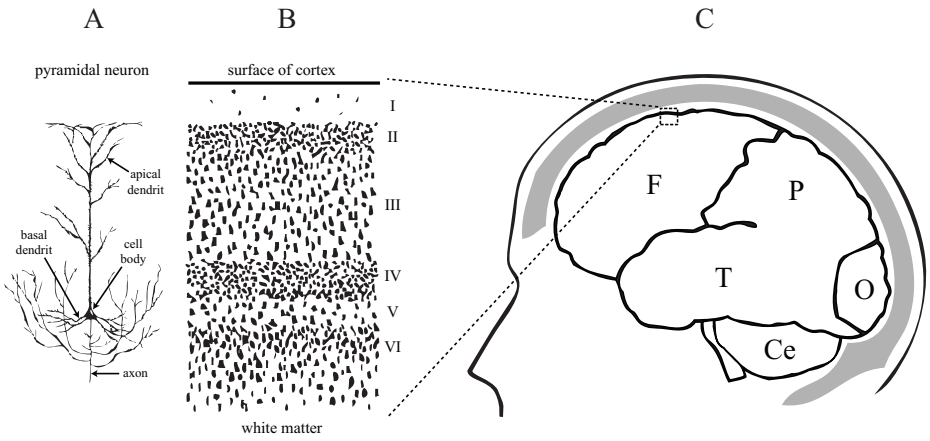


**Fig. 2. The structure of the human brain. (A) A schematic representation of a large layer V pyramidal neuron. (B) The microscopic structure of cerebral cortex comprising of six neuron layers. Spots correspond to cell bodies. (C) The macroscopic structure of the human brain: (F) frontal lobe, (P) parietal lobe, (T) temporal lobe, (O) occipital lobe, and (Ce) cerebellum.**

cortex (Kirschstein & Köhling 2009). Dendrites are the branched projections of neuron conducting the electrochemical stimulation received from other neurons to the cell body (Hari 2006a). The dendrites are divided into apical and basal depending on whether they are directed towards the surface of cortex or deeper brain parts, respectively. Axon is a thread-like projection of the neuron conducting electrical impulses, or action potentials (APs) away from the cell body to other cells (Pocock & Richards 1999). Some of the axons are covered by an electrically insulating material myelin, which forms mostly the white matter of the brain. The structure of the human brain is illustrated in Fig. 2.

EEG is a measure of the electrical activity of the brain recorded on the scalp. Neurons generally process their information by means of electrical signals, which enables the electrical recording of their activity. The primary function of neurons is to transmit information coded as a sequence of APs (Pocock & Richards 1999). In AP, the membrane potential of neuron rapidly rises and falls resulting in an electrical wave passing along the axon and leading finally to the release of a neurotransmitter into the synaptic cleft. In addition to APs, the neuronal electrical activity consists of postsynaptic potentials (PSPs), which are changes in the membrane potential of the postsynaptic terminal of a synapse. These graded potentials affect the generation of APs and are caused by the neurotransmitters released by the presynaptic neurons (Hari 2006a). Whereas the

APs are too short in duration to sufficiently sum up, PSPs having a duration of up to several tens of ms are able to produce potential changes that can be recorded on the scalp (Huttunen *et al.* 2006). EEG is thus considered to result mainly from PSPs. According to the current knowledge, the large cortical pyramidal neurons in deep cortical layers play a major role in the generation of the EEG due to their unique orientation with their long apical dendrites perpendicular to the cortical surface (Fisch 1999, Kirschstein & Köhling 2009).

### 2.2.2 Measurement of EEG

EEG is recorded on the scalp and represents generally, depending on the location of electrodes, small potential fluctuations around 10–100 $\mu$V (Niedermeyer 1999). If the recording is made on the surface of the cortex, it is called electrocorticogram (ECoG). In this case, the potential fluctuations are generally around 500–1500 $\mu$V (Niedermeyer 1999). As the EEG originates mainly from the summated electrical activity of neurons in the underlying cortex, the slow and simultaneous potential changes generated in large cortical areas are favored (Fisch 1999). The tissues lying between the neurons and the recording electrode, such as dura, skull, and skin, form an electrical volume conductor, which greatly modifies the cortical signal before it reaches the recording electrode. In addition to the attenuation, the signal spreads spatially so that the recording picked by a single electrode represents the neural activity in a wide area. Simulations have shown that about 50% of the measured scalp potential comes from sources within a 3 cm radius of the electrode center, whereas a radius of 6 cm covers 95% of the potetial (Nunez *et al.* 1997). EEG thus reflects the summation of the synchronous activity of thousands or millions of neurons with a similar spatial orientation (Huttunen *et al.* 2006).

In today's clinical practice, the EEG is most commonly recorded using the 10/20 electrode location system (Nuwer *et al.* 1998). The 10/20 system, illustrated in Fig. 3, is an internationally recognized method to describe the electrode locations based on percentual distances from certain anatomical reference points. It was developed to ensure standardized reproducibility of recordings over time and between individuals. The EEG is recorded either using bipolar or reference derivations (Koivu *et al.* 2006). In bipolar derivations, the signal is recorded between two usually adjacent electrodes. Bipolar montages are best for analyzing low to medium amplitude electrical activities that are highly localized (Fisch 1999). In reference derivations, the recording is performed using a single measurement electrode and a reference electrode commonly attached on

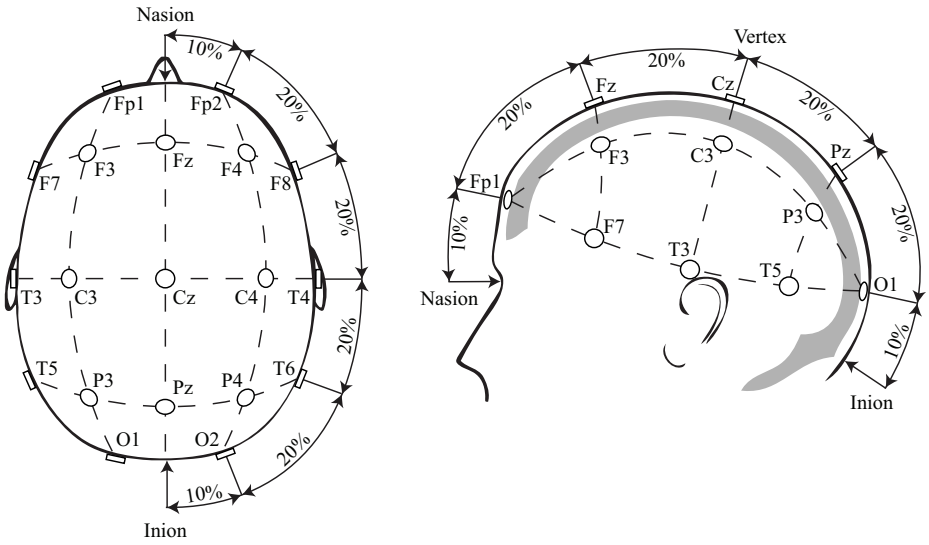


**Fig. 3. The international 10/20 electrode location system.**

mastoids or ear lobes (Koskinen 2006). Reference montages can be used to detect widespread, high amplitude potentials that form similar and coherent waveforms in adjacent electrodes (Fisch 1999). Sometimes, a common average is used as a reference. In this approach, the reference is calculated by averaging the signals from all electrodes to minimize the contribution of any single electrode to the total reference output (Fisch 1999).

Due to its low amplitude, EEG is highly sensitive to different kinds of artifacts. These are signals recorded on the EEG that do not originate from the brain and can be divided into physiological and nonphysiological artifacts. One of the major sources of physiological contamination is the eye. The retina, lining the inner surface of the eye, acts as a dipole in which the anterior pole is positive and the posterior pole is negative (Forrester *et al.* 2002). Eye movements and blinking thus result in a measurable electrical signal called electro-oculogram (EOG) that often contaminates EEG recordings, especially in the frontal montages (Hari 2006b). The electrical activity of facial muscles and heart may also distort the EEG by electromyogram (EMG) and electrocardiogram (ECG) artifacts, respectively. Nonphysiological artifacts are generated by the patient's surroundings. These distortions may originate from, for example, power lines, monitoring devices, or insufficient electrode contacts.

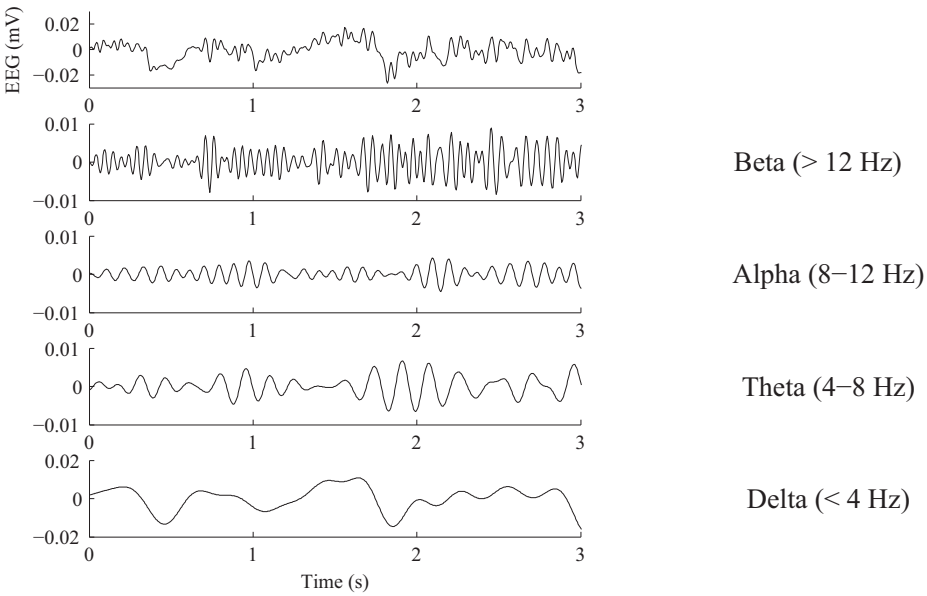


**Fig. 4. The rhythmic components separated from waking state EEG.**

### *2.2.3 Spontaneous rhythmic EEG activity*

Despite the complex structure of human cortex, the neuronal activity of the brain does not result in merely irregular EEG waves. Instead, a rhythmic EEG activity is often observed (Huttunen *et al.* 2006). The rhythmicity is considered to arise from the diverse interactions between thalamus and cortex (Fisch 1999, Huttunen *et al.* 2006). Many of the thalamic, thalamocortical, and cortical neurons have intrinsic oscillatory firing properties allowing them to participate in the generation of a spontaneous rhythmic EEG activity. Even though the frequency range of EEG has a fuzzy lower and upper limit, the clinically relevant information is considered to lie between 0.3 Hz and 70 Hz (Niedermeyer 1999). Based on the frequency of oscillations, the EEG activity has traditionally been divided into four classes: alpha, beta, theta, and delta. These rhythmic components of EEG are illustrated in Fig. 4.

#### Alpha activity

Alpha waves are oscillations in the frequency range of 8–12 Hz. They arise from the synchronous activity of thalamic pacemaker cells and are best observable during re-

laxed wakefulness (Hughes & Crunelli 2005). Strictly speaking, the term alpha activity refers to the occipital around 10 Hz oscillation appearing with eyes closed (Berger 1929, Kirschfeld 2005). Eye opening, drowsiness, and sleep suppress this activity (Tolonen & Lehtinen 2006, Huttunen *et al.* 2006). However, it has been shown that activity in alpha frequency range can also be detected in other cortical areas (Niedermeyer 1997, Hughes & Crunelli 2005). A common characteristic of all alpha waves is that they disappear when the subject is exposed to an appropriate sensory stimulation or concentrates on a mental task (Kirschfeld 2005, Huttunen *et al.* 2006). Certain neurological disorders have also been shown to reduce the spontaneous alpha oscillations (Spiegel *et al.* 2006, Hughes & Crunelli 2005).

### Beta activity

The high frequency EEG oscillations containing the frequencies above 12 Hz are called beta activity. They can be observed in healthy adults in waking state, especially when cognitively demanding tasks are performed and during excitement (Tolonen & Lehtinen 2006). Beta rhythms are most prominent in the frontal regions. GABAergic cortical inhibition is considered to have a significant role in the generation of beta oscillations. This is because beta activity has been shown to be increased by GABA-agonistic drugs (Huttunen *et al.* 2006). The upper beta range (> 30 Hz) is sometimes called as gamma range. As with alpha activity, suppression of beta activity can be related to some neurological disorders, such as cognitive impairment (Spiegel *et al.* 2006).

### Theta activity

Theta activity refers to frequency components in the 4–8 Hz range. Occipital cortical theta activity is often observed in young children, before it changes to normal adult background alpha activity (Huttunen *et al.* 2006). In older children and adults, theta rhythms occur during drowsiness and light sleep, but not in the deepest stages of sleep (Tolonen & Lehtinen 2006). The increase of spontaneous theta activity in waking state is considered to indicate cortical deafferentation from subcortical structures and is characteristic of, for example, certain mental diseases such as Alzheimer's disease and vascular dementia (Spiegel *et al.* 2006).

#### Delta activity

Delta activity includes rhythms below 4 Hz. In healthy adults, delta rhythms are normally seen only during deep sleep (Tolonen & Lehtinen 2006). Like theta, spontaneous delta activity is thought to be a sign of decreased afferent activity of cortex and can, in addition to normal sleep, be related to certain pathological phenomena like neurodegenerative diseases and metabolic or toxic disturbances (Spiegel *et al.* 2006, Binnie & Prior 1994). Short sequences of posterior delta activity can also be occasionally seen in healthy children during waking state (Sainio 2006).

## 2.3 EEG-based depth of anesthesia measurement

*"Anything that we are aware of at a given moment forms part of our consciousness, making conscious experience at once the most familiar and most mysterious aspect of our lives."*

*Susan Schneider and Max Velmans*

The most crucial behavioral states of anesthesia are related to the suppressed brain functioning. It is therefore well-founded to aim to measure the depth of anesthesia using EEG. The literature presents two approaches to this. First and the most common one is the analysis of spontaneous EEG. Second is the analysis of evoked potentials (EPs), the EEG changes following a presentation of a certain sensory stimulus. This section focuses on the first one, while the second one is briefly discussed in the end of the section.

### *2.3.1 EEG changes during anesthesia*

Determining the depth of anesthesia from EEG is based on the characteristic signal changes related to increasing concentrations of anesthetics in the blood. Due to their lipid-solubility, these drugs cross the blood-brain barrier and thereby swiftly reach the CNS after administration (Quah *et al.* 2007). In the brain, they induce a continuum of neurophysiological changes that reflects on the EEG (Stanski 1992, Sloan 1998). The EEG phenomenon can be represented using the so-called frequency progression pattern (FPP), which describes the EEG activity changes in different frequencies during continuously deepening anesthesia. Administration of a small dose of hypnotic agent

like propofol induces a state of sedation in which the EEG beta activity is increased (Brown *et al.* 2010, McCarthy *et al.* 2008). The state is called as paradoxical excitation because the drug intended to induce unconsciousness induces EEG changes normally related to excitement. As more of the drug is administered, a progressive slowing to alpha, theta, and finally to delta frequencies is seen (Kuizenga *et al.* 2001, Gugino *et al.* 2001, Kortelainen *et al.* 2008b). Simultaneously, the amplitude of EEG increases. In very deep anesthesia, the EEG changes to BSP, in which low amplitude suppression periods and high amplitude bursts take turns (Sonkajärvi *et al.* 2008). If the dose is still increased, the occurrence of bursts decreases and the periods of suppressions become longer until finally an isoelectric tracing is reached (Koskinen 2006, Brown *et al.* 2010). During emergence, the EEG patterns proceed in approximately reverse order compared to the induction (Brown *et al.* 2010, Breshears *et al.* 2010). The propofol-induced EEG changes are illustrated in Fig. 5. Similar phenomenon is seen when using other GABAergic IV or inhaled hypnotic agents, such as barbiturates, etomidate, sevoflurane, isoflurane, or desflurane (Mahla *et al.* 2005, Brown *et al.* 2010). With some anesthetics like ketamine and nitrous oxide, which primarily act through the excitatory NMDA receptors, the EEG does not follow the basic FPP and BSP is not attained (Hirota 2006, Mahla *et al.* 2005).

The effects of anesthetics in the brain are widespread affecting the topographic characteristics of EEG. Most hypnotic drugs decrease the posterior alpha activity, normally present during relaxed wakefulness, soon after beginning of administration (Dierks *et al.* 1992, Mahla *et al.* 2005). Gugino *et al.* (2001) showed that, with propofol and sevoflurane, the FPP is most prominently seen in frontal montages as the activity is highest in anterior cortex during anesthesia. This "frontal predominance" or "anteriorization" (Tinker *et al.* 1977), in addition to the convenience in terms of electrode placement, has led to the common practice of using frontal EEG for the depth of anesthesia estimation. The practice is supported by the fact that the hypnotic components of anesthesia are considered to arise from the functional suppression of prefrontal cortex, which is the most anterior part of frontal lobes (John & Prichep 2005).

### 2.3.2 Measures of depth of anesthesia

The fundamental idea of the EEG-based depth of anesthesia measurement is to be able to reliably relate the observed changes in the signal characteristics to the altered anesthetic state of the patient. Generally, the problem has been approached by develop-

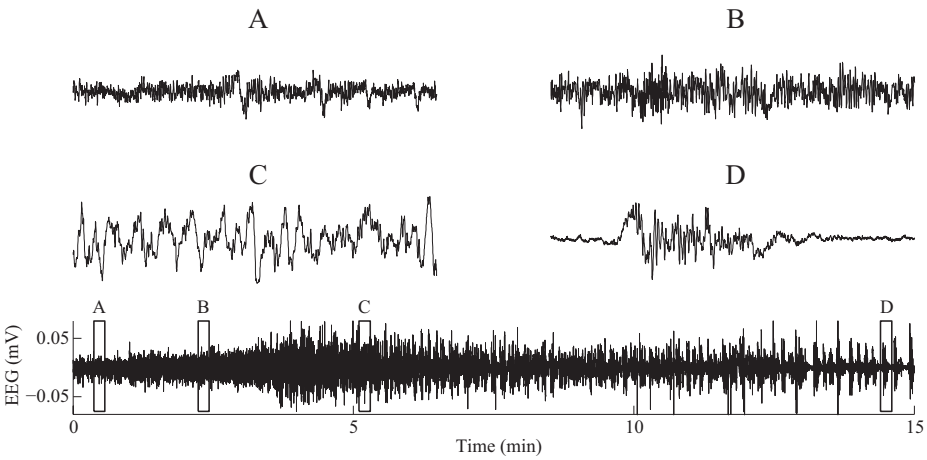


**Fig. 5. EEG during continuously deepening propofol-induced anesthesia. Propofol infusion begins at time 0. (A) Normal low-amplitude activity with eye blink artifacts. (B) Increased high-frequency activity corresponding to the paradoxical excitation. (C) High-amplitude low-frequency activity. (D) BSP. (A)–(D) correspond to 12 s signal segments.**

ing computational parameters to quantitatively describe the EEG changes related to administration of anesthetics and investigating whether they correlate with the depth of anesthesia determined by observing clinical signs. As a consequence, dozens of measures reaching from simple spectral parameters to complex indices based on nonlinear dynamics have been presented within the last two decades. The measures have also made their way into the operating rooms in the form of commercial indices in hospitals all over the world. A common property of the presented measures has been that they are somewhat reliably able to detect hypnotic endpoints, such as LVC, while the analgesic endpoints like LRT are poorly predicted (e.g. Bowdle 2006, Koskinen *et al.* 2005, Vanluchene *et al.* 2004, Struys *et al.* 2002). As the number of EEG-based depth of anesthesia measures proposed is vast and no clear-cut conclusion of their performance compared to each other in different clinical conditions can be drawn, only some of the most traditional and commonly used ones are introduced here.

## Spectral parameters

The fundamental shift of EEG activity from high to low frequencies during deepening anesthesia has made spectral analysis the most frequently used approach to the depth of

anesthesia measurement. In practice, the analysis has been carried out using the power spectrum, which presents the signal power as a function of frequency:

$$P(f) = |X(f)|^2 . \tag{1}$$

Here $f$ is the frequency and $X(f)$ is the Fourier transform of recorded signal $x(t)$. The description of how the signal power is distributed with frequency is called power spectral density (PSD). As the EEG during anesthesia exhibits a nonstationary nature, i.e. its statistical properties including spectral content vary along time, commonly the power spectra are calculated separately for short signal segments by moving a window over the original signal. This results in a spectrogram, which is a representation of the development of power spectrum as a function of time. The spectral changes of EEG during induction of anesthesia are illustrated in Fig. 6. Even though a wide variety of measures for the EEG-based depth of anesthesia estimation has been proposed, there is strong evidence that the methods utilizing nonlinear information processing do not provide essential information compared to the linear ones (Schwilden & Jeleazcov 2002, Miller *et al.* 2004, Jeleazcov *et al.* 2005). This supports the usage of power spectrum, being a linear method, in the analysis for the sake of simplicity.

Activities in different frequency bands are easily derivable from power spectrum and represent classic parameters used in the assessment of depth of anesthesia. Commonly, to describe the activity between 0 and 1 (or 0% and 100%), relative powers are used. For example, relative delta power (RDP) is calculated as

$$\mathrm{RDP} = \frac{P_{Delta}}{P_{Total}}, \tag{2}$$

where $P_{Delta}$ is the power in delta band and $P_{Total}$ is the total signal power. In addition to RDP, activities in alpha, beta, and theta bands have been used for the assessment of depth of anesthesia (Kearse *et al.* 1994, Koskinen 2006, Kuizenga *et al.* 2001, Mahon *et al.* 2008). Generally, the high activity in beta band indicates light anesthesia, while the increased delta and theta powers are associated with loss of consciousness.

Another measure quantifying the spectral information is spectral edge frequency. It is defined as the highest frequency in the EEG, i.e. the high frequency edge of the spectral distribution (Rampil 1998). The spectrum is scanned from high frequencies downward to detect the point where a predetermined threshold of power is exceeded. In measures like spectral edge frequency 95% (SEF95%) and median power frequency (MPF), the determination of threshold is avoided. Spectral edge frequency $X$% is the frequency below which $X$% of the power in the spectrum resides. MPF corresponds

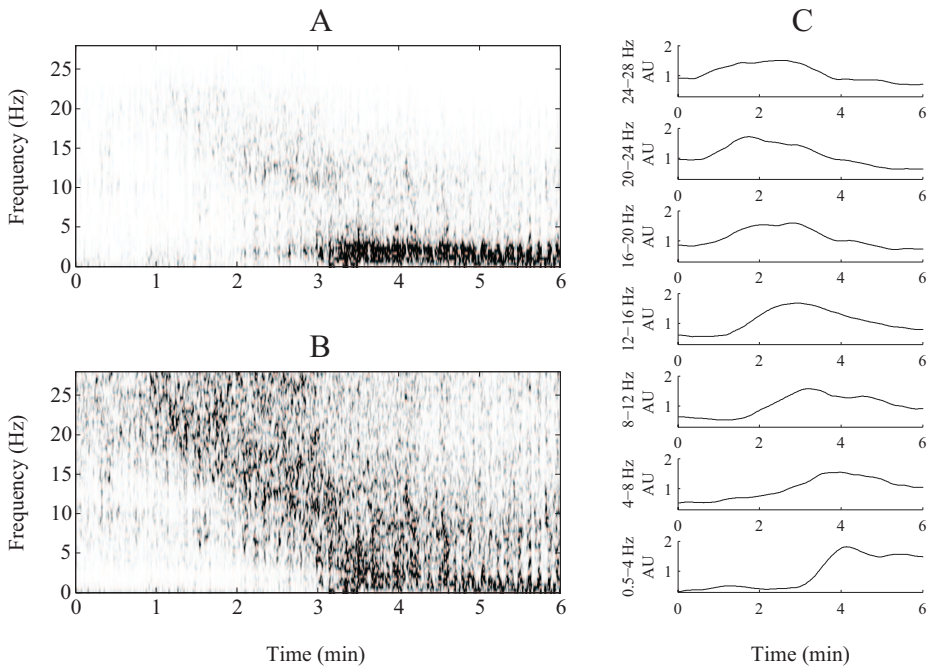


**Fig. 6. Spectral characteristics of EEG during continuously deepening propofol anesthesia. Propofol infusion begins at time 0. (A) Spectrogram. Black and white colors represent high and low activity, respectively. (B) Amplitude normalized spectrogram. The mean activity is normalized to be equal in different frequencies. (C) Spectral changes represented using activity trends in different frequency bands. The activity is given in arbitrary units (AU).**

to spectral edge frequency 50%. Both SEF95% and MPF decrease during induction of anesthesia as the power in high frequencies shifts towards lower frequencies (Tonner & Bein 2006, Bruhn *et al.* 2003, Drummond *et al.* 1991). However, due to the paradoxical excitation, an initial increase may be seen in these parameters in the beginning of induction (Katoh *et al.* 1998).

Spectral entropy (SpEn) is one of the more recently proposed depth of anesthesia measures. Its calculation resembles the calculation of Shannon entropy, which quantifies the expected value of the information contained in a message like signal (Shannon 1948). Shannon entropy of a digital signal is defined as

$$H = -\sum_{i=1}^{N_a} p(i) \log p(i), \tag{3}$$

where $N_a$ is the number of all possible amplitude values in the signal and $p(i)$ is the probability for the $i$th value. According to Eq. 3, Shannon entropy is low when the signal samples are concentrated on a small set of amplitude values and increases the more uniformly the samples spread to all possible values. In the calculation of SpEn, the Shannon equation is applied to the PSD of the signal (Powell & Percival 1979, Inouye *et al.* 1991). Therefore, it can be seen as a measure of the flatness of signal's power spectrum and is calculated as

$$H_S = -\sum_{i=f_l}^{f_h} P_n(i) \log P_n(i), \tag{4}$$

where $f_l$ and $f_h$ are the lower and higher limits of the used frequency band, respectively, and $P_n$ is the normalized power spectrum ($\sum_{i=f_l}^{f_h} P_n(i) = 1$) of the signal. Commonly, SpEn is normalized to yield only values between 0 and 1 as follows:

$$\mathrm{SpEn} = \frac{H_S}{\log N_f}. \tag{5}$$

Here $N_f$ is the number of frequency components in the range $[f_l, f_h]$. During induction of anesthesia, the wide-band EEG activity shifts to lower frequencies resulting in a more spike-like power spectrum. In SpEn, this is seen as a decrease. SpEn has therefore been suggested to indicate the changes in cortical neuronal interactions (Sleigh *et al.* 2004).

The usage of power spectrum and derived parameters for EEG analysis has also some limitations. In this approach, the EEG is assumed to be composed of a set of sine-like waves with different amplitudes and frequencies. However, this might not always be the case. For example, the waves with low frequency are often sawtoothed and hence may erroneously influence the relatively small amplitude high frequency activity in the power spectral analysis.

Fig. 7 elucidates the behavior of RDP, SEF95%, and SpEn during induction of anesthesia.

### Commercial indices

Bispectral Index, known by the trademarked acronym BIS (Aspect Medical Systems Inc., Newton, MA), is by far the most commonly used and studied commercial index of depth of anesthesia. According to the manufacturer, the technology has been used for more than 34 million patients and 3,300 scientific publications. BIS is a dimensionless univariate parameter that varies between 100 and 0, lower values indicating deeper

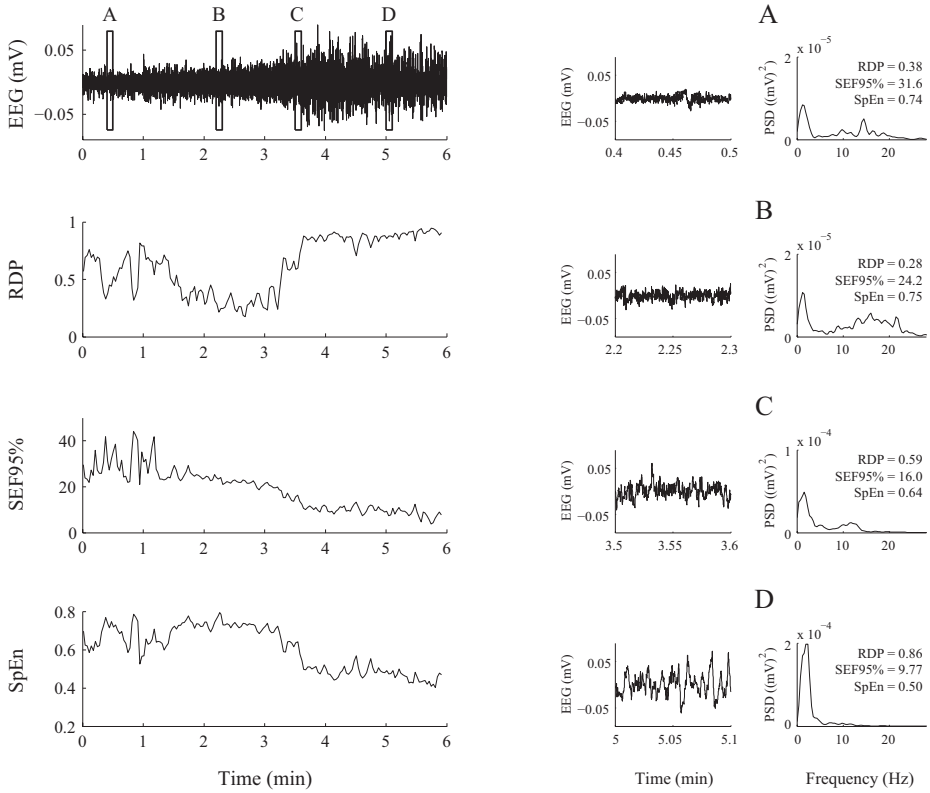


**Fig. 7. The behavior of three different EEG-derived spectral parameters (RDP, SEF95%, and SpEn) during continuously deepening propofol anesthesia. The propofol infusion begins at time 0. (A)–(D) The EEG, its power spectrum, and derived spectral parameter values at different levels of anesthesia.**

anesthesia (Gan *et al.* 1997, Glass *et al.* 1997). Although the exact description of the BIS algorithm has not been revealed, some parts of it are generally known. The variable has been constructed using a combination of time domain, frequency domain, and higher order spectral subparameters (Rampil 1998). At least four subparamaters are utilized: BetaRatio, SynchFastSlow, QUAZI, and burst suppression ratio (BSR). BetaRatio is calculated using power spectrum, while SynchFastSlow is the contribution of bispectral, i.e. higher order spectral analysis. BSR and QUAZI determine the degree of burst suppression. The first one quantifies the percentage of suppression periods in the signal, while the second one improves the detection of suppressions in the presence of a wandering baseline. The subparameters are combined using a nonlinear function so

that their weighting varies at different anesthetic levels. Their calculation is preceded by artifact removal, including elimination of ECG, EOG, wandering baseline, and high variance noise contaminations.

M-ENTROPY (GE Healthcare Finland, Helsinki, Finland) is a depth of anesthesia index based on calculation of SpEn. Unlike that of BIS, the full description of M-ENTROPY algorithm has been published (Viertiö-Oja *et al.* 2004). In M-ENTROPY, the depth of anesthesia is expressed using three variables: state entropy (SE), response entropy (RE), and BSR. SE and RE represent the SpEn calculated using frequency bands of 0.8–32 Hz and 0.8–47 Hz, respectively. The frequency components for SpEn are obtained using time windows of varying length: longer windows for lower frequencies are used. The rational behind separating SE and RE into different variables is that the EMG activity of facial muscles is considered to lie mostly between 32 and 47 Hz. As the appearance of such a signal during surgery may indicate the response to painful stimulation, the RE-SE-difference is considered to give information about the level of analgesia. SE and RE are normalized in such a way that RE becomes equal to SE when EMG power (sum of spectral power between 32 Hz and 47 Hz) is equal to zero. As a consequence, RE ranges from 0 to 100, whereas SE varies between 0 and 91, low values indicating deep anesthesia. The algorithm applied in the calculation of BSR is presented in Särkelä *et al.* (2002). As with BIS, the calculation of parameters is preceded by extensive automatic removal of artifacts (electrocautery, ECG, EMG, EOG, and movement).

In addition to BIS and M-ENTROPY, several other commercial indices, such as Narcotrend (Schultz *et al.* 2002), Patient State Index (Prichep *et al.* 2004), Cerebral State Index (Anderson *et al.* 2005), and Index of Consciousness (Revuelta *et al.* 2008), have recently been proposed. All the indices rely more or less on the quantification of the shift of EEG activity from high to low frequencies, which is a phenomenon seen with GABAergic anesthetics like propofol (Voss & Sleigh 2007). The differences mainly concern the details of how this is achieved and how, for example, various artifacts are handled. None of the indices is able to measure the effect of anesthetics primarily acting through NMDA receptors like ketamine.

### 2.3.3 Multidrug administration

One of the major reasons that the EEG has been difficult to use for assessing the depth of anesthesia is that many different classes of anesthetic drugs, all of which significantly

influence EEG, are nowadays used simultaneously (Mahla *et al.* 2005). While the effects of two different GABAergic hypnotic drugs on EEG and depth of anesthesia are mainly additive, this might not be the case with the drugs representing different pharmacodynamic profiles. Of major concern are the centrally acting analgesic drugs, such as opioids and nitrous oxide, often given as a supplement to the hypnotic agents. The mechanisms of action of these drugs differ from those of hypnotic agents resulting in distinct neurophysiological changes and thereby challenging the EEG-based depth of anesthesia measurement.

### Opioids

Most of the opioids used during general anesthesia represent similar pharmacodynamic properties, i.e. $\mu$ receptor agonism (Fukuda 2005). The EEG changes induced by these drugs are therefore comparable. When opioids are administered as single agents, the changes consist of decreasing frequency and increasing amplitude, culminating eventually in delta activity at maximal drug effect (Scott *et al.* 1985, Egan *et al.* 1996). In contrast to the GABAergic hypnotic agents, a ceiling effect is seen with opioids. Once this ceiling has been obtained, increasing opioid dosage does not further affect the EEG (Chi *et al.* 1991). BSP and flat EEG are thus not attained with opioids. Furthermore, opioids do not induce increased frontal beta activity related to paradoxical excitation (Mahla *et al.* 2005). When high doses are given, the opioids do, however, induce muscle rigidity and increase the EMG which sometimes is falsely interpreted as high frequency EEG activity (Renna *et al.* 2002). Due to the difference between EEG changes induced by opioids and hypnotic agents, EEG analysis is not routinely used for monitoring depth of opioid anesthesia (Fukuda 2005), even though for example BIS has been stated to be suitable for this purpose (e.g. Glass *et al.* 1997).

When opioids are given as a supplement to hypnotic agents, which is the common practice in the operating rooms today, the EEG-based depth of anesthesia measurement becomes difficult. Intuitively, increasing the dosage of anesthetics by adding an opioid to the hypnotic agent would result in deeper anesthesia. However, as the mechanisms of action and thereby the induced neurophysiological changes of these two drugs differ, an additive effect on EEG cannot be guaranteed. The effects of the drugs also focus on different anesthetic components (hypnosis vs. analgesia) influencing the characteristics of anesthesia, which further complicates the interpretation of EEG changes. Consequently, the multidrug anesthesia induced by combining an opioid to a hypnotic agent

has been raised as one of the major problems in the field of EEG-based depth of anesthesia measurement (e.g. Sleigh 2010, Mahla *et al.* 2005, Kissin 2000). The issue is also frequently addressed in the recent studies. A total of 46 papers, published between 1996 and 2011, were found to more or less focus on investigating the effects of opioids on depth of anesthesia assessment using EEG. No comprehensive review of this large body of literature has appeared yet. Basically, the studies approach the problem by selecting a reference measure (control variable) for depth of anesthesia and then observe if another measure is affected by the coadministration of opioids compared to this reference. The reference is generally chosen between clinical signs (e.g. separate clinical endpoints or OAA/S scale), the administration of hypnotic drug (e.g. effect-site concentration or MAC value), and EEG-based measure (e.g. BIS or activity in a certain frequency band). The observed measure is also usually chosen among these three measures. The summarized results of the 46 papers are presented in Table 2 and Fig. 8.

In nine studies, clinical signs were used as a reference for depth of anesthesia. The majority of these reported that the same anesthetic state in terms of clinical signs was reached with lower doses of a hypnotic agent and the EEG-based measure referring to lighter anesthesia when opioids were coadministrated. The results suggest that opioids mainly affect the clinical state of the patient and not as much the EEG measure. However, in two of the nine studies, the hypnotic agent and opioid showed an additive effect on EEG-derived parameter, i.e. the clinical state and EEG measure correlated well regardless of the hypnotic-opioid ratio.

The majority of the studies examined the effect of opioids by choosing the hypnotic drug administration as the reference for depth of anesthesia. From the 27 publications, 14 reported that opioids affect the EEG or EEG-derived index when given with a hypnotic drug. On the other hand, 13 studies were unable to show such an effect. When affected, EEG indices uniformly shifted towards deeper anesthesia suggesting an additive effect of the drugs. In four of the 27 studies, the coadministration of opioids was also reported to result in deeper anesthesia in terms of clinical signs.

Ten studies used an EEG-based measure as a reference for depth of anesthesia. Most of these investigated whether a coadministered opioid affects the consumption of a hypnotic agent when anesthesia is titrated using an EEG-derived index (e.g. BIS kept between 40 and 50). Seven out of eight showed an additive drug effect leading to the reduced consumption of a hypnotic agent. In addition, two studies examined the effect of coadministration of an opioid on the EEG measure itself during steady state anesthesia. From these, one reported a significant shift towards deeper anesthesia.

**Table 2. Effect of coadministration of opioids on EEG-based depth of anesthesia measurement.**

| Publication | Opioid | Hypnotic | Reference / Effect | Publication | Opioid | Hypnotic | Reference / Effect |
|---|---|---|---|---|---|---|---|
| Yufune *et al.* (2011) | R | P | H / E– | Billard *et al.* (2004) | R | D | E / H– |
| Liley *et al.* (2010) | R | P | H / E+ | Fujii *et al.* (2009) | F | P | H / E– |
| Büttner *et al.* (2010) | R | P | E / H↑ | Yumura *et al.* (2009) | F | P | H / E–, C↓ |
| von Dincklage *et al.* (2010) | R | P | H / E↓ | Mi *et al.* (2004) | F | P | C / E↑ |
| Ferenets *et al.* (2007) | R | P | H / E+ | Kodaka *et al.* (2004) | F | P | C / E↑, H↑ |
| Manyam *et al.* (2007) | R | P | H / E–, C↓ | Antunes *et al.* (2003) | F | P, I | H / E+ |
| Ferreira *et al.* (2006) | R | P | H / E↓ | Mi *et al.* (2003) | F | P | C / E–, H↑ |
| Mustola *et al.* (2005) | R | P | C / E↑, H↑ | Nakayama *et al.* (2002) | F | P | H / E– |
| Vanluchene *et al.* (2004) | R | P | H / E+ | Barr *et al.* (2000) | F | P | C / E↑ |
| Bouillon *et al.* (2004) | R | P | H / E↓ | Mi *et al.* (1999) | F | P | C / E↑, H↑ |
| Schmidt *et al.* (2004) | R | P | H / E– | Werry *et al.* (1996) | F | P | C / E–, H↑ |
| Struys *et al.* (2003) | R | P | C / E↑ | Röpcke *et al.* (1999) | F | I | E / H↑ |
| Barvais *et al.* (2003) | R | P | H / E– | Dutton *et al.* (1996) | F | I | H / E+ |
| Fechner *et al.* (2003) | R | P | E / H↑ | Schwilden *et al.* (2003) | A | P | E / H↑ |
| Nieuwenhuijs *et al.* (2003) | R | P | H / E– | Iselin-Chaves *et al.* (1998) | A | P | H / E– |
| Schmidt *et al.* (2002) | R | P | H / E+ | Nathan *et al.* (2004) | A | S | H / E–, C↓ |
| Koitabashi *et al.* (2002) | R | P | E / E↓ | Dahan *et al.* (2001) | A | S | H / E– |
| Röpcke *et al.* (2001) | R | P | E / H↑ | Forestier *et al.* (2003) | S | P | E / H↑ |
| Lysakowski *et al.* (2001) | R, F, A, S | P | C / E↑, H↑ | Hentgen *et al.* (2002) | S | P | E / H↑ |
| Strachan & Edwards (2000) | R | P | H / E↓, C↓ | Henao-Guerrero *et al.* (2009) | M | I | H / E– |
| Guignard *et al.* (2000) | R | P | H / E– | Coetzee *et al.* (1996) | T | P | H / E+ |
| Muncaster *et al.* (2003) | R | S | H / E+ | Fodale *et al.* (2005) | T | S | E / E– |
| Olofsen *et al.* (2002) | R | S | H / E+ | Vaughan *et al.* (2000) | T | I | H / E+ |

Opioid: remifentanil (R), fentanyl (F), alfentanil (A), sufentanil (S), morphine (M), tramadol (T)

Hypnotic: propofol (P), sevoflurane (S), desflurane (D), isoflurane (I)

Reference / Effect is given as $X$ / $YZ$, where $X$ is the reference against which $Y$ is compared and $Z$ is the effect in $Y$ induced by the coadministration of opioid.

$X$ and $Y$: clinical signs (C), hypnotic drug administration (H), EEG or EEG-derived index (E)

$Z$: changed (+), changed towards lighter anesthesia (↑), changed towards deeper anesthesia (↓), did not change (–)

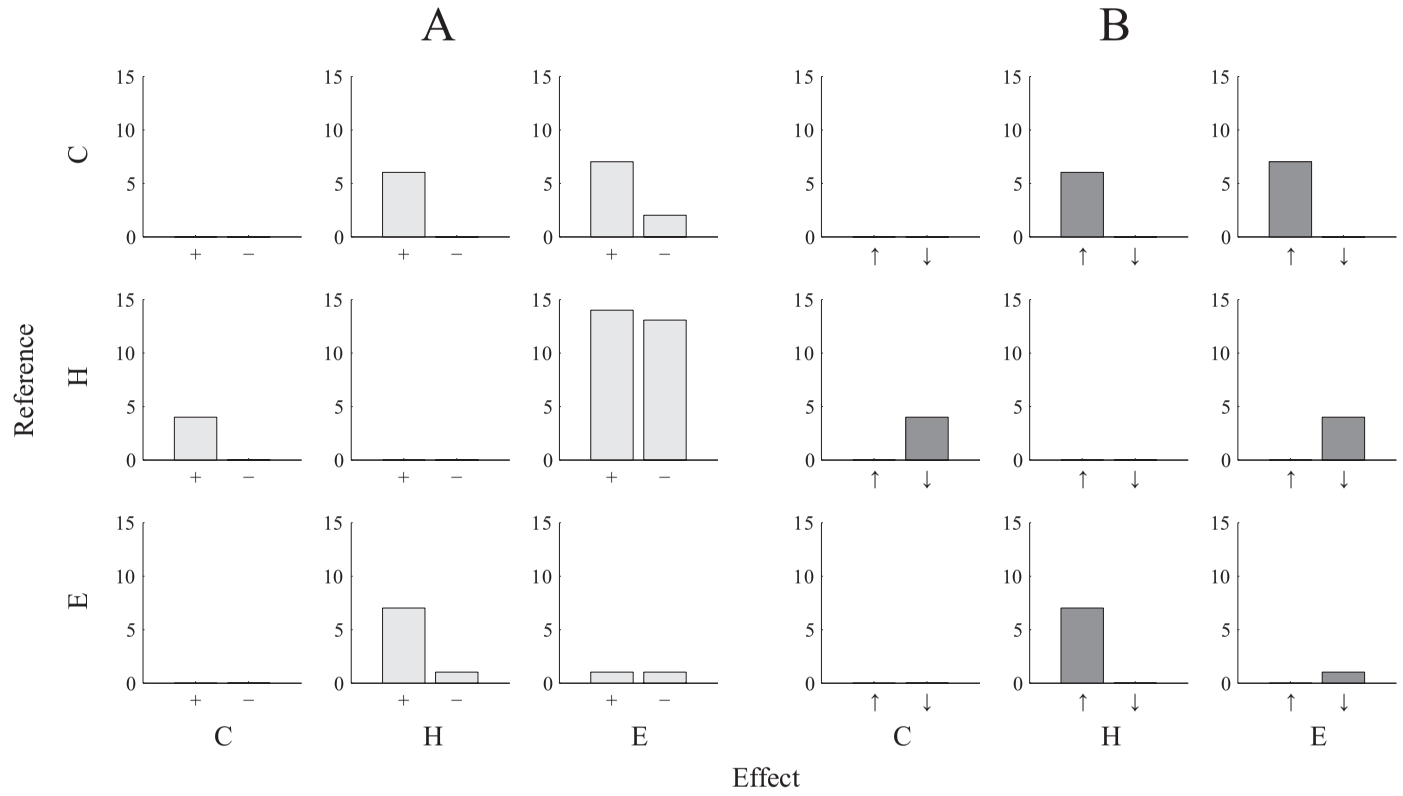


**Fig. 8. Effects of coadministration of opioids on the EEG-based depth of anesthesia measurement. Results summarized from Table 2. Bars indicate the number of studies. (A) Effects in terms of "changed" / "did not change". Here, $+$ includes all types of changes, i.e. $+$, $\uparrow$, and $\downarrow$ of Table 2. (B) The direction of effect in terms of depth of anesthesia.**

Overall, the papers published on how opioids affect the EEG-based depth of anesthesia measurement represent a heterogeneous group of studies, in which the application of different drug combinations, EEG measures, and clinical protocols fundamentally complicate the comparison of results. However, based on the findings presented above, some conclusions can be drawn. Firstly, opioids clearly affect the depth of anesthesia in terms of clinical signs when given with a hypnotic agent. There is strong evidence that this shift in the anesthetic state is not adequately reflected on the EEG-derived measures, which hinders the interpretation of commercial indices like BIS during hypnotic-opioid anesthesia. Secondly, opioids seem to somehow affect the EEG when given with hypnotic agents. Even though some studies propose the effect of these drugs on the EEG to be additive, the drugs' pharmacodynamic profiles and a number of other studies suggest otherwise. The opioids seem to somewhat uniquely change the EEG leading to altered behavior of EEG-derived measures at different anesthetic levels. This further complicates the usage of commercial indices during hypnotic-opioid anesthesia, as they have been developed for GABAergic hypnotic drugs.

### 2.3.4 Evoked potentials

In addition to the analysis of spontaneous EEG, EPs have been used for depth of anesthesia measurement. EPs are the waveforms seen in the EEG following a presentation of stimulus. Due to the low amplitude of EPs compared to spontaneous EEG, they are typically constructed by averaging tens or hundreds of EEG epochs triggered by a controlled stimulus (Koskinen 2006). EP waveforms contain peaks that are described in terms of features like latency and amplitude (Mahla *et al.* 2005). There are three basic types of EPs, auditory evoked potentials (AEPs), somatosensory evoked potentials, and visual evoked potentials, distinguished by the sensory system the stimulus is given through. All three types have been applied for depth of anesthesia monitoring, AEPs being by far the most used one (Plourde 2006). The monitoring is based on characteristic changes in the EP waveforms related to increasing concentration of anesthetic drug in the blood. For example, in AEPs, the most general anesthetics increase the latency and decrease the amplitude of the peaks in a concentration-dependent manner (Thornton & Sharpe 1998, Goto *et al.* 2001). A-Line ARX index (AAI) is a commercial index utilizing AEPs and autoregressive modeling for depth of anesthesia measurement (Plourde 2006, Jensen *et al.* 1998).

Several studies comparing the analysis of spontaneous EEG and EPs in depth of

anesthesia measurement have been published. In practice, the comparison has been usually carried out by evaluating the performance of different commercial indices like BIS and AAI. Neither of the approaches has shown a clear-cut superiority (Struys *et al.* 2002, Kreuer *et al.* 2003b, Iannuzzi *et al.* 2007, Fahlenkamp *et al.* 2010, Liao *et al.* 2011). Both spontaneous EEG and EPs seem to reveal information on the loss of consciousness but do not predict well the response to noxious stimulation (Struys *et al.* 2002, 2003). However, from the monitoring point of view, the analysis of spontaneous EEG provides certain advantages. It does not need separate equipment for the generation of stimuli. In addition, it is less susceptible to the interindividual variation in the functionality of sensory systems such as hearing impairment.

# 3 Research contributions

This chapter summarizes the research contributions of the original Publications I–V. In Paper I, a method to quantitatively describe the EEG FPP related to induction of anesthesia is proposed. The method is utilized in all four subsequent Publications (II–V). Paper II illustrates the effect of remifentanil on the relation of clinical endpoints and EEG changes, i.e. FPP, during propofol anesthesia. In Paper III, the effects of remifentanil on EEG during propofol-induced anesthesia are examined. Paper IV proposes an EEG-based technology for the assessment of depth of anesthesia during multidrug infusion with propofol and remifentanil. In Paper V, a novel approach to assess EEG changes during anesthesia by exploiting a non-linear dimensionality reduction method, Isomap, is presented. All papers utilize the same data set explained in Section 1.3, although in some studies, only a subset of it is used.

## 3.1 Quantification of EEG changes during induction of anesthesia

As explained in Section 2.3.1, hypnotics at low doses increase frequency of the EEG, whereas at high doses the EEG is depressed. This biphasic response makes it difficult to clearly distinguish the exact anesthetic state of a patient using simple measures like MPF or SEF95%. A more adequate quantitative description of the EEG changes during induction of anesthesia is therefore needed. In the original publications, two different methods for this are proposed.

### *3.1.1 The advanced r scale*

The first method, presented in Paper I, is based on the assumption that, for all patients, the EEG goes through similar activity changes in different frequency bands, i.e. FPP, during induction of anesthesia. Due to the interindividual variability in response to the anesthetic agent, the duration of this pattern may vary between individuals, but a certain phase of the pattern corresponds to the same depth of anesthesia regardless of the patient. The pattern thus relates the EEG spectral changes to the depth of anesthesia. In the presented method, activity trends calculated using eight different frequency bands

(0.5–4 Hz, 4–8 Hz, 8–12 Hz, 12–16 Hz, 16–20 Hz, 20–24 Hz, 24–28 Hz, and 0.5–28 Hz) are utilized to describe the spectral changes during a continuous fixed rate infusion of propofol. An example of such activity trends was given in Fig. 6. Using linear time scaling, the activity trends of different patients are iteratively superimposed with those of other patients leading to a uniform representation of the FPP. The superimposed trends cannot be given as a function of absolute time anymore because the trends of each patient have been scaled in time with a different individual factor. Instead, a new variable, *r*, for relative time is used. The *r* scale, representing the phase of the FPP, is defined using the beginning of propofol infusion ($r = 0$) and the occurrence of endpoint LVC ($r = 1$). It can thus be considered to describe the continuum of EEG spectral changes occurring during induction of anesthesia with propofol: the higher the value, the deeper the anesthesia.

In its original form, presented in Koskinen *et al.* (2005), the *r* scale was used to describe only the FPP between the beginning of propofol infusion and LVC. At that time, superimposing of the activity trends was performed by scaling the signals in time using the time of the LVC. The *r* values were thus strictly dependent on the occurrence of LVC. In the above-presented advanced *r* scale, the shapes of the activity trends between the beginning of infusion and the onset of BSP are used to find the optimal time scaling factor for each individual. Hence, *r* represents the phase of the EEG FPP rather than merely the relative time compared to the occurrence of a certain endpoint. However, since LVC tends to occur at a certain location on the FPP, the endpoint is still utilized to give a numerical representation for the time scaled activity trends. Because time scaling results in a unique position of LVC on the FPP for each patient, the median of the LVC locations is now used to indicate *r* value 1. While the algorithm for the calculation of FPP using iterative time scaling of activity trends is proposed in Paper I, the advanced *r* scale is presented for the first time in Paper II. The method for the calculation of new *r* scale was developed as our preliminary results showed that remifentanil affects the relation of clinical endpoints and EEG FPP and we therefore did not want to bind the calculation of FPP to the LVC. The determination of the original and advanced *r* scales is illustrated in Fig. 9 using activity trends of one frequency band.

### 3.1.2 Isomap-based approach

In Paper V, a somewhat similar but more holistic approach to quantify EEG changes during induction of anesthesia is taken. The approach consists in the fact that the contin-

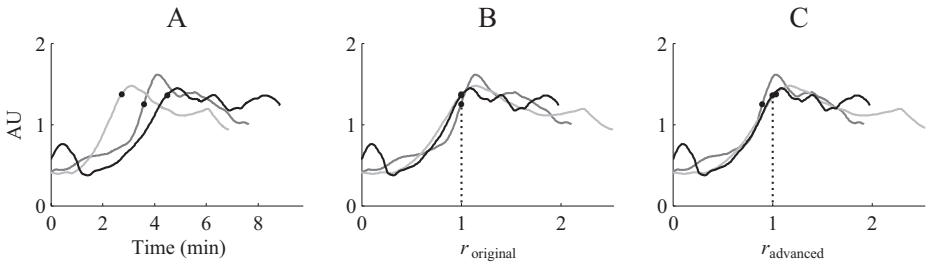


**Fig. 9. The *r* scales. The EEG activity trends of three different patients during continuously deepening propofol anesthesia given as a function of (A) time, (B) original *r* scale, and (C) advanced *r* scale. Propofol infusion begins at time 0. The trends correspond to EEG activity in 0.5–28 Hz frequency band. The dots indicate the moment of LVC.**

uum of neurophysiological changes induced by increasing concentrations of anesthetics in the blood reflects somehow on the EEG. By selecting a proper feature set, this continuum can be seen in a multidimensional feature space as a one-dimensional nonlinear manifold. With a recently proposed algorithm, Isomap, the dimensionality of the feature data can be reduced to achieve a one-dimensional embedding representing this manifold and thereby the continuum of neurophysiological changes during induction of anesthesia.

In the paper, Isomap-based approach was utilized for the estimation of *r*, representing the control variable for the depth of anesthesia. The activity trends used in the determination of *r* scale served as the feature data. The application of Isomap approach, illustrated in Fig. 10, included two parts: training and testing. In the training part, the original Isomap algorithm was utilized in a three-step manner. Firstly, a neighborhood graph is constructed. The graph, represented with a distance matrix, expresses the distance between data samples and their *k*-nearest neighbors (*k*-NN). Secondly, the shortest path, i.e. the geodesic distance, on the manifold between all sample pairs is defined. This is done by applying the Dijkstra's algorithm to the distance matrix. Thirdly, with a multidimensional scaling algorithm, a one-dimensional embedding that best preserves the manifold's estimated intrinsic geometry is constructed. To map the samples from the feature space to this one-dimensional embedding, a generalized regression neural network (GRNN) was then constructed using the training data. In the testing part, the GRNN was applied to the test samples. The new algorithm was validated with the data recorded from nine patients (R0 study group) during induction of propofol anesthesia.

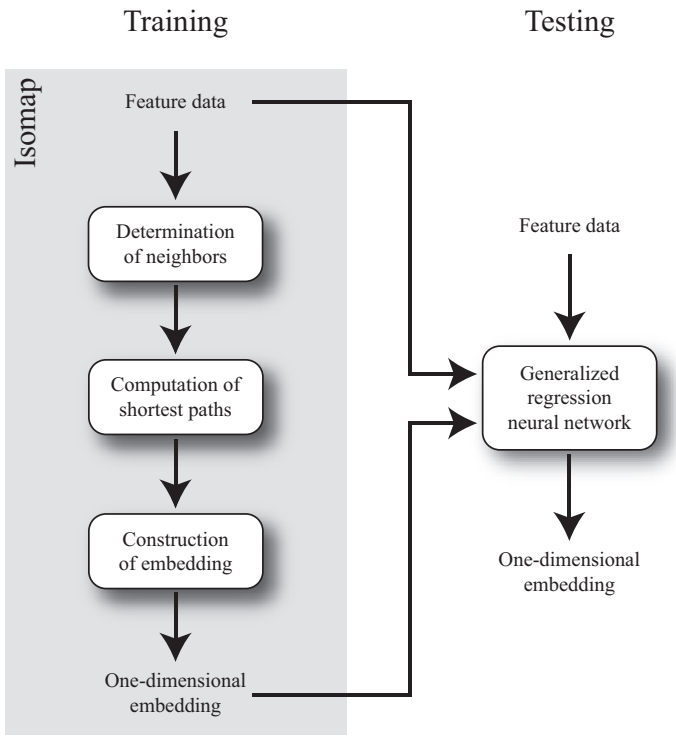


**Fig. 10. A schematic representation of the Isomap approach to EEG-based assessment of neurophysiological changes during anesthesia.**

The training-testing procedure was carried out using a leave-one-out cross-validation approach.

The strength of the Isomap-based approach compared to for example *r* scale is in its theoretical background. The EEG-based depth of anesthesia assessment requires that the signal samples are correctly associated with the corresponding anesthetic levels. In practice, the depth of anesthesia is determined using a certain control variable. However, there is always a potential error in such a variable. For example, when using drug concentration for this, temporary changes towards lighter anesthesia may be seen in the EEG due to different kinds of stimulations during the induction process even though the drug administration is continuous. This disturbs the linkage of signal samples to the correct anesthetic states. The Isomap approach, on the other hand, is fully data-driven consisting in the determination of one-dimensional embedding that represents the intrinsic geometry of the data during the shift from waking state to deep

anesthesia. It therefore is not susceptible to the error in the control variable. In fact, the one-dimensional embedding provided by Isomap approach can itself be seen as a new well-grounded control variable for the neurophysiological changes occurring during induction of anesthesia.

## 3.2 Effects of remifentanil on EEG-based depth of anesthesia measurement during propofol infusion

As presented in Section 2.3.3, the papers published on how opioids affect the EEG-based depth of anesthesia measurement represent a heterogeneous group of studies, in which the comparison of results is complicated. To fundamentally elucidate the effects of remifentanil on the depth of anesthesia in terms of clinical signs and the EEG changes during propofol anesthesia, two studies (II and III) were carried out. The opioid's influence on the onset of BSP and nonlinear entropy parameters was examined as well (Kortelainen *et al*. 2008a, 2009). However, these papers were not included in the thesis and the results are thus not reported here.

### *3.2.1 Clinical endpoints and FPP*

In Paper II, the influence of remifentanil on the relation of clinical endpoints and the spectral changes of EEG related to propofol infusion is evaluated. The patients of all three study groups (R0, R1, and R2) were included in the study. The occurrence of LC, LVC, and LRT in different groups were compared to the EEG spectral changes, i.e. the FPP determined using *r* scale. The administration of remifentanil during induction of anesthesia with propofol led to an earlier occurrence of the clinical endpoints on the FPP. A significant difference was observed between the saline (R0) and high-dose remifentanil (R2) groups in all three endpoints. In these groups, the median *r* value at LC, LVC, and LRT decreased from 0.8, 1.0, and 1.94 to 0.51, 0.72, and 0.85, respectively. The most prominent shift was seen in LRT. In all endpoints, the effect was proportional to the infusion rate of remifentanil. The mutual relation of the EEG FPP and the endpoints is thus significantly modified in a predictable and quantifiable manner by the infusion of remifentanil during propofol anesthesia. The time scaling related to the determination of *r* scale did not differ between groups indicating the propofol-induced fundamental FPP to be independent of the coadministration of remifentanil.

### 3.2.2 Spectral properties of EEG

In Paper III, the effect of remifentanil on the spectrum and quantitative parameters of EEG during induction of anesthesia with propofol was studied. Again, the data of all three study groups (R0, R1, and R2) were used. The EEG spectrograms were compared between groups after time normalized by applying the *r* scale. In addition, the group differences in 14 quantitative spectral parameters used in the depth of anesthesia estimation were examined. The following parameters were included: powers in different frequency bands (total, delta, theta, alpha, and beta), relative powers in different frequency bands (delta, theta, alpha, and beta), SpEn , BetaRatio, MPF, spectral edge frequency 90% (SEF90%), and SEF95%. The spectrograms were found to be different between groups. The high frequency (> 14 Hz) activity during light anesthesia ($0 < r < 1$) was decreased in remifentanil groups, whereas, during deep anesthesia ($1 < r < 2$), increased activity in extended alpha band (7–14 Hz) and decreased activity in delta band (0.5–4 Hz) was observed. Coadministration of remifentanil thus suppressed some of the propofol-induced EEG changes and produced some of its own. Fig. 11 illustrates the observed effect on the raw EEG and its power spectrum as a function of *r*. Statistically significant changes were seen in all fourteen quantitative parameters derived from spectrograms. The paper shows that the effect of remifentanil, when coadministered with propofol, on the power spectrum and quantitative parameters of EEG is significant and strongly dependent on the level of anesthesia.

## 3.3 Assessment of depth of propofol-remifentanil anesthesia

In Paper IV, a novel technology for the EEG-based measurement of depth of anesthesia during multidrug infusion with propofol and remifentanil is proposed. The method is based on the idea that while both propofol and remifentanil have a characteristic influence on the depth of anesthesia in terms of clinical signs, the EEG changes the drugs induce are also somewhat different. These were the key findings in Papers II and III. It was thus assumed that the effects of propofol and remifentanil would be possible to detect from the EEG separately and, by utilizing this information, make a more accurate decision about the anesthetic state of the patient. In the proposed method, the effect of propofol is determined by estimating the *r* values of signal samples. The *r* values were previously shown to be independent of the coadministration of remifentanil (Paper II)

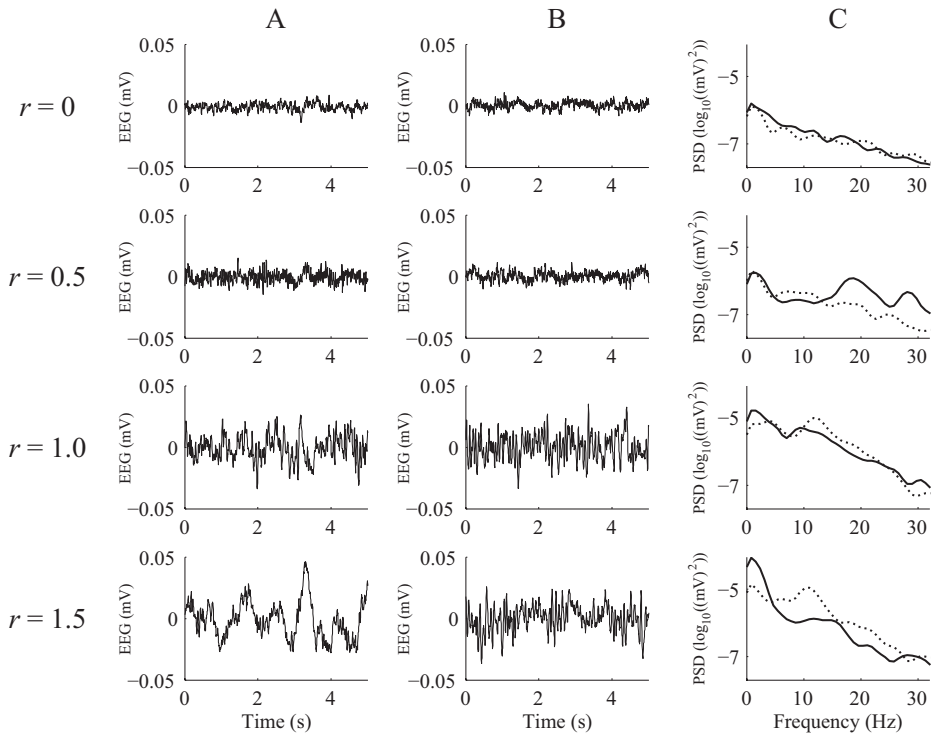


**Fig. 11. The effect of remifentanil on EEG at different levels of propofol anesthesia (*r* = 0, 0.5, 1, and 1.5). The EEG of (A) a patient not receiving remifentanil and (B) a patient receiving remifentanil during infusion of propofol. (C) PSD estimates of the signals. Continuous and dashed lines correspond to the signals in (A) and (B), respectively. While the PSD is not affected in the beginning of propofol infusion (*r* = 0), remifentanil decreases beta activity in light anesthesia (*r* = 0.5). In deeper anesthesia (*r* = 1 and 1.5), delta activity is decreased and alpha activity increased by the opioid.**

and are therefore suitable for the control variable of propofol effect. In addition to the estimation, the signal samples are classified based on whether or not they indicate the presence of remifentanil, i.e. if remifentanil has been coadministered with propofol. By applying a floating search feature selection method, well-performing subsets of EEG spectral features are achieved for the estimation and classification. These are picked from a large set of features representing powers in different frequency bands. The basis of separating the effects of propofol and remifentanil using EEG is illustrated in Fig. 12. Both estimation and classification are performed by applying a *k*-NN approach to the

signal samples in the feature space. Based on the estimation and classification results, the EEG samples are related to certain depth of anesthesia defined by clinical signs, i.e. LC, LVC, and LRT. In the paper, the technology was applied to the data of saline (R0) and high-dose remifentanil (R2) groups. Including the information about the presence of remifentanil to the estimated effect of propofol was shown to significantly improve the prediction of the patient's response to painful stimulation. The accuracy of determining the patient's clinical state in terms of LRT increased from about 70% to about 80%.

## 3.4 Summary of research contributions

The research contributions of the thesis are:

1. Two methods for the quantification of EEG changes during propofol infusion.
   - The advanced *r* scale.
   - The Isomap-based approach.
2. Description of the effects of remifentanil on the EEG-based depth of anesthesia measurement during propofol infusion.
   - The effect on the relation of clinical endpoints and EEG changes.
   - The effect on the EEG changes themselves at different levels of anesthesia.
3. A technology for the assessment of depth of propofol-remifentanil anesthesia.

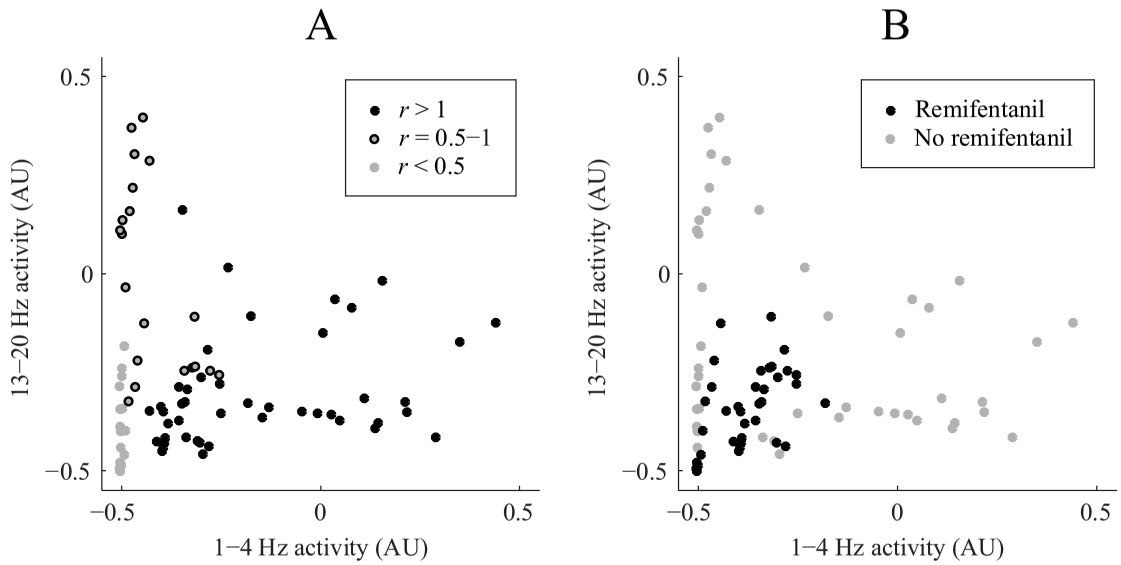


**Fig. 12. Separating the effects of propofol and remifentanil. The EEG of two patients (one receiving remifentanil, one not) during continuously deepening propofol anesthesia expressed using the activity in two frequency bands (1–4 Hz and 13–20 Hz). Each dot corresponds to a 20 s data segment. (A) Data segments labeled according to their *r* values, i.e. depth of anesthesia. The increased beta activity in light anesthesia and delta activity in deeper anesthesia is clearly seen. (B) Data segments labeled according to the coadministration of remifentanil. Remifentanil suppresses both the beta and delta activity.**

# 4 Discussion

## 4.1 Significance of results

### *4.1.1 Quantification of anesthetic EEG changes*

In the thesis, the EEG phenomenon during induction of anesthesia is described using multidimensional feature data. Both of the presented methods (Paper I and V) rely on the assumption that the continuum of neurophysiological changes induced by anesthetic drugs pose a similar multidimensional pattern of EEG changes in all patients. By tracking this pattern the depth of anesthesia can be estimated. In the literature, the main focus in the EEG-based depth of anesthesia estimation has lately been on comparing the performance of different kinds of single mathematical measures, reaching from simple spectral derivatives to recently proposed complexity parameters. The approach of assessing the effect of anesthetic drugs with a single mathematical measure assumes that the observed signal property changes somewhat monotonically, with a continuously changing anesthetic level. However, as pointed out in Section 2.3.1, instead of causing a simple suppressive effect in the cortex, the anesthetics induce a continuum of neurophysiological changes reflecting diversely on the EEG. This challenges the usage of single mathematical measures, or even a linear combination of them, for the assessment of depth of anesthesia. Considering this, the methods proposed here provide a more holistic approach in which the multidimensional dynamics of the data are taken into account.

### *4.1.2 Description of the opioid effects*

While the influence of opioids on the depth of anesthesia in terms of clinical signs is clearly synergistic with hypnotic agents, the EEG changes induced by these drugs differ due to their distinct mechanisms of action. This complicates the description of the effects of opioid on the EEG-based depth of anesthesia measurement. Consequently, as described in Section 2.3.3, the papers published on this topic so far represent a heterogeneous group of studies, in which the generalization of results is challenging and therefore clear-cut conclusions are hard to draw. Reporting, for example, the reaction of BIS to the coadministration of opioids does not sufficiently describe the relation of

EEG changes and depth of anesthesia as the index is known to comprise of multiple parameters whose contribution varies at different anesthetic levels. Since the algorithm of the index has not been revealed, the results of these kinds of studies are restricted to the specific version of BIS providing no useful long-term information.

Papers II and III present the effects of remifentanil on clinical endpoints and EEG spectral properties as a function of *r*. Since the *r* scale represents the continuum of EEG changes related to propofol infusion and is not affected by the coadministrated remifentanil, the approach provides a more convenient way to investigate the effects of opioids. The mutual relation of the clinical endpoints and the propofol induced EEG changes can be assessed. In addition, the observation of the detailed changes in the spectral properties of EEG at different anesthetic levels is made possible. The results attained are thus more general and applicable to future studies.

### 4.1.3 Technology to separate drug effects

An increasing body of literature documents the challenges related to the EEG-based depth of anesthesia measurement when supplementing hypnotic agents with opioids. As mentioned in Section 2.3.3 and also confirmed in Papers II and III, the coadministration of opioids affects both clinical endpoints and EEG changes during anesthesia hindering the interpretation of EEG-derived measures. However, very few attempts have been reported to solve this problem. In Paper IV, a solution has been provided by detecting the presence of opioids from EEG and then making a more informed decision about the clinical state of the patient. The approach was shown to significantly improve the prediction of the patient's response to noxious stimulations, which is essential during a surgical operation when the unresponsiveness to painful stimulations like skin incision is required. Recently, Liley *et al.* (2010) proposed a similar EEG-based method to dissociate the effects of propofol and remifentanil in which a fixed-order autoregressive moving-average model is applied. Paper IV is, however, the first study introducing a technology shown to actually improve the determination of the clinical state of the patient by separating the drug effects.

Measurement of analgesia using EEG is challenging. The spinal cord has the main role in delivering the sensory information to the brain. The reaction to noxious stimulation is also driven by spinal reflexes. This intuitively complicates the monitoring of pain sensation from the cortex. In the literature, the EEG has shown to be a poor predictor for analgesic endpoints (e.g. Struys *et al.* 2002). This has directed the monitoring of

analgesia to other modalities, such as heart rate and photoplethysmography (e.g. Huiku *et al.* 2007). The results presented here, however, show that the EEG gives indirect information about the analgesic state of the patient. The finding suggests that, at least during hypnotic-opioid anesthesia, the performance of the current depth of anesthesia monitors can be improved significantly.

## 4.2 Limitations and generalizability

The study was entirely based on a single data set, which poses some limitations. Firstly, the number of patients in one group was rather small. Even though special attention was paid to this by applying cross-validation, the results need to be validated with a larger amount of data. For example, the feature set used in the detection of remifentanil (Paper IV) might slightly change if the number of patients would be increased. A larger amount of data, with varying doses of opioids, is also needed to change the assessment of the effect of opioids from "on/off" to a continuous scale. Furthermore, the clinical setup somewhat restricts the generalization of the results. The data included only the induction of anesthesia, while the emergence phase was left out. The applicability of the results to the recovery from anesthesia needs to be confirmed.

The findings are potentially generalizable to other hypnotic-opioid drug combinations. The effect of hypnotic drugs generally arises from the potentiation of the GABAergic neural transmission, while most of the intraoperative opioids act through $\mu$ receptors. Due to the similar mechanisms of action, other hypnotic-opioid drug combinations are likely to produce results comparable to those presented here. However, additional studies are required to confirm this.

The study also opens possibilities for future research related to totally new topics. So far, the EEG changes during induction of anesthesia have been studied in healthy brains. One interesting possibility would be to investigate how different brain injuries affect the continuum of EEG changes related to induction of anesthesia. As the EEG frequency changes seen during anesthesia result from the oscillatory activity of distinct neural networks, it can be hypothesized that certain brain damages, such as diffuse ischemic and axonal injuries, would influence these changes. Due to the consistency of the frequency progression and high-amplitude of the EEG during induction of anesthesia, the alteration in the characteristics of anesthetic EEG is supposedly easier to observe compared to that of waking state EEG. In fact, some results indicating abnormal behavior of the EEG in response to anesthetics after a brain injury has been reported

(Myles *et al.* 2009). Hence, the changes in the time-frequency properties of the EEG during induction of anesthesia potentially provide a novel approach to study the cerebral dysfunction.

The methods proposed here for the depth of anesthesia assessment can also potentially be applied to measure other kinds of neurophysiological changes. There is evidence that epileptic seizures, for instance, are preceded by characteristic EEG changes that are detectable minutes before seizure onset (Sackellares 2008). The finding suggests that, before the actual epileptic activity begins, the functionality of the brain slowly shifts to abnormal. Similarly, although in a different time scale, the progress of a wide spectrum of neurodegenerative diseases reflects on the EEG. This is the case with for example Alzheimer's and Parkinson's disease (Jeong 2004, Fonseca *et al.* 2009). Compared to the anesthesia, these neurophysiological events provide a similar problem characterized by the increasingly altered functionality of the brain. The approaches to track EEG changes presented in this thesis could thus be possibly utilized in the prediction of epileptic seizures or early diagnosis of neurodegenerative diseases.

# 5 Summary and conclusions

In this thesis, the EEG-based depth of anesthesia measurement during multidrug infusion with a hypnotic agent and opioid is addressed. The studies, constituting five original publications, were based on a data set recorded during induction of anesthesia with propofol supplemented with varying doses of remifentanil. The work included the following three steps:

1. Quantification of EEG changes during propofol infusion.
2. Description of the effect of remifentanil on clinical endpoints and EEG changes during propofol anesthesia.
3. Development of a technology for the assessment of depth of propofol-remifentanil anesthesia.

In the first step, two methods to quantitatively describe the EEG phenomenon related induction of propofol anesthesia was developed. Both of the methods utilize the spectral changes of EEG, i.e. the FPP, for this description. In the second step, the first of the methods developed was used to describe the effects of coadministration of remifentanil on the EEG-based depth of anesthesia measurement during propofol infusion. Coadministration of opioid was shown to significantly modify the mutual relations of the EEG changes and the clinical signs, which was seen as an earlier occurrence of the endpoints on the FPP. Furthermore, remifentanil was found to significantly affect the EEG, more specifically, the power spectrum and derived quantitative parameters during propofol infusion. This effect was strongly dependent on the level of anesthesia. In step three, an EEG-based technology to assess the depth of propofol-remifentanil anesthesia was developed. The technology was designed to improve the determination of the anesthetic state of the patient by detecting the presence of remifentanil from the EEG.

The thesis provides a framework for the depth of anesthesia measurement during multidrug administration with propofol and remifentanil. Due to the similar mechanisms of action, the results are likely to be generalizable to other hypnotic-opioid drug combinations. The study thus offers potential for the development of more advanced systems for automatic monitoring of depth of anesthesia.

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# Original articles

I Kortelainen J, Koskinen M, Mustola S & Seppänen T (2007) EEG frequency progression during induction of anesthesia: from start of infusion to onset of burst suppression pattern. Proceedings of the 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Lyon, France: 1570–1573.

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