TURUN YLIOPISTON JULKAISUJA
ANNALES UNIVERSITATIS TURKUENSIS

SARJA - SER. D OSA - TOM. 1075

MEDICA - ODONTOLOGICA

THE EFFECTS OF ANESTHETIC INDUCED LOSS OF CONSCIOUSNESS ON QUANTITATIVE ELECTROENCEPHALOGRAM, AND BISPECTRAL AND SPECTRAL ENTROPY INDICES

Studies on Healthy Male Subjects

by

Kimmo Kaskinoro

TURUN YLIOPISTO
UNIVERSITY OF TURKU
Turku 2013

From the Department of Anesthesiology and Intensive Care; Perioperative Services, Intensive Care and Pain Medicine; the Turku PET Centre and Department of Clinical Neurophysiology, University of Turku and the Turku University Hospital
Turku, Finland

Research school membership: The Turku Doctoral programme of Clinical Sciences (GSCS)

Supervised by

Docent Harry Scheinin
Turku PET Centre
University of Turku

Professor Satu Jääskeläinen
Department of Clinical Neurophysiology
University of Turku and Turku University Hospital

and

Anu Maksimow MD., Ph.D.
Department Perioperative Services, Intensive Care and Pain Medicine
University of Turku and Turku University Hospital

Reviewed by

Professor Esa Mervaala
Department of Clinical Neurophysiology
University of Eastern Finland and Kuopio University Hospital

and

Professor Arvi Yli-Hankala.
Department of Anesthesiology
University of Tampere and Tampere University Hospital

Opponent

Professor Markku Hynynen
Department of Anesthesiology, Intensive Care, Emergency care and Pain Medicine
University of Helsinki and Helsinki University Hospital

The originality of this dissertation has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-5424-7 (PRINT)
ISBN 978-951-29-5425-4 (PDF)
ISSN 0355-9483
Painosalama Oy – Turku, Finland 2013

To Juska and Anniina

ABSTRACT

Kimmo Kaskinoro

THE EFFECTS OF ANESTHETIC INDUCED LOSS OF CONSCIOUSNESS ON QUANTITATIVE ELECTROENCEPHALOGRAM, AND BISPECTRAL AND SPECTRAL ENTROPY INDICES

Studies on Healthy Male Subjects

From the Department of Anesthesiology and Intensive Care; Perioperative Services, Intensive Care and Pain Medicine; the Turku PET Centre and Department of Clinical Neurophysiology, University of Turku and Turku University Hospital, Turku, Finland

Annales Universitatis Turkuensis
Painosalama Oy, Turku, Finland 2013

Changes in the electroencephalography (EEG) signal have been used to study the effects of anesthetic agents on the brain function. Several commercial EEG based anesthesia depth monitors have been developed to measure the level of the hypnotic component of anesthesia. Specific anesthetic related changes can be seen in the EEG, but still it remains difficult to determine whether the subject is consciousness or not during anesthesia. EEG reactivity to external stimuli may be seen in unconsciousness subjects, in anesthesia or even in coma. Changes in regional cerebral blood flow, which can be measured with positron emission tomography (PET), can be used as a surrogate for changes in neuronal activity.

The aim of this study was to investigate the effects of dexmedetomidine, propofol, sevoflurane and xenon on the EEG and the behavior of two commercial anesthesia depth monitors, Bispectral Index (BIS) and Entropy. Slowly escalating drug concentrations were used with dexmedetomidine, propofol and sevoflurane. EEG reactivity at clinically determined similar level of consciousness was studied and the performance of BIS and Entropy in differentiating consciousness form unconsciousness was evaluated. Changes in brain activity during emergence from dexmedetomidine and propofol induced unconsciousness were studied using PET imaging. Additionally, the effects of normobaric hyperoxia, induced during denitrogenation prior to xenon anesthesia induction, on the EEG were studied.

Dexmedetomidine and propofol caused increases in the low frequency, high amplitude (delta 0.5-4 Hz and theta 4.1-8 Hz) EEG activity during stepwise increased drug concentrations from the awake state to unconsciousness. With sevoflurane, an increase in delta activity was also seen, and an increase in alpha- slow beta (8.1-15 Hz) band power was seen in both propofol and sevoflurane. EEG reactivity to a verbal command in the unconsciousness state was best retained with propofol, and almost disappeared with sevoflurane. The ability of BIS and Entropy to differentiate consciousness from unconsciousness was poor. At the emergence from dexmedetomidine and propofol induced unconsciousness, activation was detected in deep brain structures, but not within the cortex. In xenon anesthesia, EEG band powers increased in delta, theta and alpha (8-12Hz) frequencies. In steady state xenon anesthesia, BIS and Entropy indices were low and these monitors seemed to work well in xenon anesthesia. Normobaric hyperoxia alone did not cause changes in the EEG. All of these results are based on studies in healthy volunteers and their application to clinical practice should be considered carefully.

Keywords: anesthesia, bispectral index, cerebral blood flow, consciousness, dexmedetomidine, electroencephalography, oxygen, entropy, positron emission tomography, propofol, sedation, sevoflurane, xenon.

TIIVISTELMÄ

Kimmo Kaskinoro

ANESTESIA-AINEIDEN AIHEUTTAMAN TAJUNNANMENETYKSEN VAIKUTUKSET KVANTITATIIVISEEN AIVOSÄHKÖKÄYRÄÄN SEKÄ BISPEKTRAALI- JA SPEKTRAALIENTROPIAINDEKSEIHIN
Tutkimuksia terveillä miespuolisilla koehenkilöillä

Anestesiologian ja tehohoidon oppiaine; Toimenpide-, teho- ja kivunhoitopalvelut; Turun valtakunnallinen PET keskus, Kliininen Neurofysiologia
Turun yliopisto ja Turun yliopistollinen keskussairaala, Turku

Annales Universitatis Turkuensis
Painosalama Oy, Turku, Finland 2013

Aivojen sähköisessä toiminnassa, elektroenkefalografiassa (EEG), tapahtuvia muutoksia on hyödynnetty anestesia-aineiden aivokuoreen kohdistuvia vaikutuksia tutkittaessa. EEG:an perustuvia anestesian syvyysmittareita on kehitetty mittaamaan anestesian hypnoottisen komponentin syvyyttä. Anestesia-aineiden aiheuttamia vaikutuksia nähdään EEG:ssa, mutta tajuisuuden ja tajuttomuuden erottaminen on silti hankalaa. EEG:ssa voidaan nähdä reaktiivisuutta ulkoiseen ärsykkeeseen tajuttomilla riippumatta siitä, onko tajuttomuus anestesia-aineiden vai kooman aiheuttama. Aivojen alueellisen verenvirtauksen muutoksia voidaan mitata positroniemissiotomografialla (PET), jonka tuloksia voidaan käyttää osoittamaan neuronien aktiivisuuden muutoksia.

Väitöskirjatyön tarkoituksena oli tutkia dexmedetomidiinin, propofolin, sevofluraanin ja ksenonin vaikutuksia EEG:an sekä kahden kaupallisen anestesiasyvyysmittarin, Bispectral Index (BIS) ja Entropy käyttäytymistä. Hitaasti nostettuja lääkepitoisuuksia käytettiin dexmedetomidiinilla, propofolilla ja sevofluraanilla. EEG:n reaktiivisuutta tutkittiin kliinisesti samankaltaiseksi määritetyillä tajunnan tasoilla sekä arvioitiin BIS:n ja Entropian kykyä erottaa tajuisuus tajuttomuudesta. PET-kuvauksilla tutkittiin muutoksia aivojen aktiivisuudessa tajuisuuden palatessa dexmedetomidiinin ja propofolin aiheuttaman tajunnanmenetyksen jälkeen. Lisäksi tutkittiin normobaarisen hyperoksian, jota tarvittiin typen poistamiseen elimistöstä ennen ksenon-anestesian induktiota, vaikutuksia EEG:an.

Dexmedetomidiini ja propofoli aiheuttivat nousua matalataajuisten ja korkea-amplitudisten (delta 0.5-4 Hz ja theeta 4.1-8 Hz) EEG kaistojen tehoissa portaittain nostetuilla lääkepitoisuuksilla, kun hereilläoloa verrattiin tajunnanmenetykseen. Sevofluraanilla nousua havaittiin delta-kaistalla ja alfa-hidas beta (8.1-15 Hz) kaistan tehon lisäys havaittiin sekä propofolilla että sevofluraanilla. EEG:n reaktiivisuus sanalliseen pyyntöön tajuttomassa tilassa säilyi parhaiten propofolilla ja hävisi lähes täysin sevofluraanilla. BIS- ja Entropiamonitoreiden kyky erottaa tajuisuus tajuttomuudesta osoittautui varsin huonoksi. Tajunnan palatessa dexmedetomidiinin ja propofolin aiheuttaman tajunnanmenetyksen jälkeen aktivoituivat aivojen syvät osat, ei kuorikerros. Ksenon-anestesiassa aktiivisuus lisääntyi EEG:n delta, theta ja alfa (8-12 Hz) taajuuksilla. Tasaisessa ksenon-anestesiassa BIS- ja Entropia-arvot olivat matalia ja nämä mittarit näyttivät toimivan hyvin. Normaalipaineinen korkea happipitoisuus itsessään ei aiheuttanut muutoksia EEG:an. Kaikki tulokset perustuvat terveillä vapaaehtoisilla tehtyihin tutkimuksiin ja niiden soveltamista kliiniseen työhön pitää tarkoin harkita.

Avainsanat: aivojen verenvirtaus, anestesia, bispektraali-indeksi, deksmedetomidiini, elektroenkefalografia, entropia, ksenon, positroniemissiotomografia, propofoli, sedaatio, sevofluraani, tajuisuus

TABLE OF CONTENTS

ABBREVIATIONS

3D	Three-dimensional
^{15}O	Positron emitting oxygen isotope
$[^{15}O]H_2O$	^{15}O –labeled water, a tracer substance
^{68}Ge	Germanium-68
ACC	Anterior cingulate cortex
ASA	American Society of Anesthesiologists
BIS	Bispectral index
BGO	Bismuth germanate
BS	Burst suppression
CBF	Cerebral blood flow
CO_2	Carbon dioxide gas
CT	Computed tomography
dB	Decibel
ECG	Electrocardiogram / -graphy
EEG	Electroencephalogram / -graphy
EMG	Electromyogram / -graphy
EOG	Electrooculogram / -graphy
Et	End tidal
FFT	Fast Fourier Transformation
FOUR	Full Outline of UnResponsiveness
FRD	False discovery rate
GABA	Gamma-aminobutyric acid
Hz	Hertz
ICU	Intensive care unit
i.v.	Intravenous
LOC	Loss of consciousness
LV	Latent variable
MAC	Minimum alveolar concentration
MBq	MegaBecquerel
MF	Median frequency
Min	Minute(s)
MRI	Magnetic resonance imaging
NMDA	N-methyl-D-aspartate
mSv	MilliSievert
O_2	Oxygen gas
OAA/S	Observer's Assessment of Alertness and Sedation scale
$PaCO_2$	Partial pressure of arterial carbon dioxide
PaO_2	Partial pressure of arterial oxygen
PET	Positron emission tomography
P_K	Prediction probability
PLS	Partial least-squares
qEEG	Quantitative EEG
rCBF	Regional cerebral blood flow
RE	Response entropy

REM	Rapid eye movement
ROC	Regaining of consciousness
s	Second(s)
SD	Standard deviation
SE	State entropy
SED	Sedation
SEF95	95% spectral edge frequency
SPECT	Single-photon emission computed tomography
SPM	Statistical Parametric Mapping
T½	Half-life
TVAR	Time-varying autoregressive
µV	microvolt

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I-V.

I Kaskinoro K, Maksimow A, Georgiadis S, Långsjö J, Karjalainen P, Scheinin H, Jääskeläinen SK. EEG responsiveness to verbal command at anesthetic-induced loss of consciousness. Submitted for publication

II Kaskinoro K, Maksimow A, Långsjö JW, Aantaa R, Jääskeläinen SK, Kaisti K, Särkelä M, Scheinin H. Wide individual variability of Bispectral index and Spectral Entropy at loss of consscciousness during increasing concentrations of dexmedetomidine, propofol and sevoflurane. Br J Anaesth 2011; 107: 573-580.

III Långsjö JW, Alkire MT, Kaskinoro K, Hayama H, Maksimow A, Kaisti KK, Aalto S, Aantaa R, Jääskeläinen SK, Revonsuo A, Scheinin H. Returning from oblivion: imaging the neural core of consciousness. J Neurosci 2012; 32: 4935-4943.

IV Laitio R, Kaskinoro K, Särkelä M, Kaisti KK, Salmi E, Maksimow A, Långsjö JW, Aantaa R, Kangas K, Jääskeläinen SK, Scheinin H. Bispectral index, entropy, and quantitative electroencephalogram during single-agent xenon anesthesia. Anesthesiology 2008; 108:63-70.

V Kaskinoro K, Maksimow A, Scheinin H, Laitio R, Aantaa R, Kärki T, Hinkka-Yli-Salomäki S, Jääskeläinen SK. Normobaric hyperoxia does not induce significant electroencephalogram changes in healthy male subjects. Internet of Neuromonit 2009: 6 (1).

1. INTRODUCTION

Consciousness has puzzled philosophers for centuries. Explaining the cellular and neurological events underlying consciousness is one of the greatest challenges researchers currently face. In 2005, the journal *Science* listed the 125 biggest questions that will be the focus of scientific research during this century. The problem of understanding consciousness was the second on this list. So far, scientists have only scraped the surface of this intriguing phenomenon (Kennedy and Norman 2005, Miller 2005).

Anesthesia agents cause a reversible unconscious state, and therefore provide a tool for investigating the mechanisms of consciousness (Alkire et. al 2008, Stamatakis et al. 2010, Schrouff et al. 2011). Anesthesia agents act in mainly two ways; either by increasing the transmission of primary inhibitory neurotransmitter gamma-aminobutyric acid (GABA) or by decreasing the activation of the excitatory N-methyl-D-aspartate (NMDA) receptors. The most commonly used anesthesia agents like the intravenously (IV) used propofol and the volatile sevoflurane act mainly via $GABA_A$ receptors (Ghiani et al. 1996, Alkire and Haier 2001, Salmi et al. 2004). Ketamine and xenon in turn are drugs that cause anesthesia through the inhibition of NMDA receptors (White et al. 1982, Franks et al. 1998). Selective α_2- adrenoceptor agonists, like dexmedetomidine, can also promote both sedation and analgesia (Scheinin and Schwinn. 1992, Lakhlani et al. 1997).

Anesthesia agents affect the brain in many ways; they induce alterations in its electrical activity, blood flow and metabolism (John et al. 2001, Kaisti et al. 2002). Changes in electrical activity can be measured with electroencephalography (EEG). In clinical anesthesiology, EEG-based anesthesia depth monitors are used to measure the depth of anesthesia in order to optimize the use of anesthesia agents. Changes in the activity of different brain areas can be assessed by measuring changes in the regional cerebral blood flow (rCBF) using positron emission tomography (PET).

The purpose of this thesis was to look for specific EEG markers for the changes between consciousness and unconsciousness when using dexmedetomidine, propofol and sevoflurane at low sedative doses up to loss of consciousness, and when using xenon at anesthetic concentrations. The ability of two commercial anesthesia depth monitors Bispectral Index (BIS) and Entropy to separate consciousness from unconsciousness when using dexmedetomidine, propofol and sevoflurane was also evaluated. Changes in rCBF between consciousness and unconsciousness states were evaluated with the same subjects who received dexmedetomidine and propofol in the EEG study. Changes in rCBF were measured with a PET scanner. The performance of BIS and Entropy monitors were also evaluated during xenon anesthesia. Xenon anesthesia induction requires denitrogenation i.e. breahting 100% oxygen for one hour to get nitrogen out from the body. The effects of this normobaric hyperoxia on the EEG were therefore also studied.

2. REVIEW OF THE LITERATURE

2.1. Consciousness

2.1.1. Consciousness in psychology

The Latin root for the word consciousness is *conscio*, which is formed by the coalescence of *cum* meaning "with" and *scio* meaning "know". The original Latin meaning for being conscious of something was to share knowledge of it with someone or with oneself. The words conscious and consciousness first appeared early in the 17th century. Later, two more words followed: self-conscious and self-consciousness (Zeman 2008). Consciousness is often equated to wakefulness, interaction and communication with the environment and with others in the manner that wakefulness normally implies. Consciousness can also be used more broadly to refer to our overall patterns of behavior. Conceptually, wakefulness is just one state of consciousness, such as sleep, coma and anesthesia (Zeman 2001). The term self-consciousness includes knowledge, individual awareness and the ability to recognize one's own body, for example in mirrors. In humans, this feature develops around the age of 20 months, and it has been shown that also some animals, for example monkeys and dolphins, are conscious of themselves (Hampton 2001, Smith et al. 2003, Rochat 2012).

Without attention there is no consciousness, because attention allows information to remain long enough in the working memory to be processed (Cohen et al. 2012). Consciousness is considered to consist of two major components; content of consciousness (awareness) and level of consciousness (wakefulness) (figure 1). In conscious wakefulness both components are present. When both of these decrease, the state of consciousness gradually changes from drowsiness to sleep and even to coma. Interestingly, absent awareness can coincide with a state reminding of wakefulness, such as during sleepwalking and in a vegetative state (Bassetti et al. 2000, Laureys 2005). In normal, physiological sleep consciousness disappears during slow wave sleep, and there only a minimal amount of stimuli are received from the outside world. On the other hand, in rapid eye movement (REM) sleep activity can be seen in brain areas that are active also during wakefulness (Maquet et al. 1996, Braun et al. 1997). Electrophysiological and brain imaging studies have shown that awareness and wakefulness can be extremely difficult to define and can even be present with or without each other (Revonsuo 2001, Ovadia-Caro et al. 2012, Owen 2013). In a minimally conscious state, hearing one's name induces a much more widespread activation of a subject's brain than do other, meaningless sounds. In addition, near to normal electrophysiological patterns of sleep, contrary to those characteristic of a vegetative state, can be seen. In a vegetative state, which is wakefulness without awareness, likewise behavioral changes can been seen, but no distinct electrophysiological sleep or wake patterns are evident (Laureys et al. 2004, Landsness et al. 2011). The so-called locked-in syndrome most often results from a brainstem lesion, caused by an infarction, hemorrhage or trauma to this area. In this syndrome, most of the motor system does not function and the only way to communicate is by eye blinks or eye movements, though the patient is fully conscious

(Patterson and Grabois 1986). In coma, consciousness is completely lost. Patients typically lie with their eyes closed unable to respond. In fact, general anesthesia is considered a reversible drug-induced coma (Brown et al. 2010).

2.1.2. Consciousness in medicine

In medicine it is important to measure the level of consciousness, because the urgency of treatment can depend on the level of consciousness. The method for measuring consciousness should be validated, standardized, and so easy to use that everyone who uses it can get the same result corresponding to a given level of consciousness (Bordini et al. 2010). For this reason, many clinical scales have been developed for measuring the level of consciousness. One idea behind these scales is that everyone treating the patient understands each other, which helps in avoiding misunderstandings concerning the condition of the patient. The Glasgow coma scale (table 1) was introduced in 1974 and soon became the gold standard for assessing the level of consciousness in brain injury patients (Teasdale and Jennett 1974). This scale is still used in clinical every day work world wide. Wijdicks et al. introduced a new coma scale in 2005 called Full Outline of UnResponsiveness (FOUR), which consists of four different responses instead of the three responses in the Glasgow scale. The advantage of the FOUR score is that it can be used to differentiate locked-in syndrome from a vegetative state and from coma (table 2) (Wijdicks et al. 2005).

There are several medical reasons for unconsciousness or altered consciousness. Different kind of processes which cause increase in the intracranial pressure such as; trauma, hemorrhage (spontaneous or result from trauma) and hydrocephalus (caused by many reasons) can lead to changes in consciousness (Saatman et al. 2008, Diringer et al. 2011, Carroll et al. 2012, Zare et al. 2013). Also diffuse axonal injury and trauma or hemorrhage in the brainstem can alter consciousness without any increases in the intracranial pressure. (Lee et al. 1998, Dammann et al. 2011). Several neurological disorders, for example strokes, epileptiformic seizures and infections in the central nervous system, can decrease the level of consciousness or lead to unconsciousness (Pfister et al.1993, Dostovic et al. 2012, Lambert et al. 2012). On the other hand, many systemic diseases, such as endocrine and metabolic as well as overdoses of drugs can affect the level of consciousness (Abe et al. 2007, Casaletto 2010, Anaforoglu et al. 2012, Bonds et al. 2012).

2.1.3. Consciousness in anesthesiology

General anesthesia involves five drug-induced reversible conditions: hypnosis (loss of consciousness), amnesia, analgesia, hemodynamic stability despite the stress response and immobility (Chamberlin and Eikermann 2010). Hypnosis and amnesia are produced by anesthesia-agents. The other components are based on other specific drugs; pain medication for analgesia and neuromuscular blocks for immobilization. Hemodynamic stability is made up of two components; good pain relief and adequate hypnosis. Some of the anesthesia-agents used in general anesthesia are also used in intensive care units (ICU) for sedation, with much smaller doses. Although the anesthesia mechanisms on receptor level are extensively studied, the mechanism

which causes unconsciousness is not known. To generalize, anesthetic drugs either increase the transmission of primary inhibitory neurotransmitter GABA (Salmi et al. 2004) or decrease the activation of the excitatory NMDA receptors (White et al. 1982).

The incidence of awareness during general anesthesia varies between 0.18% and 0.8% (Sandin et al. 2000, Errando et al. 2008). Intraoperative awareness is usually a traumatic experience. Dreaming during anesthesia is much more common with over 20% incidence, and most dreams are reported to be similar to normal dreams during sleep and are considered pleasant (Leslie et al. 2007, Leslie et al. 2009). Consciousness during general anesthesia is difficult to measure. In general, loss of consciousness (LOC) in anesthesiology is usually defined as a loss of motor response to a verbal command (Vanluchene et al. 2004a). Unresponsiveness is used as a synonym for unconsciousness, but by definition it is not the same thing (Sanders et al. 2012). There are several criteria which should be met before a verbal command leads to a response (figure 2). At doses near the unconsciousness threshold, some anesthetics block the working memory and patients may fail to respond because they immediately forget what they were asked to do (Veselis et al. 2002). When the isolated forearm technique (in which a tourniquet is applied to the arm before a neuromuscular block agent is administered) is used, some patients can move their hand by command, but after anesthesia they deny having been awake (Russell and Wang 1997).

Several anesthesia depth monitors have been developed to measure the level of anesthesia. Some of them are based on measuring the EEG signal and others use middle latency auditory-evoked responses to EEG. Also combinations of EEG and evoked potentials have been studied (Schneider et al. 2003, Bruhn et al. 2006, Jordan et al. 2008). There are several scoring systems for measuring the level of sedation in intensive care patients. They usually include descriptions of the level of consciousness, agitation and pain, for example the Observer's Assessment of Alertness/Sedation Score (OAA/S, table 3) (Chernik et al. 1990). EEG based anesthesia depth monitors have also been studied in ICU sedation and they have been compared to sedation scoring systems (Fraser and Riker 2005, Karamchandani et al. 2010, Yaman et al. 2012).

Table 1. Glasgow coma scale

		Score
Eye opening	spontaneously	4
	to speech	3
	to pain	2
	none	1
Verbal response	orientated	5
	confused	4
	inappropriate	3
	incomprehensible	2
	none	1
Motor response	obeys commands	6
	localizes to pain	5
	withdraws to pain	4
	flexion to pain	3
	extension to pain	2
	none	1
Maximum score		15

Table 2. Full Outline of UnResponsiveness

		Score
Eye response	eyelids open or opened, tracking, or blinking to command	4
	eyelids open but not tracking	3
	eyelids closed but open to loud voice	2
	eyelids closed but open to pain	1
	eyelids remain closed with pain	0
Motor response	thumps-up, fist or peace sign	4
	localizing to pain	3
	flexion response to pain	2
	extension response to pain	1
	no response to pain or generalized myoclonus status	0
Brainstem reflexes	pupil and corneal reflexes present	4
	one pupil wide and fixed	3
	pupil or corneal reflexes absent	2
	pupil and corneal reflexes absent	1
	absent pupil, corneal, and cough reflex	0
Respiration	not intubated, regular breathing pattern	4
	not intubated, Cheyne-Stokes breathing pattern	3
	not intubated, irregular breathing	2
	breathes above ventilator rate	1
	breathes at ventilator rate or apnea	0
Maximum score		16

Table 3. Observer's Assessment of Alertness/Sedation Scale

Subscore	Responsiveness	Speech	Facial Expression	Eyes
5	Responds readily to name spoken in normal tone	Normal	Normal	Clear
4	Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed, mild ptosis
3	Responds only after name spoken loudly or repeatedly	Slurring/slowing	Marked relaxation	Glazed, marked ptosis
2	Responds after mild prodding or shaking	Few recognizable words		
1	Does not respond to mild prodding or shaking			

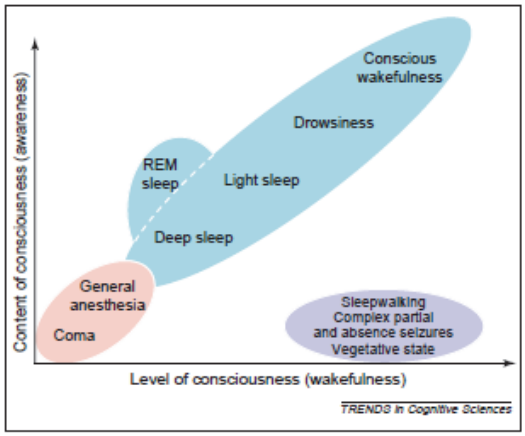


Figure 1. Oversimplified illustration of the two major components of consciousness: the level of consciousness (i.e. wakefulness or arousal) and the content of consciousness (i.e. awareness or experience). In normal physiological states level and content are positively correlated (with the exception of dream activity during REM-sleep). Patients in pathological or pharmacological coma (that is, general anesthesia) are unconscious because they cannot be awakened. Dissociated states of consciousness (i.e. patients being seemingly awake but lacking any behavioral evidence of 'voluntary' or 'willed' behavior), such as the vegetative state or much more transient equivalents such as absence and complex partial seizures and sleepwalking, offer a unique opportunity to study the neural correlates of awareness.(Laureys, Trends in Congnitive Science 2005)(Reprinted with the permission of the copyrigth holder)

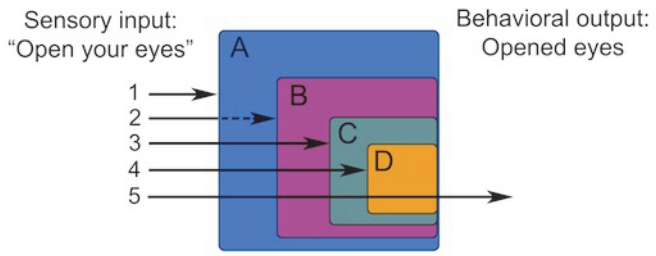


Figure 2. Conscious responsiveness schematic. Sensory input results in purposeful behavioral output only when all aspects of conscious information processing (A, conscious state;B, awareness and comprehension of the stimulus) and motor readiness (C, will and intention to respond; D, ability to respond) are functional. Arrows represent signal processing in different consciousness states: 1, all stimuli blocked from reaching consciousness (deep anesthesia or brain death); 2, dreaming during sleep or anesthesia, surrounding stimuli may (but not necessarily) (slashed arrow) influence dream content; 3 deficient will to act (e.g. anterior cingulate lesion); 4, inability to respond regardless of total awareness (e.g. awareness during anesthesia); 5, commands lead to purposeful responses (normal waking consciousness). (Långsjö et al. J. Neurosci 2012)(Reprinted with the permission of the copyright holder)

2.2. Electroencephalography and anesthesia depth monitors based on processed EEG signal

2.2.1. Electroencephalography (EEG)

Part of the brain's electrical activity is conducted to the scalp of the head. Most of the generated electric potentials cancel each other out, and thus have no net effect outwards, and only a tiny part of the electric potentials from the most superficial layers of the cortex contribute to the signals. Electroencephalography is method for measuring these potentials, which are mainly generated by the excitatory and inhibitory postsynaptic potentials from the pyramidal cells. These cells have a large number of dendrites, which extend perpendicularly to the cortical surface, and create dipole layers with synchronous postsynaptic potentials (Creutzfeldt et al.1966). EEG measures voltage differences between two electrodes, and this difference is the sum of the regional cortical electrical activity (Buzáski et al. 2003, Connolly et al. 2003, Ebersole et al. 2003,). Voltage differences have to be amplified by amplifiers, because the measured potential differences are very small, in the range of a few to hundreds of microvolts (μV). After amplification, signals may need further processing to eliminate unwanted frequencies caused by technical limitations of EEG recording equipments. Two kind of filters, high-pass and low-pass, are used to filter out unwanted signal activity like high/low frequency noise and external signals from e.g. the mains current (Connolly et al. 2003). In summary, EEG measures potential differences between two electrode locations, and this difference reflects the electrical activity of the cortical neurons within a few square centimeters below the electrodes.

The International federation of the Societies for Electroencephalography and Clinical Neurophysiology has developed an international 10/20 and lately 10/10 systems for the positioning of the EEG electrodes. Standardization of the electrode placement

enables comparison of recordings between individuals. These standard positioning systems use anatomical landmarks (nasion, inion, ears etc), and the electrodes are named by their locations (T= temporal C= central etc.) and numbered to indicate the side (unpaired=left, paired=right), or are marked as Z to indicate midline. Generally, in clinical practice, 19 electrodes are used to cover the whole scalp, which enables a precision of approximately 3-5 cm for the localization of cortical electrical events (Connolly et al. 2003, Ebersole et al. 2003). The 10/10 system or high resolution EEG (up to 128 channels) increase spatial resolution of scalp EEG up to millimeters as do intracranial electrodes (Lesser and Arrory 2005, Jurcak et al. 2007).

In addition to low number of electrodes, poor spatial resolution of routine EEG is due to several variables; the cerebrospinal fluid and the scalp are relatively conductive compartments, and activation potentials therefore spread across a wide area by volume conduction and the signal from an EEG electrode does not reflect activity changes just under the electrode. Other bioelectric potentials like electrocardiogram (ECG), electromyogram (EMG) and electro-oculogram (EOG) also disturb or may interfere with EEG signals (Rampil 1998). A low impedance between the skin and the electrode is important, because the voltage level is quite low (average <100μV). Thus, the EEG signal will inevitably contain several artifacts, which should visually be recognized and rejected before any further processing.

The raw EEG signal contains frequencies from near 0 hertz (Hz) to >100 Hz and usually the amplitude varies from 20 to 100 μV in adults. The rhythmic oscillations are commonly divided into the following frequency bands: delta < 3 Hz, theta 3-8 Hz, alpha 8-13 Hz, beta 13 – 30 Hz and gamma 30-70 Hz. Theta activity occurs in drowsiness and light sleep in healthy adults, and delta activity can be detected in deep slow wave sleep. Alpha activity appears occipitally in adult subjects during relaxed wakefulness when the eyes are closed, and disappears when the eyes are opened or when the subject falls asleep. Beta activity is commonly present in awake adults and children (Kellaway 2003, Radtke 2003) Beta activity is usually divided into three main types. The first type of beta activity is pre-central, and occurs predominantly over frontal and central regions and increases in drowsiness. The second, posterior dominant type can be seen in children of 1-2 years of age, and the third type is generalized beta activity, which is induced by drugs (Westmoreland 2009). Sensory, motor and cognitive processing may produce gamma oscillations, which are not always easy to separate from muscle activity and may be difficult to observe in scalp electrodes. (Pfurtscheller and da Silva 2005). The general features of awake EEG remain fairly unchanged during adult life (Dustman et al 1999).

Different anesthesia agents have distinct dose dependent effects on the frequency and amplitude of the EEG, but there are also some general features common to many of these drugs. In general, low (sub-anesthetic) concentrations of many general anesthetic agents induce a decrease in the EEG amplitude, a decrease in the power of the alpha band, and an increase in the beta band (‘beta activation’), especially in the frontal brain regions. In deep, surgical levels of anesthesia, the amplitude of the EEG gradually increases and the frequency decreases towards the theta and delta bands. As

the anesthesia deepens, some anesthetics produce a pattern called burst suppression (BS), alternating sequences of short bursts of activity (with high frequency and amplitude) and suppression (almost inactive EEG). If the concentration of an anesthesia drug becomes even higher, total electrical silence i.e. suppression can occur (amplitude < 5μV); this kind of EEG is called inactive. (John and Prichep 2005)

Considering the effects that anesthetics have on the different EEG bands, it should be remembered that there are both absolute and relative increases in slow frequencies although other frequencies may also increase. The two main types of the delta waves are generated in different brain regions: 0.5-1 Hz are of cortical origin and the 1-4 Hz activity originates from thalamocortical neurons. Several mechanisms are thought to be related to the origin of the delta activity; sleep mechanisms and a burst suppression pattern generator. Generalized delta can also be a consequence of seizures, and it can dominate EEG during anesthesia. Delta activity is commonly seen in deeper stages of anesthesia irrespective of the drug, and it is a dominant phenomenon in ketamine anesthesia as ketamine does not produce BS. The alpha-beta, called sigma activity, which appears during anesthesia in the frontal regions, is physiologically different from the alpha activity seen in the occipital area during wakefulness. Beta activity is commonly seen in frontal brain areas during the induction of anesthesia, and it gradually slows to alpha activity as the anesthesia continues. In addition to changes in the EEG activity within certain frequency bands, propofol and etomidate can cause beta spindles "sigma rhythm", which resemble sleep spindles, even during otherwise continuous suppression of the EEG. Fast gamma activity has been shown to be phasic in propofol and ketamine anesthesia and during slow wave sleep, whereas in REM sleep it is continuous (Jäntti and Sloan 2008).

EEG reacts to external stimuli in clinically unconscious patients irrespective of whether the unconscious is caused by coma or by anesthesia agents (Hartikainen et al. 1995, Hartikainen et al. 1999, Young 2000, Fischer and Luaute 2005, Aho et al. 2011, Lule et al. 2013). In comatose patients, EEG reactivity to external stimuli even without any clinically detected external reaction predicts a better outcome than nonreactive EEG (Young 2000). In anesthesia, painful stimulation like a skin incision or intubation can cause different kinds of reactions in the EEG; alpha, beta, and delta-arousal i.e. increase in the band powers (Kox et al. 2006, Aho et al. 2011). In burst suppression isoflurane anesthesia, palm vibration, electrical median nerve stimulation, auditory stimuli, and light flashes have been shown to induce bursts in the EEG (Yli-Hankala el al. 1993, Hartikainen et al. 1995a, Hartikainen et al. 1995b). Preserved EEG reactivity is a critical feature when choosing combination of anesthesia drugs are utilized in operations where neurophysiolocical monitoring is needed, as in the surgical treatment of epilepsy and scoliosis (Lotto et al. 2004, Oda et al. 2007, Balvin et al. 2010).

2.2.2. Processed EEG

2.2.2.1. Power spectral analyses

Visual analysis of an analog EEG signal requires a great deal of expertise and understanding of the scientific context, and still it may be compromised by subjective interpretation. Another option is to record the signal digitally and perform quantitative

signal analyses either on- or off-line. The analog signals vary smoothly from moment to moment, while digital signals have a specific value over time. For this reason, in the digital recording the sampling rate should be 4-10 times higher than the highest frequency of the signal in interest. Also time window of quantitative (qEEG) analysis should be long enough to reliably calculate power of low frequency activity, e.g., two seconds window allows analysis of frequencies down to 1Hz. Additionally, a low pass filter can be used to eliminate higher frequencies. Usually in an EEG recording, the sampling rate is above 250 Hz. A Fast Fourier Transformation (FFT) algorithm is used to transform the signal from time domain to the frequency domain and this gives a mathematical description called the power spectrum of the EEG of the occurrence and amount of different frequencies. FFT spectrum is frequency spectrum of summated regular sine wave activity, not EEG signal. From this power spectrum various numerical estimates can be calculated to describe EEG in quantitative terms. These include the total power (μV^2) and the absolute and relative powers of each frequency band of the EEG. Other qEEG variables include the peak frequency (the frequency of the highest peak in the spectrum), spectral edge frequency (SEF) 95% (the frequency below which 95% of the total power is) and the median frequency (MF) designating the frequency below which 50 % of the total power of the EEG resides (Rampil 1998).

2.2.2.2. Calculating bispectrum and the Bispectral Index

In bispectrum calculation, relationships between two sinusoid frequencies formed by FFT are analyzed. If there is no phase relationship, the bispectrum is equal zero and if two independent waves have phase relation, the bispectrum energy is high (Rampil 1998).

An anesthesia depth monitor, the Bispectral Index Score (BIS), was introduced by Aspect Medical systems in 1996. The index is based on EEG recordings from over 1500 patients, anesthetized in a wide variety of ways. With the help of these EEG recordings, BIS was developed empirically using EEG variables processed with e.g. FFT and bispectrum calculation that best correlated with anesthesia endpoints. The BIS uses these variables to compose one numerical variable, the bispectral index (100 - 0), to reflect the level of anesthesia (Rampil 1998). The validation was done with propofol, midazolam, isoflurane and alfentanil. BIS has been shown to be a good predictor of reaction to a skin incision in propofol/alfentanil and isoflurane/alfentanil anesthesia (Vernon et al.1995).

Three different processed variables are used to calculate the bispectral index: burst suppression ratio, the percentage time of suppressed EEG, the SynchFastSlow, which is ratio of the log ratio of the sum of all bispectrum peaks in the 0.5-47 Hz frequency range and the sum of the bispectrum in the 40-47 Hz frequency range; and the BetaRatio, which is the log of the ratio of the two frequency bands 30 – 47 Hz and 11 -20 Hz. Sometimes the BIS monitor is called a ‘black box’, because the calculation algorithm for weighting these three variables has not been published. There are some expectations that the BetaRatio is weighted during light hypnosis, the SynchFastSlow during surgical levels of anesthesia and the Burst Suppression Rate in very deep anesthesia (Rampil 1998, Bruhn et al. 2000, Dahaba 2005). In conclusion, the BIS

monitors single channel EEG activity in frontopolar derivations and calculates a numeric value to reflect the level of anesthesia. The full awake state has a value of 100, 50 -60 predicts low probability of responsiveness, subjects with a value below 50 are probably unconscious and 0 appears at electrographic silence (Technology Overview: Bispectral Index, www. aspectms.com).

Several studies have been conducted with the BIS monitor; it has been shown to lower the consumption of anesthesia drugs (Gan et al. 1997, Song et al. 1997, Shafiq et al. 2012) and improve recovery from anesthesia (Gan et al. 1997, Song et al. 1997). Also reduction in the incidence of nausea and vomiting has been shown (Liu 2004). A somewhat positive correlation between BIS and the prevention of post operative delirium has also been found (Chan et al. 2013).

In a study by Chan and co-workers (2013), 921 elderly patients, 60 years or older, were divided into a BIS-guided group or a routine care group. The BIS was recorded in both groups, but in the routine care group anesthesiologists were not allowed to see it. There was a significantly lower consumption of anesthetic agents (a 21 % reduction in propofol and a 30 % reduction in volatile anesthetics) in the BIS group compared to the standard care group. The incidence of delirium was reduced from 24 % to 15% when BIS was used. Post operative cognitive dysfunctions, which may result from long-lasting neurotoxicity of general anesthetics, appeared in both groups and there were no differences in the prevalence during one week between the groups, but after three months the prevalence was lower in BIS group (10.2% vs 14.7%) (Chan et al. 2013).

Variable results on the capability of the BIS monitor to differentiate consciousness from unconsciousness have been published. There are few factors, which may explain the differences between the results. The drug administration scheme was varied from study to study, different concentrations have been used and also the intervals for changing the concentrations have varied. In addition the method of assessing unconsciousness has not been same in the different studies and the intervals of testing consciousness have varied. As a result, the prediction probabilities have varied between 0.9 to 0.7 (Ibrahim et al. 2001, Schneider 2003, Iannuzzi et al. 2005, Ellerkmann et al. 2004, Lysakowski et al. 2009). One more factor that can influence the BIS value is muscle artifact. A couple of studies have described how both sugammadex and neostigmine/glycopyrrolate can increase stable BIS values in otherwise stable anesthesia in patients who show high EMG activity (Vasella et al. 2005, Aho et al. 2012, Dahaba et al. 2012). However, also the opposite has been seen (Illman et al. 2010). In intensive care units, BIS values have been correlated to sedation scales in mechanically ventilated critically ill patients. The correlation between BIS and sedation scores has been generally good, although some variation when using different drugs has been seen (Hernandez-Gancedo et al. 2007, Sackey et al. 2007, Karamchandani et al. 2010, Yman et al. 2012).

The time delay in the analysis of the BIS may limit its value in preventing awareness intraoperatively. The duration of the calculation delay varies between 20 to 60

seconds, and depends on the level of anesthesia and whether the level is stable or changing (Pilge et al. 2006, Zanner et al. 2009). In a large randomized, double-blinded, multicenter trial, almost 2500 adult patients with a high risk of awareness, undergoing operations like cesarean section, high-risk cardiac surgery and acute trauma with hypovolemia, were recruited and divided into a BIS group and a routine care group. In the routine care group, 11 subjects reported awareness in different kinds of operations, and in the BIS group there were no reports of awareness. The reduction of the risk of awareness was 82% when using BIS (Myles et al. 2004). In three large studies, two with 2000 (Avidan et al. 2008) and 6000 (Avidan et al. 2011) high-risk patients, and one with an unselected population of 21000 patients (Mashour et al. 2012), subjects were randomized into a BIS guided group or a minimum alveolar concentration (MAC) guided croup, >0.7MAC in high-risk and >0.5MAC in unselected population study. In the two high-risk patient studies, the same amount or even more cases of intraoperative awareness were seen in the BIS group compared to the MAC guided group. In the unselected population, there was no difference between the BIS group and the MAC guided group. However, according to the post hoc analyses, BIS monitoring may reduce the intraoperative awareness compared to routine care.

2.2.2.3. Calculating Spectral entropy of the EEG and Entropy monitor

Biological signals are usually irregular and complex and do not in fact, fulfill the criteria for signal analysis with parametric FFT calculation. Entropy as a physical concept describes the amount of irregularity in a system. A high value of entropy corresponds to multiple waveforms in different phases. Anesthetics and sedatives increase the regular behavior of the EEG signal, which led to the idea of measuring the entropy of the EEG to assess the hypnotic component of general anesthesia (Bruhn et al. 2000).

The power spectrum in spectral entropy is calculated by squaring all amplitudes which are got from Fourier transformation. After that, power spectrum is normalized by coefficient so that the sum of normalized power spectrum is equal to one. Finally, entropy value from 1 (maximum irregularity) and 0 (complete regularity) is then calculated using the total number of frequency components (Vieritö-Oja et al. 2004).

Entropy module (GE Healthcare S/5^{TM}) computes the time-frequency balanced spectral entropy (Entropy) of the EEG using varying time windows and for different frequencies measured from the EEG (Vieriö-Oja et al. 2004). Inter-individual variability in the EEG signal does not influence the quantification of the Spectral Entropy, because it is not dependent on the frequency of the signal.

The Spectral entropy calculates two indices from different ranges of the raw EEG-signal. The State entropy (SE) is calculated from frequency bands 0.8- 32 Hz, and contains mainly EEG signals, but may contain EMG signals also. The Response entropy (RE) uses frequencies between 0.8 – 47 Hz and it contains more EMG activity from muscles in the forehead. In the commercial device monitor these indices are scaled 91- 0 for SE and 100- 0 for RE, high values indicating an awake and alert state,

and lower values a deepening level of anesthesia. The manufacturer's recommendation is to keep both indices between 60-40 during surgical anesthesia. The indices are calculated more frequently than BIS index, every 10 s using a sampling frequency of 400 Hz. Variable time windows are used for different frequencies; the shortest time window of 1.92 s for high frequencies (32- 47 Hz) and the longest 60.16 s for low frequencies (<2Hz). The EEG signal is divided into 0.64 s epochs for automatic artifact detection and rejection. The detection eliminates artifacts that are caused by electrocautery, electrocardiogram and pace-makers, eye movements, and other movements (Viertiö-Oja et al. 2004).

When using propofol, thiopental, sevoflurane and isoflurane, Entropy has been shown to indicate the depth of hypnosis (Vakkuri et al 2004). SE and RE seem to be useful for measuring the effect of sevoflurane on the EEG (Ellerkmann et al. 2004). Also in dexmedetomidine sedation, the Entropy seemed to perform well (Maksimow et al. 2007). Entropy monitoring reduces the consuption of drugs and shortens recovery from anesthesia when compared to standard clinical practice (Vakkuri et al. 2005). In another study Jiahai et al.(2012), with patients undergoing off-pump coronary artery bypass graft surgery, Entropy reduced the consumption of propofol and sufentanil. Also the need for vasoactive medication was lower when using Entropy monitor than in the control group (Jiahai et al. 2012). There are no large studies with entropy to prevent awareness, like BIS have.

BIS and Entropy monitors have been compared in a couple of studies. The performances of these monitors have been found good in general anesthesia induced with propofol (Duncan et al. 2006). BIS, RE and SE have been found to detect different sedation levels reliably, however, variation in the performance between BIS and SE has been reported; in some of these studies BIS has been better, and in others SE, and in some studies there have been no differences between these two commercial indices (Ellerkmann et al. 2004, Schmidt et al 2004, Vanluchene et al. 2004a, Vanluchene et al. 2004b, Iannuzzi et al. 2005, Ellerkmann et al. 2006). When comparing propofol sedation with nitrous oxide sedation, SE and RE do not decrease when nitrous oxide is used (Andersson and Jakobsson 2004). In another study because of large intra- and inter-individual variability, neither BIS nor entropy were able to predict the sedation level (Haenggi et al. 2009). Studies in intensive care units with mechanically ventilated patients have given contradictory results too, a couple of studies have found good correlation between BIS, Entropy and sedation scores (Fraser and Riker 2005, Hernandez-Gancedo et al 2007, Karamchandani et al. 2010, Yaman et al. 2012) and in one study the correlation was poor (Walsh et al. 2008).

2.3. Effects of anesthetics and oxygen on EEG

2.3.1. Dexmedetomidine

Dexmedetomidine is a selective α_2-adrenoceptor agonist, which has sedative, anxiolytic and analgesic effects. It has minimal effects on respiratory and cardiovascular functions (Venn et al. 2001, Maze and Angst 2004). The sedative

effects of dexmedetomidine are mediated via the brain stem nucleus locus coeruleus. Is has an important role in the modulation of vigilance, and it has been shown to have the highest density of α_{2A}-adrenoceptors in the brain. The α_{2A}-subtype has been shown to be the primary mediator of the sedative properties of α_2- agonists (Scheinin et al. 1994, Aston-Jones et al. 1994, Lakhlani et al. 1997). In dexmedetomidine sedation, patients are can be aroused and are able to communicate if provoked by a loud verbal or light physical stimulus (Venn et al. 1999, Bhana et al. 2000, Venn et al. 2001, Ramsay and Luterman 2004, Cormack et al. 2005). High concentrations of dexmedetomidine lead to deep sedation, from which some of the subjects cannot be aroused by external stimuli (Hsu et al. 2004). Sedation induced by dexmedetomidine has been reported to mimic normal physiological sleep and endogenous sleep pathways have been shown to be involved (Nelson et al. 2003, Huupponen et al. 2008). The features mentioned above make dexmedetomidine almost an ideal sedative agent to be used in the ICU.

Infusion of dexmedetomidine increases the EEG power in the slow frequency bands; the largest increases are observed in the delta band with high concentrations of dexmedetomidine. A decrease in the high frequency beta power but no change in the low beta/alpha power has also been reported (Haenggi et al. 2006, Maksimow et al. 2007). When compared to normal sleep, dexmedetomidine causes spindles activity similar to physiological sleep spindles in N2 sleep (Huupponen et al. 2008). During epilepsy surgery, it is desirable that the EEG spike activity can be recorded despite anesthesia. When dexmedetomidine has been used in combination with sevoflurane, spike activity has remained unchanged during epilepsy surgery (Oda et al. 2007). In children dexmedetomidine have been compared to natural sleep, and the differences are increased powers in theta alpha and beta bands. It has also been found that dexmedetomidine does not affect the interpretation of the EEG (Mason et al. 2009). When dexmedetomidine sedation has been compared to midazolam sedation in children, fewer changes were seen in the EEG peak frequency and amplitude in dexmedetomidine sedation than in midazolam (Aksu et al. 2011).

2.3.2. Propofol

Propofol was introduced in 1986, and it soon became the most commonly used intravenous (i.v.) anesthetic agent. It can be used in anesthesia induction and during maintenance, and also for providing sedation in the ICU (Sneyd 2004). The sedative/hypnotic effects of propofol are mediated through the $GABA_A$ receptors (Ghiani et al. 1996, Trapani et al. 2000, Alkire and Haier 2001, Salmi et al. 2004). Rapid recovery and favorable operation conditions are the main advantages of propofol sedation (Trapani et al. 2000). It also has a few disadvantages: a reduction in blood pressure and a relatively high incidence of apnea. Also the injection can cause pain, which can be reduced by chancing the emulsion constitution (Trapani et al. 2000, Rau et al. 2001). In the ICU and during long-term infusions (>48h), also other problems can occur. The propofol solution contains triglycerides and in critically ill patients this can increase plasma triglyceride levels (Sneyd 2004). The most serious disadvantage is propofol infusion syndrome, including metabolic derangements and

organ system failure can even lead to death. It was first described in children, but has also been reported in adults. The mechanism of the propofol infusion syndrome is unknown, but it is usually related to high doses of propofol (5mg/kg/h) and long infusions (48h) (Bray 1998, Kang 2002, Diedrich et al. 2011).

Propofol infusion causes biphasic EEG effects. First, an increase in alpha and beta activity is seen, which is then followed by an increase in delta activity and simultaneous decreases in alpha and beta activities at deeper levels of anesthesia (Kuizenga et al. 2001, Koskinen et al. 2005). During anesthesia induction with propofol an increase in beta activity in the frontal EEG derivations spreading to more posterior regions is accompanied with a decrease in alpha activity and an appearance of delta activity in posterior regions. When the sedation deepens towards LOC, delta and theta powers increase also in the anterior brain regions (Gugino et al. 2001). An increase in $alpha_2$(10.25-12.5 Hz), low $beta_1$(12.75-20) and high $beta_2$(20.25-30 Hz) bands has been found with sedative doses of propofol, and with a larger concentration also an increase in the delta with almost no change in the theta power has been observed (Kishimoto et al. 1995). A high- density EEG study, with dense electrode array 256 electrodes, compared natural sleep to propofol anesthesia. At LOC slow waves appear, which resemble slow waves in natural sleep. However, the propofol induced slow waves are spatially blurred compared to the slow waves of sleep, and the propofol slow waves do not include spindles. Another finding is an increase in gamma(25-50 Hz) activity that persisted throughout LOC (Murphy et al. 2011). Propofol infusions are routinely used to treat status epilepticus, though propofol has also been shown to induce clinical seizure-like motor phenomena (San-Juan et al. 2010, Smith 2011), but these have not had EEG verification of epileptic activity (Jääskeläinen et al. 2003).

2.3.3. Sevoflurane

The volatile anesthesia agent sevoflurane was first synthesized in 1970, but it wasn't approved for clinical use until 1990. Sevoflurane is a halogenated methyl isopropyl ether and because it is volatile, its administration requires a special vaporizer. The sedative/hypnotic effects of sevoflurane are probably mediated via $GABA_A$-receptors (Salmi et al. 2004). However, volatile anesthetics influence also other recepors in the central nervous system; e.g., they potentiate inhibitory glycine receptors (Sonner et al. 2003), some anesthetics inhibit nicotine acetycholine receptors (Violet et al. 1997) and potentiate serotonin type 3 receptors (Parker et al. 1996). Activation of two-pore-domain potassium channels in thalamus caused hyperpolarisation and inactivation of this mechanism needed to arousal (Alkire et al. 2009). Sevoflurane enables fast anesthesia induction through inhalation, because the blood and brain are rapidly saturated and because it doesn't cause respiratory irritation. Absorption to slowly equilibrating tissues is minimal allowing fast recovery (Yasuda et al. 1991). The induced decrease in blood pressure is dose related, but in clinically relevant concentrations, sevoflurane preserves cardiac output, whereas a high concentration may lead to cardiovascular collapse. High concentrations also decrease ventilation leading to apnea (Patel and Goa 1996). In clinical use, during surgical anesthesia, sevoflurane is usually administered at end tidal (Et) concentrations of 2-3 %. The

MAC, i.e. the concentration at which 50% of a population does not react to a skin incision, for sevoflurane varies from 1.4% to 2.8% increasing with age (18 -85 years) (Eger 1994, Brown 1995, Mapleson 1996). Sevoflurane can also be used in ICU sedation at lower concentrations (approximately Et 0.6%) (Mesnil et al. 2011). Sevoflurane has been found to have cardioprotective effects in patients undergoing coronary surgery with cardiopulmonary bypass (De Hert et al. 2004).

The EEG effects produced by sevoflurane are typical to anesthesia agents. First comes a slowing, e.g. a decrease in frequency and an increase in amplitude, and when the concentration of the drug rises, the EEG changes towards burst suppression. With sevoflurane, just like with propofol, biphasic effects are seen: first an increase in alpha and beta bands, then a decrease in the same frequencies and an increase in delta activity. Frontal predominance of EEG activity occurs with deepening levels of sedation (Gugino et al. 2001, Kuizenga et al. 2001, Jäntti and Sloan 2008). Several studies have shown that sevoflurane can produce epileptiform spikes or even electrographic seizures and sometimes even clinical convulsions. There are studies showing dose-dependently increase in epileptic EEG activity at high concentrations (1.5-2 MAC) of sevoflurane in non-epileptic adults (Sato et al. 2002, Jääskeläinen et al. 2003). On the other hand, one study did not find any epileptic reactivity under similar conditions (Iijima et al. 2000). Mask induction with sevoflurane which leads to quick increase of MAC up to 2.0, have been shown to produce epileptic activity in both adults and children (Julliac et al. 2007, Sonkajärvi et al. 2009, Schultz et al. 2012). Hyperventilation during mask induction with sevoflurane have been associated to epileptic activity (Yli-Hankala et al. 1999, Vakkuri et al. 2000, Kurita et al. 2005).

2.3.4. Xenon

Xenon is a noble gas present in the atmosphere at a small, 1:20 000, concentration, and it is purified from air by distillation. Xenon was first used for anesthesia in humans over 60 years ago (Cullen and Gross 1951). Because it is rare and the manufacturing process is quite challenging and expensive, and because the 1.0 MAC for xenon is high, about 60% Et, its clinical use is limited. The anesthetic effects of xenon are mediated via the inhibition of N-methyl – D aspartate glutamate receptors and unlike most other anesthetic agents, Xenon does not affect the $GABA_A$- receptor system (Nagele et al. 2005, Salmi et al. 2008). Xenon provides good cardiovascular stability during anesthesia, and recovery from xenon anesthesia is very rapid (Goto et al. 2004, Coburn et al. 2005, Cremer et al. 2011, Schaefer et al. 2011, Neukirchen et al. 2012).

The effects of xenon anesthesia on the EEG were first described in 1955 by Morris et al. who found a decrease in alpha activity and an increase in slow wave EEG activity. Since then, a limited number of studies have been conducted in humans. Slow wave activity is most prominent in the posterior regions of the brain, and this phenomenon is different form the EEG effects of volatile anesthetics (Jäntti and Sloan 2008). In one study with three subjects, surgical levels of xenon produced increases in theta and gamma activity increases with no change in the delta band (Johnson et al. 2003).

2.3.5. Oxygen

The concentration of oxygen (O_2) in the air is 21%. Oxygen is necessary for (aerobic) life and all mammals breathe it in from the air. At high altitudes hypobaric hypoxia can cause mountain sickness, lung and cerebral edema (Hackett and Roach 2001). Athletes use hypobaric or normobaric hypoxemia to improve their oxygen intake. A hypobaric hypoxic condition is reached at an altitude of about 2000-2500m, and normobaric hypoxia conditions at normal altitudes by lowering the oxygen concentration. Neither of these conditions increases the risk for mountain sickness (Schommer et al.2012). Ventilation with normobaric hyperoxia is usually used in the ICU. Many studies in animals have show that hyperoxia causes lung injury, but limited data is available from studies in humans (Sinclair et al. 2004, Altemeier and Sinclair 2007) or its effects on brain function. Normobaric hyperoxia reduces heart rate and cardiac output and increases systemic vascular resistance. The effects on the heart may be secondary to changes in vascular resistance (Anderson et al. 2010). Hyperbaric hyperoxia is used in the treatment of many different cases, for example diving accidents (Sayer et al. 2009), carbon monoxide poisoning (Sinkovic et al. 2006) and some infections (Tsuneyoshi et al. 2001).

Hypobaric normoxia does not cause EEG changes, but hypobaric hypoxia causes a decrease in alpha activity and an increase in slow activity (Kraaier et al. 1988). Hyperbaric hyperoxia can cause seizures, but the incidence is quite low, only 2.4 per 100000. During hyperbaric hyperoxia increases in delta, theta and beta activity can be seen in the EEG. The seizures show typical generalized tonic-clonic EEG changes, but an increase in theta and a decrease in alpha activity can be seen before the seizures (Litscher et al. 1990, Visser et al. 1996, Yildiz et al. 2004). There are no data on normobaric hyperoxia or its potential harmful brain effects.

3. AIMS OF THE STUDY

The present study was designed to investigate the effects of four different anesthetic agents: dexmedetomidine, propofol, sevoflurane and xenon, on the electrical activity of the brain using EEG, BIS and Entropy monitoring. One aim was to look for possible differences in the neurophysiological activity between sedation/ consciousness and unconsciousness when using different anesthetic agents, and to find out if these different states could be assessed with methods based on the EEG. Another aim was to evaluate clinical implications and usefulness of processed EEG variables (qEEG, BIS, SE and RE) to predict unconsciousness when using different anesthetic agents. PET methodology was used to identify the specific brain areas where activation changes between consciousness and unconsciousness. Anesthesia induction using xenon requires denitrogenation with normobaric hyperoxia. The effects of this procedure on the EEG were studied to evaluate possible harmful brain effects of normobaric hyperoxia and to confirm that the qEEG changes during xenon anesthesia were caused by the drug alone.

Aim	**Publication**
1. To examine differences in EEG reactivity during sedation and at LOC with three different types of anesthesia agents; dexmedetomidine, propofol and sevoflurane	I
2. To find out, how reliably BIS and Entropy monitors can differentiate sedation from LOC.	II
3. To find out and locate changes in neural (brain) activation between the clinical stages of responsiveness and unresponsiveness.	III
4. To study the effects of xenon on raw EEG signal and quantitative EEG variables and to find out how BIS and Entropy monitors perform during xenon anesthesia.	IV
5. To investigate the possible harmful central nervous system effects of normobaric hyperoxia with quantitative EEG, and to evaluate its possible additive effects on the behaviour of qEEG variables during xenon anesthesia.	V

4. MATERIALS AND METHODS

4.1. Subjects

A total of 57 nonsmoking, right-handed healthy male volunteers participated in three studies (Table 4), which are referred to in the text by the study numbers 1a, 1b and 2. The original publications are referred to in the text by the Roman numerals I-V. Volunteers were recruited through advertisements for the study placed on bulletin boards around the Turku University Campus, or through e-mail. First, all interested candidates received an e-mail including detailed information about the study design, the aims of the study, and the study procedures. After reading the information volunteers were interviewed face-to-face. During the interview, the physician completed a questionnaire regarding the participants' general health, medications, previous operations and experiences with anesthesia.

The subjects had to meet all of the following inclusion criteria: male, age 18-30 years, American Society of Anesthesiologists (ASA) physical status I, right handedness and written informed consent. Exclusion criteria included chronic medication, history of alcohol/drug abuse, previous psychiatric disorder, nausea in connection with previous anesthesia, regular use of nicotine containing products, cardiac arrhythmia, blood donation 90 days prior to the study, a prior PET or single-photon emission computed tomography (SPECT) study (in studies 1b, 2), abnormality in pre-study laboratory tests, and any contraindication to a magnetic resonance imaging (MRI) study (in studies 1b, 2), which was done to all included subjects participating in the PET studies. For those subjects who met the tight inclusion criteria of the study, the study protocol, the dose of radiation (in studies 1b, 2) and other study related issues and risks were carefully explained. All subjects went through a detailed physical examination including auscultation of the heart, lungs and the abdomen, palpation of the abdomen, Allen's test to assure the collateral circulation of the palm via the ulnar artery (studies 1b, 2), estimation of any intubation difficulties, measurement of blood pressure and a 12-lead ECG. A laboratory screen was carried out on all subjects: blood samples for blood cell count, serum creatine, serum alkaline phosphatase, serum aspartate aminotransferase and serum alanine phosphatase and a urine sample for drug screening. Volunteers were informed about the right to discontinue at any point during the study.

Table 4. Characteristics of study subjects in the studies (1-2) and subsequent publications (I-V)

	STUDY 1a				
	STUDY 1b				STUDY 2
Study drug	Dexmedetomidine	Propofol	Sevoflurane	Xenon(Oxygen)	Xenon
N	10	10	10	10	17
Age (yr)	19-26	19-28	21-30	21-30	20-27
Height (cm)	172-183	177-190	171-186	173-198	170-193
Weight (kg)	60-88	66-92	62-84	64-94	67-100
Publication(s)	I,II, III	I, II, III	I, II	V	IV

4.2. Study designs

The Ethical Committee of the Hospital District of Southwest Finland and the National Agency for Medicine approved the study protocols. All studies had an open and non-randomized design.

In Study 1a, EEG, BIS and spectral entropy were continuously recorded starting from the awake state (resting eyes closed) to the LOC and ending in the regaining of consciousness (ROC) during an increasing concentration of dexmedetomidine (n=10), propofol (n=10) and sevoflurane (n=10). Each concentration was maintained for 10 minutes (min). The concentration for dexmedetomidine was 1.0 ng ml^{-1} to start with and was increased first 0.5 ng ml^{-1} and then 0.25 ng ml^{-1} until LOC was reached (i.e. 1.0-1.5-1.75-2.0 etc ng ml^{-1}). Propofol concentrations started from 1.0 μg ml^{-1}, the first increase was 0.5μg ml^{-1} and following increases were 0.25 μg ml^{-1} until LOC was reached (1.0-1.5-1.75-2.0 etc μg ml^{-1}). Sevoflurane was started at a concentration of 0.5 % Et and increased 0.25 % Et until LOC was reached (0.5-0.75-1.0 etc %Et). The results from study 1a are reported in I and II.

In Study 1b, the same subjects from the dexmedetomidine (n=10) and propofol (n=9, because of problems with PET-scanner and the subject was rejected) groups in study 1a were sedated again, about one month later, using an individually defined concentration of the same drug, which was used to produce LOC in study 1. Drug concentrations were started at 50 % of the concentration needed to produce LOC, and increased 25 % using approximately 12 min intervals until LOC was reached. Regional cerebral blood flow was measured at each concentration using positron emission tomography and ^{15}O- labeled H_2O as the PET tracer. The results from this study are reported in III.

In study 2, BIS and Entropy (n=17) and EEG (n= 8) were studied at 1.0 MAC xenon anesthesia. Data collection was started at the awake state and continued through LOC to ROC. The results of this study are reported in IV.

In study 1a, the effects of normobaric hyperoxia to the EEG were studied in subjects (n=10) breathing 100% oxygen with a tight face mask during one hour. EEG was collected throughout the period. After this denitrogenation, anesthesia was induced with xenon. Xenon induction causes agitation, and for that reason we did not get any artifact free EEG, BIS or Entropy data. The results of this study are reported in V.

All subjects in studies 1a and 1b were interviewed twice, just after the emergency form anesthesia and 10-30 min later. Results of these interviews have been reported in Noreika et al. 2011. Also heart rate variablility dynamics for propofol and dexmedetomidine in stydy 1a have been reported. (Tarvainen et al. 2012).

4.3. Sedation and monitoring

All subjects were instructed to avoid alcohol use or any medication for 48 hours, and to fast from midnight prior to the beginning of the study. The subjects received no pre-

medication. The radial artery (in study 1b and 2) was cannulated for arterial sampling and one or two forearm veins were cannulated for drug administration (studies 1a, 1b, 2), $H_2{}^{15}O$ PET tracer boluses (studies 1b and 2) and Ringer' solution (studies 1a, 1b) or NaCl 0.9% (study 2) infusions were used to keep the i.v. line open.

ECG and peripheral oxygen saturation were recorded throughout the studies. The noninvasive blood pressure was measured at the beginning and the end of the study in studies 1a and 1b, and throughout the study in study 2. Invasive blood pressure, muscle relaxation (train-of-four) and nasopharyngeal temperature were measured in study 2. End-tidal (Et) carbon dioxide (CO_2) and Et sevoflurane concentrations were measured in study 1a. For all these measurements, a GE Datex-Ohmeda S/5 anesthesia monitor (GE Healthcare, Helsinki, Finland) was used, and parameters were recorded automatically every 10 s with the S/5 Collect software (GE Healthcare, Helsinki, Finland). The partial pressures for arterial oxygen and CO_2, were measured using a portable blood-gas measurement device (i-STAT, Abbot Laboratories, Birmingham, U.K.) (studies 1b and 2) and blood samples for measuring drug concentrations in the blood were taken (study 1b). Airway pressure, concentrations of O_2, CO_2 and xenon (study 2) in the ventilation circuit were recorded during anesthesia with a closed-loop anesthesia ventilator (PhysioFlex, Dräger, Lübeck, Germany).

In study 1a, dexmedetomidine (Precedex 100 μg ml^{-1}, Orion, Espoo, Finland) was administrated i.v. using a target-controlled infusion scheme aiming at increasing pseudo-steady-state plasma concentrations at 10 min intervals. A Harvard 22 syringe pump (Harvard Apparatus, South Natick, MA, USA) connected to a portable computer running the Stanpump software (available at http://anesthesia.stanford.edu/pkpd/) and the pharmacokinetic parameters of Talke et al. were used (Talke et al. 2003). Propofol (Propofol Lipuro 10 mg ml^{-1}, B. Braun Melsungen AG, Pfieffewiesen, Melsungen, Germany) was administrated i.v. with the same infusion system and scheme as dexmedetomidine, using the Marsh et al. pharmacokinetic model (Marsh et al. 1991). Sevoflurane (Sevorane, Abbot, Scandinavia AB, Solna, Sweden) was administrated by inhalation using a tight facemask and a calibrated sevoflurane vaporizer with online %Et sevoflurane measurement. Throughout study 1a, consciousness was tested by requesting the subjects to open their eyes and the motor response (eye opening) was considered a meaningful response compatible with consciousness. Consciousness was tested at 5 min intervals at each drug concentration (i.e. at 4 and 9 min of each 10 min level) until LOC and thereafter at 1 min intervals after the drug administration was discontinued. LOC was defined as unresponsiveness to the request and sedation (SED) as the last meaningful response (i.e. 5 min before the LOC-testing indicating unresponsiveness). ROC was defined as the first meaningful response to the request after the study drug was discontinued.

In study 1b, the same subjects from the dexmedetomidine and propofol groups in study 1a got the same drug again with the same infusion system. Infusions were started at 50% of the individual predetermined concentration for LOC in the study 1a. Infusions were increased with 25% at 12 min intervals until LOC was reached if necessary over the drug concentration needed to LOC in study 1a. LOC was tested 8

min after the infusion was started or increased. PET-scanning was started 2 min after LOC testing. In the dexmedetomidine group, infusion was continued after LOC at the same level and ROC was achieved through gentle touch and verbal stimulation, after which a PET-scan was taken. After this, the infusion was continued and subjects were allowed to lose consciousness again, and a LOC II PET scan was taken. In the propofol group, infusion was terminated after the LOC scan and consciousness was tested at 1 min intervals. The ROC scan was taken once consciousness was regained.

In study 2, subjects breathed 100% oxygen through a tight 5 cmH_2O continuous positive airway pressure-mask for one hour for denitrogenation. After that, subjects were told to hold their breath to avoid breathing any room air while the pressure mask was changed to a tightly fitting regular face mask connected to the closed loop anesthesia ventilator. After that, induction with xenon was carried out by changing the inhalated O_2 concentration from 100% to 25% thus letting the xenon concentration in the gas mixture rise. The subjects continued breathing spontaneously via the face mask. After loss of consciousness, muscle relaxation was induced by administering a 0.8 mg /kg bolus of rocuronium (Esmeron 10mg/ml, Organon, Helsinki, Finland) and endotracheal intubation was performed when muscle relaxation was achieved. After approximately two hours, which was the time required for the PET scans, xenon administration was discontinued and the muscle relaxation was reversed with a combination of neostigmine and glycopyrrolate (Robinul-Neostigmine, Wyeth Lederle, Helsinki, Finland). Subjects were extubated as they regained spontaneous breathing and consciousness. The first two subjects were given anti-emetics for nausea. Thereafter, anti-emetics were given prophylactically prior to the discontinuation of xenon. The anti-emetics included dehydrobenzperidol (DHBP 1.25mg/ml, OTL Pharma, Paris, France), dexamatasone (Oradexon 5mg/ml, Organon, Helsinki, Finland) and ondansetron (Zofran 2 mg/ml, GlaxoSmithKline, Helsinki, Finland).

4.4. Recording of cortical EEG effects

4.4.1. EEG, BIS and Entropy monitoring

EEG was recorded continuously using a Galileo (Medtronic, Florence, Italy) EEG acquisition system. The recordings were made with standard International 10/20 Electrode Placement System locations (linked mastoid reference) using ElectroCap (Electro-Cap International, inc Eaton, Ohio, USA) with Ag-AgCl electrodes. Electrode impedances were kept below 2 kΩ. The sampling rate was 256 Hz and the signals were band-pass filtered with a 0.1-70 Hz frequency range. Eye movements, ECG, sub-mental EMG and breathing movements were recorded with four channels for detection of artifacts (Study 1a).

In study 2 (n=8), an eight-channel EEG was continuously recorded throughout the study. Digital EEG equipment GE Datex-Ohmeda S/5 EEG Module, M- EEG (GE Healthcare, Helsinki, Finland), Ag-AgCl electrodes and the International 10/20 Electrode Placement System were used. The bipolar montage included the F4 – C4, F3 – C3, T6 – O2 and T5 – O1, derivations covering the midfrontal-central and posterior temporal-occipital regions of both hemispheres. The skin was prepared to keep the

electrode impedance under 5 kΩ, and the electrodes were fixed with Grass electrode paste (Astro-Medical; Grass Instrument Division, W. Warwick, RI, USA). The digital sampling frequency was 100 Hz and the pass band of the EEG module was 0.5 – 30 Hz.

The skin of the forehead was cleaned with an alcohol swab and disposable EEG electrode strips for recording BIS (BIS XP, algorithm version 4.0, smoothing rate 15 s, Aspect Medical systems) and spectral entropy (GE Datex-Ohmeda S/5 Entropy Module, GE Healtcare) were positioned on the forehead as recommended by the manufactures. The positioning of the electrodes is shown in figure 3. The side of the forehead for BIS and Entropy strips was randomized. BIS and Entropy indices were recorded at 10 s intervals with a portable computer running the S/5 Collect software.

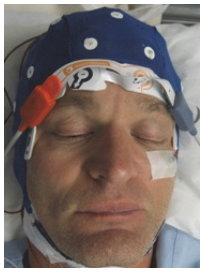


Figure 3. BIS and Entropy strip electrodes placed on the forehead. The picture is published with the permission of the subject.

4.4.2. Processing of the EEG signal

In all studies, the raw EEG signal was first visually analyzed off line by an expert in clinical neurophysiology, professor Satu Jääskeläinen (S.J.). In publication I, the original EEG channels were re-referenced to a Hjort type reference, the average of the four nearest electrodes source derivation, for example F3-F3'=F3-(Fp1+Fz+C3+F7)/4. Standard short-time Fourier transformation was applied to all EEG derivations for both reference systems (MATLAB function spectrogram). Based on subject-by-subject visual inspection of the raw EEG signal and the derived spectrograms (time frequency plots) by an expert in clinical neurophysiology (S.J.), the F3 and F4 electrodes with Hjort reference were selected for further analyze. During this part of the analysis, several types of EEG artifacts were also detected. The artifacts were not individually processed in order to preserve the continuity of the signals, and not to distort the time-frequency resolution in further analyses. Prior to a Kalman smoother spectral estimation, the signals were down-sampled to 90 Hz. Explanations for Kalman smoother spectrum estimations of non-stationary EEG as well as comparisons with traditional approaches have been described before (Tarvainen et al. 2004). For selected midfrontal EEG channels, spectral estimates were obtained with a Kalman smoother based methodology aiming towards optimal time-frequency resolution. A time-varying autoregressive (TVAR) model was used and estimates of the parameters were obtained with a Kalman smoother algorithm. Using the obtained non-parametric special estimates as a side reference, the following selections were made: AR model order p=22, update coefficient $UC=5\cdot10^{-6}$. Next, nearby parameters were averaged

resulting in a time resolution of 1 s. Time-varying power spectra were then obtained as in the ordinary stationary methodology, i.e. AR parametric spectrum estimation, from the momentary parameter estimates and the estimated variance of the signal. Finally, band powers were calculated for delta (0.5-4 Hz), theta (4.1-8 Hz), alpha-slow beta (8.1-15 Hz) and high beta (15.1-30 Hz) EEG frequency bands. Finally the obtained EEG band powers where logarithmically transformed to decibels (dB) before statistical analyses.

In publication IV, raw EEG data was visually analyzed by an expert in neurophysiology (S.J.), and artifact contaminated EEG segments were excluded from raw EEG visually. The epoch length was 4 s. All EEG variables were calculated from the baseline before xenon administration (6-184 epochs) and steady state anesthesia (74-75 epochs). EEG data was processed with Matlab 6.5 (The Mathworks Inc. Natick, MA, USA). Absolute power spectra (μV^2/Hz) of each epoch were obtained with the psd –function of Matlab. The psd –function utilizes fast Fourier transformation with Hanning –windowing. Power spectra from individual epochs were averaged to obtain final power spectra for each analysis period. Absolute band powers (μV^2) were calculated from the power spectra in the following bands: delta (1.0-3.2 Hz), theta (3.5-8.0 Hz), and alpha (8.2-13.0 Hz), beta (13.2-30 Hz), total power (1.0-30.0 Hz). Additionally, SEF95 from a frequency range of 1.0 – 30.0 Hz was calculated. The relative power (%) for each band was calculated by dividing the power in each frequency band by the total power.

The EEG in publication V was collected from resting subjects with their eyes closed. After the removal of artifacts by a specialist in clinical neurophysiology (S.J.), EEG derivations F3, F4, T3, T4, C3, C4, P3, and P4 with linked ears reference were selected for quantitative analysis. The EEG signal was further processed using commercial software (Insight II, Prism, Spectrum, Averaged developed by Persyst Development corporation Prescott, AZ 86305 USA) to estimate the Power Spectral Density of a discrete-time EEG –signal using Welch's averaged, modified periodogram method. QEEG variables were calculated for the baseline (1 min period before oxygen breathing) and oxygenation (1 min period after approximately 1 hour 100% oxygen breathing). Artifact free 4 sec epochs form these periods were accepted for a power spectral analysis. Power spectra from individual epochs were averaged to obtain the final power spectral for both periods. Absolute EEG power (μV^2) was calculated from the total power spectrum (0.30.0 Hz), and separate band- powers for the following frequency bands: delta (0-3 Hz), theta (3.25-7.75 Hz), alpha (8-13 Hz), beta (13.25-25 Hz) and gamma (25.25-30 Hz).

In publication II, the BIS and Entropy values were the average of three values around 30 s before consciousness was tested. The awake values were averages of three values after a 1 min baseline registration. In publication IV, the BIS and Entropy values were single values at awake, time points 1, 2, 3, and 4 min after LOC, during steady state anesthesia and after ROC. Sensitivity and specificity were calculated into pooled data over all subjects during two periods, first during 5 min before and after LOC and similarly before and after ROC.

4.5. Positron Emission Tomography (PET)

In publication III**,** a previously described PET procedure for measuring rCRF was used (Kaisti et al. 2002). Scans were obtained with an ECAT EXACT HR+ PET scanner (Siemens/CTI) and [^{15}O]H_2O (300 MBq) was used as the tracer. The tracer was administered as a 15 s bolus infusion followed by a 90 s List Mode activity acquisition in three- dimensional (3D) mode. Arterial blood activity was measured using a peristaltic roller pump and a bismuth germanate (BGO) crystal detector system (Allogg) cross-calibrated with the scanner. All [^{15}O]H_2O scans were corrected for detector dead time, tracer decay, and measured tissue photon attenuation, and reconstructed into a 128x128 matrix using a 3D transsaxial Hann filter with a 4.6 mm cutoff. The field-of-view was 30 cm, resulting in a pixel size of 300 mm/128= 2.34 mm. Photon attenuation in the tissue was taken into account according to transmission scans obtained using three external circulating germanium-68 (^{68}Ge) rod sources. Individual 1.5 T MRIs were acquired for neuroanatomy (Gyroscan Intera CV Nova Dual; Philips Medical Systems).

[^{15}O]H_2O images were computed into quantitative parametric rCBF images using arterial blood tracer activity data and tracer kinetic modeling (Kaisti et al. 2002). Images were then realigned, coregistered, and spatially normalized to the Montreal Neurological Institute space using the processing routines implemented within the Statistical Parametric Mapping (SPM) software package (SPM-8; Wellcome Department of Cognitive Neurology, University College London, England; available at www.fillion.ucl.ac.uk/spm) running under MATLAB 2009b (Math-Works). All normalized PET images were smoothed using an isotopic Gaussian kernel of 12 mm full-width at half-maximum.

Images were analyzed for overall patterns of condition-related rCBF changes using partial least-squares (PLS) software (PLS-software;http://www.rotman-baycrest.on.ca/index.php?section=84). PLS is a multivariate analysis technique used to detect optimal covariation between brain voxel-values and the experimental design (Lobaugh et al 2001, Lin et al. 2003). A mathematical description of the method has been given in detail previously (McIntosh et al 1996, McIntosh and Lobaugh 2004).

Analyses focused on four primary issues. First, brain areas that changed their function with the changing state of consciousness, independent of drug effects were indentified. Three scans (LOC, ROC and LOC-2) obtained from the dexmedetomidine group (n=8, due to one missing and one damaged scan) were analyzed. Second, as having been suggested that the anesthesia-induced change in consciousness is related to changing functional connectivity within the frontoparietal network (Imas et al. 2005, Alkire et al. 2008, Boveroux et al. 2010, Boly et al. 2011, Ku et al. 2011), changes in parietal functional connectivity between the ROC and the LOC-2 scans of the dexmedetomidine group were assessed using seed PLS (McIntosh et al. 2003). These particular scans were the least influenced by changes in drug levels or extemporaneous stimulation effects. Third, to understand the generalizability of the results across agents, the four scans (baseline, SED, LOC, ROC) obtained from the propofol group

were analyzed for propofol-induced effects on consciousness (n=9, due to a missing scan). Fourth, a combined analysis of the propofol and the dexmedetomidine groups was performed to reveal the condition-related (rather than drug-specific) effects on consciousness (n=17).

4.6. Statistical analysis

Repeated measures of the analysis of variance model and then multiple paired t-tests were used for the analysis of statistical differences in qEEG variables (I). No change in verbal stimulation was used as a null hypothesis at a single time point compared to a reference. Average band powers (over 10 s length ending 10 s before LOC testing) for the EEG channel and each subject were used as a reference. Single time points (-9,-8,..60 s; total number of points 70) were proportional to each LOC testing. False discovery rate (FRD) (Benjamini and Hochberg 1995) was used for the correction of multiple comparisons, drug, EEG channel, EEG band and LOC- testing, 5040 computations with two sided paired t-tests. These were done in Matlab (The MathWorks Ind., Natic, MA, USA). In publication IV, log-transformed qEEG variables were analyzed with the repeated-measures of the analysis of variance model, condition (baseline/anesthesia) and derivation (frontal/occipital) as the within factors. In publication V, side (left/right), (F3,F4,C3,C4,P3,P4,T3,T4) and time (before and after oxygenation) as within-factors. The Bonferroni correction was used for multiple comparisons. Statistical analyses were done with SAS EG (version 8.2 (IV) and version 4.1 (V); SAS Institute Inc., Cary, NC, USA).

In publications II and IV, the performance of BIS and Entropy was analyzed by calculating Prediction probability (P_K). It was used to describe how reliably these indices can differentiate unconsciousness form consciousness or different states of anesthesia. P_K values show the reliability of these indices, value: 0.5 means that there is a 50/50 chance of differentiating the two states and value 1 means that these indices always predict the state correctly. The Jack-knife method were used to estimate P_K and its standard error, based on the assumption that all assessments were independent. The responsive states SED and ROC were pooled together and the unresponsive state represents LOC. Also P_K –values were calculated between the awake and LOC (II). In publication IV LOC and ROC were selected as reference points for the P_K analyses. P_K analyses were done with Excel 2000 (Microsoft Corporation, Redemond, WA, USA) using a spreadsheet macro, P_KMACRO (Smith et al. 1996). A Bonferroni corrected paired t-test was used to evaluate differences between P_K values at different states. For statistical analyses in publication II, Matlab version 6.5 and Matlab Statistical Toolbox version 4.0 were used (The MathWorks Inc., Natick, MA, USA), and in publication IV, SAS (version 8.2; SAS institute INC., Cary, NC, USA).

For PET data in publication III, permutation tests (McIntosh et al. 1996) were used and 1000 permutations were computed to define the statistical significance of each latent variable (LV) arising from the PLS analyses. A bootstrap estimation of the standard error (SE; 1000 iterations) was used to define the reliability of the identified priority. This provides evidence of the stability of the findings rather than simply demonstrating the effect (McIntosh and Lobaugh 2004). Voxels with priorities >3.3

times their standard error (corresponding to an approximate $p< 0.001$ on a two tailed normal distribution) were considered reliable. In PLS, correcting for multiple-comparisons is not necessary.

P values less than 0.05 were considered statistically significant. Values are presented as the mean (standard deviation(SD)), unless otherwise stated.

5. RESULTS

5.1. Drug concentrations required to induce unconsciousness

In study 1, dexmedetomidine target concentrations needed to produce LOC varied between 1.5-2.5 ng ml^{-1} and the mean (SD) concentration was 1.93 ng ml^{-1}(0.37) (I,II). The subjects received the same drug in study 1b, and only in three of ten subjects LOC was reached at the same concentration as for the first time. Five subjects needed a 25% higher concentration and one subject needed a 50% lower concentration for LOC than in study 1a (III). In study 1b, the targeted mean concentration of dexmedetomidine was 2.1 (0.6) and measured mean concentration 53% higher (varying between 10 - 88 %) at 3.2 (1.3) (III). In study 1a, the propofol target concentrations needed to induce LOC varied between 1.75-3.25 μg ml^{-1} and the mean (SD) concentration was 2.2 μg ml^{-1} (0.56) (I,II). The same subjects (n=9, due to a missing scan) received propofol again in study 1b; six subjects reached LOC at the same concentration, two needed 25% less and one needed 25% more propofol than in the first study (III). The targeted mean (SD) concentration was 2.19 (0.61) and the measured mean concentration 1.79 (0.58) was 18% lower than targeted concentrations (varying between -32% to 9%) (III). In study 1a, the sevoflurane concentrations needed to reach LOC varied between 0.75 -1.5 % Et. The mean concentration was 0.93 (0.26) (I, II). In xenon anesthesia the mean concentration to induce LOC was 66.4 (2.4) % Et (IV).

5.2. Effects of dexmedetomidine, propofol, sevoflurane and xenon on EEG

Dexmedetomidine, propofol and sevoflurane caused increases in all measured band powers from awake to LOC (Table 5), except sevofurane in the theta band. Further increases were seen from SED to LOC in the delta band with dexmedetomidine and sevoflurane. In addition, the theta increase was seen with dexmedetomidine and propofol, and an increase was seen in the alpha-slow beta band with propofol and sevoflurane. From LOC to ROC, decreases were seen in the alpha-slow beta band with dexmedetomidine and propofol (I). During steady state xenon anesthesia, increases were seen in both the midfrontal-central (F4-C4) and temporo-occipital (T6-O2) derivations, in total ($p<0.001$) and delta ($p <0.001$) and theta ($p<0.001$) powers. The alpha power increased in the midfrontal-central area ($p=0.030$) (IV).

EEG reactivity to verbal stimulation at SED level was seen with all drugs and almost all bands; only with sevoflurane a beta band reaction was not seen (Figure 4). Biphasic reactivity was seen with dexmedetomidine in the delta band and with propofol in the alpha-slow beta band (Figure 4). At LOC, the reactivity to verbal stimulation was much less prominent, but was still seen with dexmedetomidine as an increase in the delta band on the left side. With propofol, reactivity was seen as an increace in the delta band, and a delayed increase in high beta and a decrease in the theta bands were detected (Figure 4). With sevoflurane, the reactivity was minimal at LOC. At ROC, verbal stimulation caused increased power in all bands with dexmedetomidine and biphasic effects in the delta and theta bands. Beta arousal was seen with propofol (an

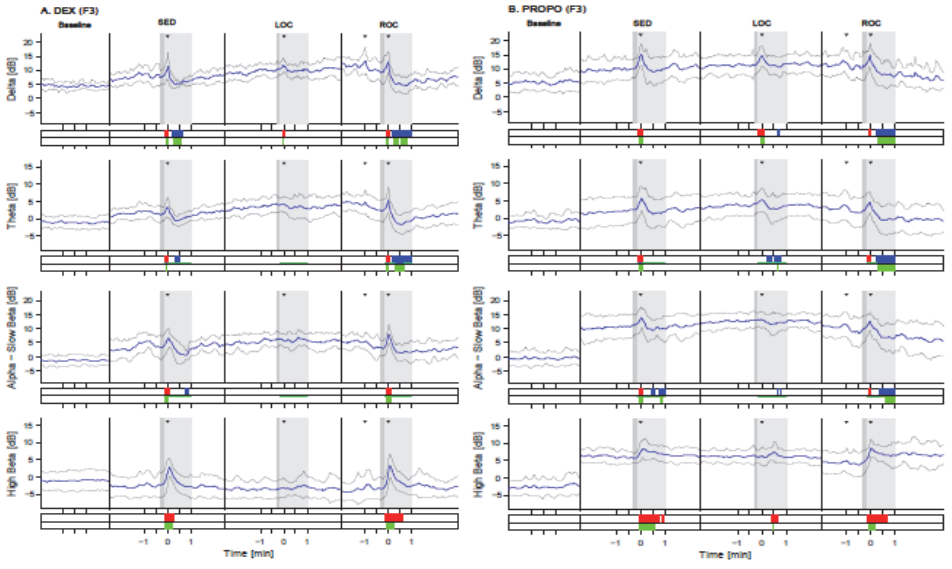
increase in high beta and a decrease in lower frequencies). With sevoflurane, a biphasic effect was seen in the delta band, and an increase in the activity of all bands was detected. (Figure 4) (I).

Table 5

EEG band powers (dB) at different levels of dexmedetomidine, propofol or sevoflurane anesthesia.

	AWA		SED		LOC		ROC		ANOVA p
EEG Band	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Dexmedetomidine									
Delta	4.20*	(1.31)	7.60*	(2.52)	10.35	(2.31)	9.38	(3.90)	<0.001
Theta	-1.07*	(1.97)	1.31*	(2.12)	4.05	(2.21)	2.31**	(3.15)	<0.001
Alpha – Slow Beta	-1.23*	(2.01)	3.32	(4.10)	6.23	(2.55)	3.05*	(2.62)	<0.001
High Beta	-1.13*	(3.00)	-2.26	(3.59)	-3.55	(2.54)	-3.41	(2.94)	0.038
Propofol									
Delta	5.45*	(2.87)	10.27	(3.16)	11.50	(3.33)	11.26	(4.80)	<0.001
Theta	-1.29*	(1.50)	2.35*	(3.72)	4.17	(2.98)	2.42	(3.95)	<0.001
Alpha – Slow Beta	-0.73*	(2.13)	11.28*	(3.60)	13.11	(2.65)	10.05*	(4.50)	<0.001
High Beta	-2.65*	(2.96)	5.70	(1.41)	6.21	(2.22)	4.64	(3.24)	<0.001
Sevoflurane									
Delta	3.43*	(4.06)	4.99*	(4.08)	8.32	(3.93)	7.66	(2.78)	0.002
Theta	-1.01	(2.33)	-0.61	(5.48)	0.74	(5.61)	-0.17	(2.88)	0.65
Alpha – Slow Beta	0.30*	(2.61)	1.99*	(4.16)	5.71	(4.11)	5.10	(3.49)	<0.001
High Beta	-2.64*	(1.60)	4.72	(3.12)	5.23	(1.95)	3.60	(3.86)	<0.001

Band powers (dB) for channel F3 (there were no differences between sides), group means (SD), for AWA (awake, no drug, eyes closed, duration 10 seconds, at the middle of Baseline, see Fig. 2), SED, LOC and ROC (duration 10 seconds, ending 10 seconds before LOC-testing, see Fig. 2 dark gray areas). Repeated measures ANOVA (p-values, channel F3). Paired t-tests for: AWA to LOC, SED to LOC, ROC to LOC. Statistical significant changes (FDR q=0.05, p<0.026)*, with p<0.05 (uncorrected) **.(Publication I)



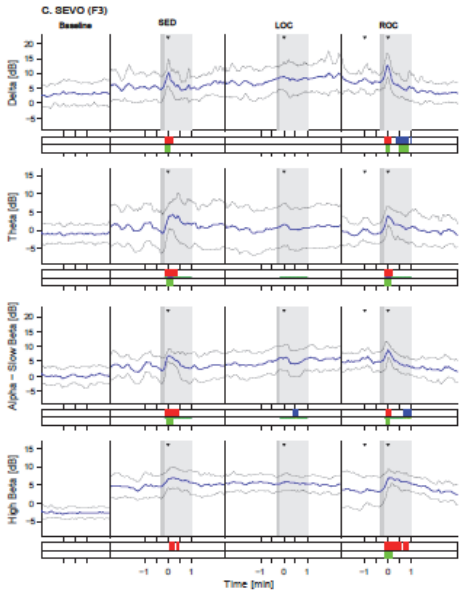


Figure 4 Band power changes at around verbal stimulation. Band powers in decibels (dB), mean (blue lines) ± SD (black lines), channel F3 (Hjorth reference) for A dexmedetomidine (DEX, n=10), B propofol (PROPO, n=10), and C sevoflurane (SEVO, n=10). Delta = delta (0.5-4 Hz), Theta = theta (4.1-8 Hz), Alpha = alpha - slow beta (8.1-15 Hz), and Beta = high beta (15.1-30 Hz). Black markers ▼ indicate verbal stimulation. Gray areas indicate reference periods (dark) and testing periods (light). Statistically significant increases (red) and decreases (blue) for p<0.05 (uncorrected) based on two sided paired t-tests. After FDR corrected are seen green p<0.0095.(Pubilcation I)

5.3. Effects of dexmedetomidine, propofol, sevoflurane and xenon on BIS and Entropy

Dexmedetomidine, propofol and sevoflurane decreased both BIS and Entropy index values at LOC compared to the awake state. Also P_K values were good when the awake state was compared to LOC. But when comparing the responsiveness states (SED and ROC) to unresponsiveness (LOC), P_K values were relatively low (table 6). Despite wide variability between the subjects (Figure 5), the changes from SED to LOC were statistically significant with all of the drugs in the BIS indices and in SE with dexmedetomidine and propofol. The only significant increases in these indices form LOC to ROC were seen with propofol in both BIS and SE (II).

Index values from BIS and Entropy monitors in xenon anesthesia were low, median values (BIS 26, SE 18 and RE 18) were comparable with deep anesthesia. Prediction probabilities to separate awake from LOC were low (BIS 0.46, SE 0.66, RE 0.62). Other P_k values were near or exactly 1; for LOC vs intubation (1), for intubation vs deeper anesthesia (0.82- 0.88) and anesthesia vs ROC (0.89-1) (IV).

Table 6. Prediction probability (P_K) (standard error) for Bispectral index (BIS), State Entropy (SE) and Response Entropy (RE) with different drugs.

	BIS	SE	RE
Responsiveness (SED, ROC) and LOC			
Dexmedetomidine	0.62 (0.11)	0.58 (0.12)	0.59 (0.12)
Propofol	0.73 (0.10)	0.72 (0.10)	0.72 (0.10)
Sevoflurane	0.70 (0.11)	0.52 (0.12)	0.62 (0.11)
Awake and LOC			
Dexmedetomidine	1.00 (0.00)***	0.97 (0.03)***	0.95 (0.05)***
Propofol	1.00 (0.00)***	1.00 (0.00)***	1.00 (0.00)***
Sevoflurane	1.00 (0.00)***	0.89 (0.08)***	0.97 (0.03)***

***P_K value differs from 0.5 ($p<0.001$). No other statistically significant ($p<0.05$) differences between two indicators or between indicator and P_K = 0.5 were observed after Bonferroni correction (k=3). SED = last testing event when the subject still responded; LOC = Loss of consciousness, i.e. first testing event when the subject did not respond; ROC = return of consciousness, i.e. first testing event when the subject responded after drug administration was terminated; Awake = baseline after one min of the start of data registration. (Puplication II) (Reprinted with permission of the copyright holder)

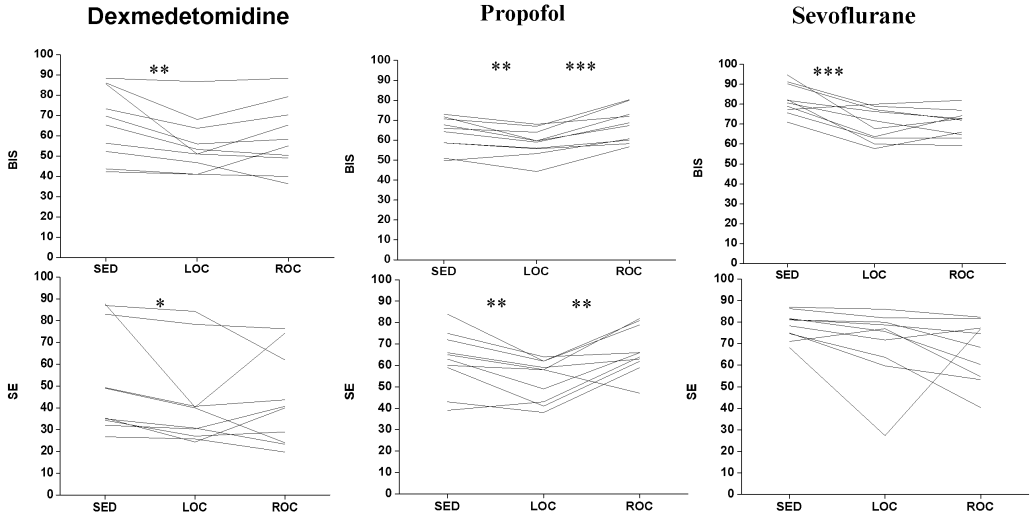


Figure 5 Individual BIS and SE values during SED (i.e. last meaningful response), LOC (i.e. the first event when the subject no longer responded), and ROC (i.e. the first meaningful response after discontinuation of the study drug) for all three drugs. Paired t-test statistics (SED vs LOC and LOC vs ROC) are presented with asterisks (* P< 0.05, **P<0.01, ***P<0.001) (Publication II) (Reprinted with permission of the copyright holder)

5.4. Regional cerebral blood flow in the emergence of consciousness

Using the same infusion rate of dexmedetomidine that caused LOC, consciousness was restored by touching and with verbal stimulation in all subjects. Increased activation level, which was seen as an increase in rCBF in PET scans was detected in

the following brain areas: the anterior cingulate cortex (ACC) ($p<0.001$), the median frontal lobe ($p<0.001$), the midline thalamus ($p<0.001$), the hypothalamus ($p<0.001$), the locus coeruleus/parabrachial area of the brainstem ($p<0.001$), the cerebellum ($p<0.001$) and in portions of the lateral orbital frontal ($p<0.001$) and parietal lobes ($p<0.001$). With propofol, ROC was reached after the infusion was terminated. Significant increases in activation were seen in the anterior arousal networks of the thalamus ($p<0.001$), brainstem ($p<0.001$), hypothalamus ($p<0.001$) and the dorsal AAC ($p<0.001$) and also in the precuneus/posterior cingulate region ($p<0.001$). Propofol induced even less neocortical activation than dexmedetomidine.With dexmedetomidine, functional connectivity was studied in conscious but sedated (ROC) and in unconscious state (LOC-2). The inferior parietal cortex was functionally connected with ACC and other frontal regions more in conscious state compared with the unconscious state. In the combined analysis of arousal from unconsciousness, dexmedetomidine and propofol groups were combined together. Activation was seen in the thalamus ($p<0.001$), hypothalamus ($p<0.001$), locus coeruleus/parabrachial area ($p<0.001$) and ACC ($p<0.001$). (III)

5.5. Effects of hyperoxia on EEG

After one hour of oxygenation a slight increase in delta power in frontal and temporal EEG derivations was observed. In addition, a minor decrease was seen in the posterior derivations in the alpha band. None of these changes that may have been related to slight decrease in vigilance were significant. No epileptiform activity or other focal or generalized abnormalities during or at the end of the one hour oxygenation were detected in a visual off-line analysis of the EEG by an expert in clinical neurophysiology (S.J.).(V)

6. DISCUSSION

6.1. Methodological aspects

6.1.1. Study design

In studies 1a and 1b (I,II,III) we did not use any sedation scales to measure the level of sedation. Therefore, we could not compare the sedation level to any clinically used scales. We only used a verbal command to ask the subjects to open their eyes, because we wanted to disturb the subjects as little as possible. For the same reason we measured the subjects' blood pressure only at the beginning and end of these studies. In studies 1a and 1b, we wanted to induce unconsciousness, not deeper sedation. Had we tested or disturbed the subjects more, higher drug concentrations might have been needed to induce unconsciousness. All external stimuli can induce changes in the EEG and may influence it for an extensive period of time. In study 1a (I,II), we increased the drug concentrations with small amounts at 10 min intervals to determine the individual drug concentration needed to LOC for each subject, and we tested the consciousness twice during these steps. We defined unconsciousness as the lack of a motor response (=eye opening), when the subject was asked to open his eyes. Consciousness was lost, according to this criterium, somewhere between the two consecutive tests. In study 1b (III), we used the previously assessed individual concentrations of dexmedetomidine and propofol to reach LOC. Consciousness was tested after 8 min from the starting of the infusion or after the target drug concentration was increased. PET scans were performed two min after the LOC-testing, because we didn't want the possible disturbance caused by the testing to influence the scan result. This two min period was determined after a visual EEG analysis, by an expert in clinical neurophysiology, off-line from the raw EEG signals in study 1a. After two min, all EEG-disruptions caused by the testing at LOC had disappeared from the EEG.

Study 2 (IV) on xenon anesthesia, consisted of two parts and in both studies PET scans were performed in addition to EEG, BIS and Entropy monitoring. Xenon anesthesia was induced via a tight face mask and after LOC, muscle relaxation was induced and intubation performed after relaxation. Consciousness was tested in 10 s intervals before LOC and ROC. Agitation and the subjects' movements at induction caused artifacts in the EEG. Also the induction procedure itself and testing at 10 s intervals may have caused disruptions in anesthesia depth indices and in the EEG signal. These protocols were designed primarily for PET studies and thus, the conditions were not ideal for EEG recording.

BIS and Entropy data were collected throughout the studies. The strip electrodes were positioned on the forehead almost as recommended by the manufactures, but the exact optimal placing could not be accomplished because these electrodes are not designed to be used at the same time. The sides of the BIS and Entropy electrodes were randomized, as it has been shown that BIS and Entropy can give different values when measured at the same time on both sides (Niedhart et al. 2006, Ozcan et al. 2009). In study 1a (II), the BIS and Entropy values used in the analyses were the average of

three consecutive values just before consciousness was tested. The values were recorded at 10 s intervals. By averaging the values, we wanted to diminish the influence of individual aberrant values on the results. In study 2(IV), BIS and Entropy were also collected throughout the entire study. After LOC both the BIS and Entropy values decreased. This may indicate true deepening of the anesthesia but it could also be at least partly related to the influence of the muscle relaxant used in III (Aho et al. 2012, Dahaba et al. 2012). Delay in calculating process may also explain the observed decrease after LOC (Pilge et al. 2006, Zanner et al. 2009). At steady state xenon anesthesia, BIS and Entropy index values were low, indicating deep anesthesia. However, we did not use any painful stimuli to test whether the xenon anesthesia in this study would have been sufficient for surgical interventions. Previously, it has been shown that low BIS values with xenon are not necessarily indicative of deep anesthesia (Goto et al. 2000).

In study 1a (V), subjects breathed oxygen through a tight continuous positive pressure mask for one hour. A baseline EEG was collected before the mask was attached. The uncomfortable feeling caused by the mask could therefore influence the results, but on the other hand, data from the oxygenated state was collected after one hour with the mask, and during this time, subjects should have become accustomed to the mask. We did not measure the Et CO_2 concentration or arterial blood gas samples after oxygenation and for this reason there may have been a risk of spontaneous hyperventilation, which is known to have a slowing effect on the EEG (Kennealy et al. 1986).

6.1.2. EEG signal recording and processing

Recording the EEG signal in anesthesiological studies is quite complicated, but it is even more challenging in anesthesiological PET studies. During sedation, when consciousness is diminished, involuntary movements can occur and disturb the EEG recording. Also electronical equipment like infusion pumps, computers and anesthesia monitors may cause artifacts in EEG signals. In PET studies, the head should be just in the right position, and this may cause an uncomfortable and even painful stimulus especially if some of the electrodes are between the head and the surface of the plastic head holder where the subject's head is lying.

In study 1a, to avoid disturbances from EEG recordings and electronical equipment, the distance from the EEG electrodes to the EEG recording system was kept as short as possible, additionally the distance from other electronical equipments to the EEG recording system was kept as long as possible. Also the influence of the infusion pump and other equipment was checked online by an expert in clinical neurophysiology (S.J.) from the raw EEG signal, before the recording was started. The only way to minimize the influence of involuntary movements was to calm the subjects by verbal commands.

In study 2, there were many disturbances during induction with xenon and during ROC and for this reason, only the awake and steady state anesthesia EEG could be analyzed. During the induction, the EEG was contaminated by motor artifacts related

to positioning of the mask and additionally, some of the subjects became agitated and moved their limbs. After muscle relaxation, intubation and the positioning of the subjects caused EEG artifacts. In the steady state anesthesia, some equipment related artifacts like the train-of-four EMG-stimulator, ventilator, or the PET scanner itself could have contaminated the EEG signals. All artifacts containing epochs were rejected visually off line before qEEG analysis. At ROC, the EEG could not be analyzed.

EEG data were processed in different ways in these EEG studies. In study 1a (I), the whole continuing signal was processed mathematically using three methods; Hjort referencing, short-time Fourier transformation and Kalman smoother spectral estimation. After the primary analyses, the power spectral variables were calculated. These methods are validated to process these kinds of signals without causing significant distortion. One limitation of the EEG analyses was that we did not analyze the high frequency gamma band, even though our sampling rate in this study would have allowed that, and even when there is evidence, that propofol increases gamma activity (Murphy et al. 2011). The reason for not analyzing the gamma band was the presence of contaminating muscle- and other artifacts in the signal especially during awake, SED and ROC. In study 2 (IV), artifacts were rejected and power spectral variables were calculated form 4 s epochs. Fast Fourier transformation, which is not optimal for nonlinear signal analysis nevertheless FFT is widely used for EEG-signal analysis despite its theoretical shortcoming, was used also in this study. Power spectral analyses were done from pre-determined epochs, not from continuous data, and therefore some changes could have been missed in the analysis.

6.2. General discussion

6.2.1. Ethical considerations

When healthy volunteers are anesthetized for purely scientific purposes without any medical benefit for themselves, thorough ethical consideration is required. Although anesthesia is considered to be very safe for healthy ASA I persons, every possible risk was carefully explained to each subject. All side effects related to these studies, including nausea, drowsiness, and soreness of the throat related to intubation (only in study 2), and the possibility of pain and hematomas associated with cannulations, were carefully explained. All possible serious adverse events were considered before the studies and anticipated with rescue medications (muscle relaxant, opioids, antiarythmical and vasoactive medicine), intubation equipments (subjects breathed spontaneously in all studies except in study 2) and a rescue ventilation system in case of respiratory failure. All equipment was checked before each subject. In studies 1a and 1b, there were two anesthesiologists present to take care of the subject and to administer the study drug as well as to conduct the study. In addition, one nurse was present just for taking care of the subject, and one or two nurses to help in the study implementation and EEG technician took care of the EEG equipment and recording. In study 2, there were two or three anesthesiologist and one or two other physicians present. In addition, one nurse was involved in taking care of the subject and two or three to help in the study. Subjects were not allowed to go home before they had eaten

something, and they all had to have an escort who spent the following night with them. Escorts were informed about the study and they were given a phone number to call if any problems arose. There were no serious adverse events in any of the studies included in this thesis.

Ionizing radiation may damage cellular DNA, which can lead to gene mutations, deletions, or translocations. These may cause inheritable disorders in germ cells and be carcinogenic in somatic cells (Mustonen and Salo 2002). The risks of the low-level irradiation used in nuclear medicine are mainly stochastic in adults. This means that there is no "safe dose" and although the dose correlates with the risk of e.g. cancer, it does not correlate with the severity of the cancer. Also the time in which the dose is received is fairly insignificant, and the total risk is determined by the accumulative dose during one's lifetime (Paile 2002). In studies 1b and 2, subjects received 2-5.7 mSv doses of radiation, the maximum dose allowed in the Turku PET centre is 10 mSv for one subject. The doses of our studies corresponded to the background radiation the subject would receive during 0.5-1.5 years in the Nordic countries. In diagnostic procedures like computed tomography (CT) scans, radiation doses can be 5-15 mSv. According to the International Commission of Radiation Protection, the individual risk of cancer increases 5% if the radiation dose is 1000 mSv. The ethical aspects of using radiation in these studies were carefully considered and explained to the participants.

6.2.2. EEG and unconsciousness

Anesthesia agents increase the low frequency, large amplitude EEG activity and decrease the high frequency, low amplitude activity of an EGG towards the unconscious state (Sleigh and Galletly 1997, Gugino et al. 2001, Johnson et al. 2003). Changes in band powers vary for different anesthesia agents, but the overall result is towards low frequencies and high amplitude in the EEG with increasing drug concentrations. EEG reactivity can be seen in clinically unconscious patients during anesthesia or coma (Hartikainen et al. 1995a, Hartikainen et al. 1999, Young 2000, Fisher and Luaute 2005, Aho et al. 2011), and in coma patients it is considered a sign of good prognosis irrespective of the clinical unresponsiveness (Young 2000). All these changes can be seen also in raw-EEG both on and off line. Raw-EEG interpretation on line is challenging and should be done by an expert on clinical neurophysiology and even then the results may not comparable between neurophysiologists.

We investigated the effects of three different anesthesia agents on EEG at low dose levels just reaching unconsciousness, and the effects of one agent in 1.0 MAC anesthesia. It has been shown that high concentrations of dexmedetomidine increase slow delta and theta activity (Maksimow et al. 2007). In our study, even low to moderate concentrations of dexmedetomidine had similar effects on the EEG. In an unconscious state caused by dexmedetomidine, we still observed EEG reactivity to verbal stimulation, which was detected as a sudden increase in the delta band power and may be related to delta arousal (Kox et al 2006, Aho et al. 2011). The most prominent EEG change for propofol towards LOC has been reported to be an increase

in delta activity, with simultaneous increase in beta activity (Kishimoto et al. 1995, Kuizenga et al. 2001). In our study, the most prominent alteration with propofol was an increase in the alpha-slow beta band during gradual change from the awake state towards LOC, but also increases in the theta and delta bands were seen. EEG reactivity in propofol induced anesthesia has not been reported in detail, and we found that reactivity to a verbal command can be seen as a sudden increase in the delta and delayed increase in high-beta band powers, and as delayed decrease in theta band power. These delta and high-beta increases could be related to delta and beta arousals (Kox et al 2006, Aho et al. 2011). Sevoflurane has been shown to increase EEG power both in the delta and the beta bands (Kuizenga et al. 2001, Jääskeläinen et al. 2003, Schlunzen et al 2004). We also found similar increases in the EEG power from awake to SED/LOC, but between SED and LOC none of these changes were significant. EEG reactivity to a painful stimulus has been previously seen in increases in the delta and beta band powers (Aho et al. 2011). We did not find any significant EEG reactions to a verbal command at LOC level of sevoflurane. In conclusion, with these low doses of anesthesia agents, EEG changes were seen between awake to LOC with all drugs and and almost in all bands. Also from SED to LOC changes in EEG band powers were seen with all these three drugs but there were no specific EEG changes to differentiate responsiveness from unresponsiveness. Differences in EEG reactivity at LOC between these drugs we used may be specific for these drugs. It is also possible that as the drug related dose response curve is different between these drugs, at LOC state the subjects were deeper sedated with one drug than with some other drug, in spite of that we increased drug concentrations in small amounts. Based on these findings, it is impossible to say from an EEG if the subject is deeply sedated but still responsiveness or not responsiveness.

A previous study with xenon describes increases in the delta, theta and gamma bands (Johnson et al. 2003). In xenon anesthesia we found increases in the delta, theta and alpha powers. Our EEG recording in this study did not allow the analysis of the gamma band, because of the low sampling rate. But we used the Entropy module, and from low RE (0.8-47 Hz) values it can be concluded that in the frontal area, there probably was not much activity in the gamma band. In the previous study gamma activity was detected in more posterior regions (Johnson et al. 2003). In publication V, we did not found any significant EEG changes during hyperoxia antedated xenon anesthesia induction. Based on this finding, we may say that changes in EEG during xenon anesthesia are not influenced by previous hyperoxia and it does not cause any epileptiformic activity.

6.2.3. BIS and Entropy and unconsciousness

BIS and Entropy monitors have been shown to reduce the consumption of anesthesia agents and to prevent awareness during anesthesia (Myles et al. 2004, Vakkuri et al. 2004, Vakkuri et al. 2005, Chan et al. 2013). On the other hand, three large studies have shown that BIS cannot prevent intraoperative awareness (Avidan et al. 2008, Avidan et al. 2011, Mashour et al. 2012). Time delay in calculating the index values limit the performace of these monitors to prevent awareness, with BIS monitor delay varies between 20-60 s and it is longer when the level of anesthesia is changing (Pilge

et al. 2006, Zanner et al. 2009). In Entropy monitor time delay varies between 26 to 86 s for SE when the level of anesthesia is changing (Kreuzer et al. 2012). In our study, BIS and Entropy could not differentiate sedated consciousness from unconsciousness when using low doses of dexmedetomidine, propofol and sevoflurane although they performed well in differentiating the awake state from deep sedation and LOC. During steady state xenon anesthesia, BIS and Entropy seemed to perform reliably, but during induction and emergence, there were delays in detecting the clinical state. Delay in the calculation of these indices (Pilge et al. 2006, Zanner et al. 2009, Kreuzer et al. 2012) can be caused this delays in deceting the clinical state. A part of the low values can be explained by the influence of the muscle relaxant on frontal EMG signals super imposing on EEG (Aho et al. 2012, Dahaba et al. 2012). Both of these monitors have been developed to measure the level of deep surgical anesthesia, not to simply detect the unconscious state. On the other hand, in order to prevent awareness, the main measured variable is unconsciousness, and the detection of possible return of consciousness during anesthesia is of utmost importance.And for that reason the "therapeutic window" should be carefully considered, index values form 40 to 60 are recommended by manufactures, but there are no good scientific data to support these values. The index value 60 for both of these monitors may be too high to prevent awareness.

6.2.4. Cerebral blood flow in the emergence of consciousness

In many neuroimaging studies on anesthesia, findings have been assumed to indicate correlates of consciousness and its neural mechanisms (Heinke and Schwarzbauer 2002, Alkire et al. 2008, Brown et al. 2010). In this kind of reasoning, one has to remember that changes induced by drugs can be more prominent than the changes which are related to alterations in consciousness itself. In our study, we used the same level of dexmedetomidine infusion which caused LOC and restored consciousness by light stimulation. With this kind of an approach the drug level stays constant, the drug effect can be eliminated and the areas which are truly related to changing levels of consciousness can be found. We also investigated the return of consciousness with propofol after the infusion was discontinued. In both groups, the first reactivated areas were similar including the brainstem, the thalamus, the hypothalamus and the anterior cingulate cortex. These areas are phylogenetically old brain structures, as opposed to the neocortex. This finding can partly explain, why the anesthesia depth monitors that record and process mainly cortical activity cannot detect subtle changes in consciousness accurately.

6.2.5. Problems to define unconsciousness

In anesthesiology loss of consciousness is traditionally defined as loss of responsiveness to a verbal command, but generally differentiating consciousness from unconsciousness is not so simple. Normally conscious person is considered to be awake and connected to the environment and the term "connected consciousness" describes that situation. On the other hand, in hypnagogic and hypnopompic hallucinations subjects can be conscious and connected to the environment but still be unable to move, because of the REM sleep like paralysis (Cheyne et al. 1999). Another example is sleepwalking, when subject is spontaneously responsive but

unconscious and do not follow commands (Howell 2012). It is also possible to be in connected consciousness, but show no spontaneous responsiveness. In isolated forearm technique, subjects may move their unparalyzed hand by command while no spontaneous movements are detected (Russel and Wang 1997). In our studies we used loss of motor responsiveness to a verbal command to define unconsciousness. However, it is possible, that our subjects were not unconsciousness during studies. Sedation could have been so deep, that they did not have will to response to the request. In studies 1a and 1b all subjects were interviewed twice by a psychologist (Noreika et al. 2011) after the study and almost 60% of the subjects reported having subjective experiences: 9/10 in dexmedetomidine group reported, mostly dream like experiences. In propofol group, only 3/10 had subjective experiences and even in xenon group, unless no EEG data could be collected because of agitation and short duration of xenon administration (only couple of min) 7/10 of the subjects had, subjective experiences. None of the subjects, however, reported that they had heard request to open their eyes but had no will to do it.

6.2.6. Clinical implications

The EEG reaction to a verbal stimulus in a clinically defined state of unconsciousness varied with different anesthesia agents and between individual healthy subjects. This finding may help clinical anesthesiologist to plan their anesthesia drugs for operations where neurophysiological measurements are needed. These results may also help in combining different drugs in these kinds of operations. On the other hand, verbal stimulation may alter the cerebral activity and thus elicit changes in the EEG. This should be considered when assessing sedative and anesthetic drug effects with EEG based methods to avoid inaccurate conclusions. In further studies, consciousness should be determined more definitive, not only with presence or absence of motor responsiveness. Also further EEG data analysis should probably be grouped mainly by EEG reactivity and not by anesthetic agents.

The rather poor performance of BIS and Entropy in differentiating sedated consciousness from unconsciousness should be remembered, if these anesthesia depth monitors are used during anesthesia. These monitors can be used as a supplemental monitoring device during general anesthesia, but one must also carefully monitor and follow the clinical signs, especially if a muscle relaxant is used.

The finding that deep brain structures are the areas whose activation reflects the consciousness state may be one reason for the rather poor performance of the BIS and Entropy to differentiate sedated consciousness from unconsciousness. In the future studies, focus should be in more careful detection of different states of consciousness. Differencies between conscious and unconscious states in functional connectivity may provide a new way to study consciousness. Also effective connectivity, where one barin area has direct influence to another, and alterations in this phenomenon may provide new possiblities to measure consciousness. Further studies should focus on the possibility to measure differencies in connectivity with EEG or even to develop connectivity measures based anesthesia depth monitors. The finding that deep brain

structures are the areas whose activation reflects the conscious state, provokes ideas that are still more science fictional than realistic. Perhaps the state of consciousness could be altered by magnetic impulses which can effects these deep structures (Scheinin et al. 2012).

Normobaric hyperoxia does not have a significant influence on the EEG, and this finding can help clinical physicians in using high concentrations of oxygen if it is needed to treat the patient in the ICU. Furthermore, normobaric hyperoxia which is required before xenon anesthesia does not significantly interfere with EEG based monitoring of depth of xenon anesthesia.

These results are based on studies in young healthy volunteers and the number of subjects is low. For these reasons, the direct clinical implications should be carefully considered and further studies are recommended.

7. SUMMARY AND CONCLUSIONS

1. At sedative concentrations of dexmedetomidine, propofol and sevoflurane EEG reactivity was seen with all drugs and within almost all EEG bands, except with sevoflurane in beta band. In the unconsciousness state at similar levels of anesthesia, EEG reactivity persisted with propofol whereas it almost disappeared with sevoflurane.

2. Wide inter-individual variability in the BIS and Entropy indices at LOC, induced by dexmedetomidine, propofol and sevoflurane, caused that these indices perform poorly in detecting unconsciousness.

3. Arousal from dexmedetomidine and propofol induced unconsciousness state caused activation in deep phylogenetically old brain structures; the brainstem, the thalamus, the hypothalamus and the anterior cingulate cortex. This finding may explain the poor performance of EEG based anesthesia depth monitors in differentiating the conscious and unconscious states during emergence and why patient awareness during general anesthesia may not always be detected.

4. Xenon anesthesia caused an increase in the slow frequency band power, but did not increase the beta bower. BIS and Entropy seem to perform well during steady-state xenon anesthesia.

5. Normobaric hyperoxia did not influence EEG, nor did it interfere with qEEG variables used to monitor xenon anesthesia.

8. ACKNOWLEDGEMENTS

These studies were carried out at the Department of Anesthesiology and Intensive Care and at the Turku PET Centre, in collaboration with the Department of Clinical Neurophysiology, University of Turku and Turku University Hospital during years 2006-2013. I wish to thank Professor Klaus Olkkola, Head of the Department of Anesthesiology and Intensive Care, for being supportive towards the anesthesiological research performed at the PET Centre, and Professor Juhani Knuuti, Director of the Turku PET Centre for the use of the excellent facilities of the Turku PET Centre. These studies were financially supported by the AGA Research Foundtation, the Academy of Finland and EVO grants of Turku University Hospital.

I express my gratitude to Docent Juha Perttilä, Head of the Intensive Care Unit and Docent Erkki Kentala, Head of Surgical Ward, for their effort in arranging sufficient periods for scientific work.

I owe my greatest gratitude to my supervisors, Docent Harry Scheinin, Professor Satu Jääskeläinen and Anu Maksimow. Harry has always been an excellent team leader, and his huge expertise of anesthesiologic research and scientific mind have made this whole project possible. I have learnt very much about analytic and clear-minded thinking from you. I am most grateful to Satu for teaching me the basics of neurophysiology and supporting me throughout this project. You were very busy in your own work, but still you always arrange time to meet and discuss. Anu, you have been an excellent every-day supervisor. Your role was not only supervisor of this work, it was much more, you have done lot of work for this project.

Professor Esa Mervaala and Professor Arvi Yli-Hankala are warmly thanked for excellent and constructive review of this thesis.

I want to thank Docent Riku Aantaa, Head of the Perioperative Services, Intensive Care and Pain Medicine, for being such a support for this project. You have always given your quick and straightforfard answers and comments. And you have always tried to arrange me time to do scientific work, when I need it.

The PET anesthesiology rechearch group is warmly acknowledged for their positive spirit and support during this project. I want to thank Elina Salmi for helping me all the practical issues for arranging PET studies. Ruut Laitio is acknowledged for collobration with xenon studies. I warmly thank Kaike Kaisti, you have thought me all that I know about PET. Especially I want to thank Jaakko Långsjö, you have always helped me in writing and other problems and your enthusiasm scientific attitude is admired. All other co-workers in PET Centre and also all laboratory and radiographers are thanked for their effort.

Mika Särkelä is thanked for excellent technical support and for offering the monitoring equipment and for his valuable in this project. Sargo Aalto is thanked for PET analyses and for the enlightening point of views. Professors Michael Alkire, Antti

Revonsuo and all other coauthors are warmly acknowledgement. Helen Cooper is thanked for revision of the English language.

Nurses form clinical neurophysiology Pia Aalto, Anne Enala and Tuula Jokela are acknowledgement for their work with EEG. Anesthesia nurse Outi Brummer-Kallio is warmly acknowledgement for everyday arrangements. Physicist Tarmo Kärki is thanked for all technical support with EEG. I want to thank Stefanos Georgiadis for EEG analyses and for new ideas to make these analyses.

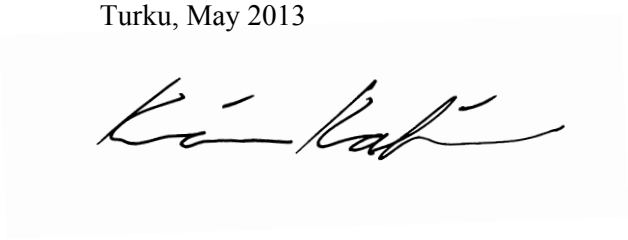
Colleagues Petri Aaltonen, Ville-Veikko Hynninen, Juha Grönlund, Antti Liukas, Marko Peltoniemi, Teijo Saari, Urmas Savolainen, Oki Söderholm, Tomi Vainio and Jyrki Vihe are especially mentioned among the staff anesthesiologists for making TYKS a pleasant place to work.

I express my appreciation to all volunteers who participated in these studies.

I express my sincere gratitude to my parents Marjatta and Kauko Kaskinoro, you are always support and helped me whenever I have needed. I wish to thank my sister Heidi and my brother Janne for their support.

Finally, I want to thank the most important people in my life, Anniina without you I have not finished this project yet. And my son Juska, you have showed me the real meaning of live.

Turku, May 2013



9. REFERENCES

Abe M., Kaizu K., Matsumoto K. A case report of acute renal failure and fulminant hepatitis associated with edaravone administration in a cerebral infarction patient. Ther Apher Dial 2007; 11: 235-240.

Aho A. J., Kamata K., Yli-Hankala A., Lyytikäinen L. P., Kulkas A., Jäntti V. Elevated BIS and Entropy values after sugammadex or neostigmine: an electroencephalographic or electromyographic phenomenon? Acta Anaesthesiol Scand 2012; 56: 465-473.

Aho A. J., Lyytikäinen L. P., Yli-Hankala A., Kamata K., Jäntti V. Explaining Entropy responses after a noxious stimulus, with or without neuromuscular blocking agents, by means of the raw electroencephalographic and electromyographic characteristics. Br J Anaesth 2011; 106: 69-76.

Aksu R., Kumandas S., Akin A., Bicer C., Gumus H., Guler G., Per H., Bayram A., Boyaci A. The comparison of the effects of dexmedetomidine and midazolam sedation on electroencephalography in pediatric patients with febrile convulsion. Paediatr Anaesth 2011; 21: 373-378.

Alkire M. T., Haier R. J. Correlating in vivo anaesthetic effects with ex vivo receptor density data supports a GABAergic mechanism of action for propofol, but not for isoflurane. Br J Anaesth 2001; 86: 618-626.

Alkire M.T., Asher C.D., Franciscus A.M., Hahn E.L. Thalamic microinfusion of antibody to voltage-gated potassium channel restores consciousness during anesthesia. Anesthesiololgy 2009; 110: 766-773.

Alkire M. T., Hudetz A. G., Tononi G. Consciousness and anesthesia. Science 2008; 322: 876-880.

Altemeier W. A., Sinclair S. E. Hyperoxia in the intensive care unit: why more is not always better. Curr Opin Crit Care 2007; 13: 73-78.

Anaforoglu I., Yildiz B., Incecayir O., Algun E. A woman with thyrotoxicosis- and hyperemesis gravidarum-associated Wernicke's encephalopathy. Neuro Endocrinol Lett 2012; 33: 285-289.

Anderson K. J., Harten J. M., Booth M. G., Berry C., McConnachie A., Rankin A. C., Kinsella J. The cardiovascular effects of normobaric hyperoxia in patients with heart rate fixed by permanent pacemaker. Anaesthesia 2010; 65: 167-171.

Anderson R. E., Jakobsson J. G. Entropy of EEG during anaesthetic induction: a comparative study with propofol or nitrous oxide as sole agent. Br J Anaesth 2004; 92: 167-170.

Aston-Jones G., Rajkowski J., Kubiak P., Alexinsky T. Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. J Neurosci 1994; 14: 4467-4480.

Avidan M. S., Jacobsohn E., Glick D., Burnside B. A., Zhang L., Villafranca A., Karl L., Kamal S., Torres B., O'Connor M., Evers A. S., Gradwohl S., Lin N., Palanca B. J., Mashour G. A. Prevention of intraoperative awareness in a high-risk surgical population. N Engl J Med 2011; 365: 591-600.

Avidan M. S., Zhang L., Burnside B. A., Finkel K. J., Searleman A. C., Selvidge J. A., Saager L., Turner M. S., Rao S., Bottros M., Hantler C., Jacobsohn E., Evers A. S. Anesthesia awareness and the bispectral index. N Engl J Med 2008; 358: 1097-1108.

Balvin M. J., Song K. M., Slimp J. C. Effects of anesthetic regimens and other confounding factors affecting the interpretation of motor evoked potentials during pediatric spine surgery. Am J Electroneurodiagnostic Technol 2010; 50: 219-244.

Bassetti C., Vella S., Donati F., Wielepp P., Weder B. SPECT during sleepwalking. Lancet 2000; 356: 484-485.

Bhana N., Goa K. L., McClellan K. J. Dexmedetomidine. Drugs 2000; 59: 263-268; discussion 269-270.

Benjamini Y, Hochberg Y: Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Statist Soc B Met. 1995; 57:289-300

Boly M., Garrido M. I., Gosseries O., Bruno M. A., Boveroux P., Schnakers C., Massimini M., Litvak V., Laureys S., Friston K. Preserved feedforward but impaired top-down processes in the vegetative state. Science 2011; 332: 858-862.

Bonds D. E., Miller M. E., Dudl J., Feinglos M., Ismail-Beigi F., Malozowski S., Seaquist E., Simmons D. L., Sood A. Severe hypoglycemia symptoms, antecedent behaviors, immediate consequences and association with glycemia medication usage: Secondary analysis of the ACCORD clinical trial data. BMC Endocr Disord 2012; 12: 5.

Bordini A. L., Luiz T. F., Fernandes M., Arruda W. O., Teive H. A. Coma scales: a historical review. Arq Neuropsiquiatr 2010; 68: 930-937.

Boveroux P., Vanhaudenhuyse A., Bruno M. A., Noirhomme Q., Lauwick S., Luxen A., Degueldre C., Plenevaux A., Schnakers C., Phillips C., Brichant J. F., Bonhomme V., Maquet P., Greicius M. D., Laureys S., Boly M. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology 2010; 113: 1038-1053.

Braun A. R., Balkin T. J., Wesenten N. J., Carson R. E., Varga M., Baldwin P., Selbie S., Belenky G., Herscovitch P. Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. Brain 1997; 120 (Pt 7): 1173-1197.

Bray R. J. Propofol infusion syndrome in children. Paediatr Anaesth 1998; 8: 491-499.

Brown B., Jr. Sevoflurane: introduction and overview. Anesth Analg 1995; 81: S1-3.

Brown E. N., Lydic R., Schiff N. D. General anesthesia, sleep, and coma. N Engl J Med 2010; 363: 2638-2650.

Bruhn J., Bouillon T. W., Shafer S. L. Bispectral index (BIS) and burst suppression: revealing a part of the BIS algorithm. J Clin Monit Comput 2000; 16: 593-596.

Bruhn J., Myles P. S., Sneyd R., Struys M. M. Depth of anaesthesia monitoring: what's available, what's validated and what's next? Br J Anaesth 2006; 97: 85-94.

Bruhn J., Ropcke H., Hoeft A. Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. Anesthesiology 2000; 92: 715-726.

Buzsáki G, Traub RD, and Pedley TA. The cellular basis of EEG activity. In: Ebersole JS and Pedley TA, eds. Current practice of Clinical Electroencephalography. 3rd ed. Lippincott Williams & Wilkins, Philadelphia, 2003: 1-11.

Carroll C. P., Cochran J. A., Guse C. E., Wang M. C. Are we underestimating the burden of traumatic brain injury? Surveillance of severe traumatic brain injury using centers for disease control international classification of disease, ninth revision, clinical modification, traumatic brain injury codes. Neurosurgery 2012; 71: 1064-1070.

Casaletto J. J. Is salt, vitamin, or endocrinopathy causing this encephalopathy? A review of endocrine and metabolic causes of altered level of consciousness. Emerg Med Clin North Am 2010; 28: 633-662.

Chamberlin N. L., Eikermann M. This is no humbug: anesthetic agent-induced unconsciousness and sleep are visibly different. Anesthesiology 2010; 113: 1007-1009.

Chan M. T., Cheng B. C., Lee T. M., Gin T. BIS-guided Anesthesia Decreases Postoperative Delirium and Cognitive Decline. J Neurosurg Anesthesiol 2013; 25: 33-42.

Chernik D. A., Gillings D., Laine H., Hendler J., Silver J. M., Davidson A. B., Schwam E. M., Siegel J. L. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol 1990; 10: 244-251.

Cheyne J. A., Rueffer S. D., Newby-Clark I. R. Hypnagogic and hypnopompic hallucinations during sleep paralysis: neurological and cultural construction of the night-mare. Conscious Cogn 1999; 8: 319-337.

Coburn M., Kunitz O., Baumert J. H., Hecker K., Haaf S., Zuhlsdorff A., Beeker T., Rossaint R. Randomized controlled trial of the haemodynamic and recovery effects of xenon or propofol anaesthesia. Br J Anaesth 2005; 94: 198-202.

Cohen M. A., Cavanagh P., Chun M. M., Nakayama K. The attentional requirements of consciousness. Trends Cogn Sci 2012; 16: 411-417.

Connolly MB, Sharbrough FW, and Wong PK. Electrical fields and recording techniques. In: Ebersole JS and Pedley TA, eds. Current practice of Clinical Electroencephalography. 3rd ed. Lippincott Williams & Wilkins, Philadelphia, 2003: 72-99.

Cormack J. R., Orme R. M., Costello T. G. The role of alpha2-agonists in neurosurgery. J Clin Neurosci 2005; 12: 375-378.

Cremer J., Stoppe C., Fahlenkamp A. V., Schalte G., Rex S., Rossaint R., Coburn M. Early cognitive function, recovery and well-being after sevoflurane and xenon anaesthesia in the elderly: a double-blinded randomized controlled trial. Med Gas Res 2011; 1: 9.

Creutzfeldt O. D., Watanabe S., Lux H. D. Relations between EEG phenomena and potentials of single cortical cells. I. Evoked responses after thalamic and erpicortical stimulation. Electroencephalogr Clin Neurophysiol 1966; 20: 1-18.

Cullen S. C., Gross E. G. The anesthetic properties of xenon in animals and human beings, with

additional observations on krypton. Science 1951; 113: 580-582.

Dahaba A. A. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. Anesth Analg 2005; 101: 765-773.

Dahaba A. A., Bornemann H., Hopfgartner E., Ohran M., Kocher K., Liebmann M., Wilfinger G., Metzler H. Effect of sugammadex or neostigmine neuromuscular block reversal on bispectral index monitoring of propofol/remifentanil anaesthesia. Br J Anaesth 2012; 108: 602-606.

Dammann P., Asgari S., Bassiouni H., Gasser T., Panagiotopoulos V., Gizewski E. R., Stolke D., Sure U., Sandalcioglu I. E. Spontaneous cerebellar hemorrhage--experience with 57 surgically treated patients and review of the literature. Neurosurg Rev 2011; 34: 77-86.

De Hert S. G., Van der Linden P. J., Cromheecke S., Meeus R., Nelis A., Van Reeth V., ten Broecke P. W., De Blier I. G., Stockman B. A., Rodrigus I. E. Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. Anesthesiology 2004; 101: 299-310.

Diedrich D. A., Brown D. R. Analytic reviews: propofol infusion syndrome in the ICU. J Intensive Care Med 2011; 26: 59-72.

Diringer M. N., Bleck T. P., Claude Hemphill J., 3rd, Menon D., Shutter L., Vespa P., Bruder N., Connolly E. S., Jr., Citerio G., Gress D., Hanggi D., Hoh B. L., Lanzino G., Le Roux P., Rabinstein A., Schmutzhard E., Stocchetti N., Suarez J. I., Treggiari M., Tseng M. Y., Vergouwen M. D., Wolf S., Zipfel G. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care 2011; 15: 211-240.

Dostovic Z., Smajlovic D., Dostovic E., Ibrahimagic O. C. Stroke and disorders of consciousness. Cardiovasc Psychiatry Neurol 2012; 2012: 429108.

Duncan D., Kelly K. P., Andrews P. J. A comparison of bispectral index and entropy monitoring, in patients undergoing embolization of cerebral artery aneurysms after subarachnoid haemorrhage. Br J Anaesth 2006; 96: 590-596.

Dustman R. E., Shearer D. E., Emmerson R. Y. Life-span changes in EEG spectral amplitude, amplitude variability and mean frequency. Clin Neurophysiol 1999; 110: 1399-1409.

Ebersole JS. Cortical Generators and EEG voltage fields. In: Ebersole JS and Pedley TA, eds. Current practice of Clinical Electroencephalography. 3rd ed. Lippincott Williams & Wilkins, Philadelphia, 2003: 12-32.

Eger E. I., 2nd. New inhaled anesthetics. Anesthesiology 1994; 80: 906-922.

Ellerkmann R. K., Liermann V. M., Alves T. M., Wenningmann I., Kreuer S., Wilhelm W., Roepcke H., Hoeft A., Bruhn J. Spectral entropy and bispectral index as measures of the electroencephalographic effects of sevoflurane. Anesthesiology 2004; 101: 1275-1282.

Ellerkmann R. K., Soehle M., Alves T. M., Liermann V. M., Wenningmann I., Roepcke H., Kreuer S., Hoeft A., Bruhn J. Spectral entropy and bispectral index as measures of the electroencephalographic effects of propofol. Anesth Analg 2006; 102: 1456-1462.

Errando C. L., Sigl J. C., Robles M., Calabuig E., Garcia J., Arocas F., Higueras R., Del Rosario E., Lopez D., Peiro C. M., Soriano J. L., Chaves S., Gil F., Garcia-Aguado R. Awareness with recall during general anaesthesia: a prospective observational evaluation of 4001 patients. Br J Anaesth 2008; 101: 178-185.

Fischer C., Luaute J. Evoked potentials for the prediction of vegetative state in the acute stage of coma. Neuropsychol Rehabil 2005; 15: 372-380.

Franks N. P., Dickinson R., de Sousa S. L., Hall A. C., Lieb W. R. How does xenon produce anaesthesia? Nature 1998; 396: 324.

Fraser G. L., Riker R. R. Bispectral index monitoring in the intensive care unit provides more signal than noise. Pharmacotherapy 2005; 25: 19S-27S.

Gan T. J., Glass P. S., Windsor A., Payne F., Rosow C., Sebel P., Manberg P. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. Anesthesiology 1997; 87: 808-815.

Ghiani C. A., Tuligi G., Maciocco E., Serra M., Sanna E., Biggio G. Biochemical evaluations of the effects of loreclezole and propofol on the GABAA receptor in rat brain. Biochem Pharmacol 1996; 51: 1527-1534.

Goto T., Hanne P., Ishiguro Y., Ichinose F., Niimi Y., Morita S. Cardiovascular effects of xenon and nitrous oxide in patients during fentanyl-midazolam anaesthesia. Anaesthesia 2004; 59: 1178-1183.

Goto T., Nakata Y., Saito H., Ishiguro Y., Niimi Y., Suwa K., Morita S. Bispectral analysis of the electroencephalogram does not predict responsiveness to verbal command in patients emerging from xenon anaesthesia. Br J Anaesth 2000; 85: 359-363.

Gugino L. D., Chabot R. J., Prichep L. S., John E. R., Formanek V., Aglio L. S. Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane. Br J Anaesth 2001; 87: 421-428.

Hackett P. H., Roach R. C. High-altitude illness. N Engl J Med 2001; 345: 107-114.

Haenggi M., Ypparila H., Hauser K., Caviezel C., Korhonen I., Takala J., Jakob S. M. The effects of dexmedetomidine/remifentanil and midazolam/ remifentanil on auditory-evoked potentials and electroencephalogram at light-to-moderate sedation levels in healthy subjects. Anesth Analg 2006; 103: 1163-1169.

Haenggi M., Ypparila-Wolters H., Hauser K., Caviezel C., Takala J., Korhonen I., Jakob S. M. Intra- and inter-individual variation of BIS-index and Entropy during controlled sedation with midazolam/remifentanil and dexmedetomidine/remifentanil in healthy volunteers: an interventional study. Crit Care 2009; 13: R20.

Hampton R. R. Rhesus monkeys know when they remember. Proc Natl Acad Sci U S A 2001; 98: 5359-5362.

Hartikainen K. M., Rorarius M., Peräkylä J. J., Laippala P. J., Jäntti V. Cortical reactivity during isoflurane burst-suppression anesthesia. Anesth Analg 1995a; 81: 1223-1228.

Hartikainen K., Rorarius M., Mäkelä K., Peräkylä J., Varila E., Jäntti V. Visually evoked bursts during isoflurane anaesthesia. Br J Anaesth 1995b; 74: 681-685.

Hartikainen K., Rorarius M. G. Cortical responses to auditory stimuli during isoflurane burst suppression anaesthesia. Anaesthesia 1999; 54: 210-214.

Heinke W., Schwarzbauer C. In vivo imaging of anaesthetic action in humans: approaches with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Br J Anaesth 2002; 89: 112-122.

Hernandez-Gancedo C., Pestana D., Perez-Chrzanowska H., Martinez-Casanova E., Criado A. Comparing Entropy and the Bispectral index with the Ramsay score in sedated ICU patients. J Clin Monit Comput 2007; 21: 295-302.

Howell M. J. Parasomnias: an updated review. Neurotherapeutics 2012; 9: 753-775.

Hsu Y. W., Cortinez L. I., Robertson K. M., Keifer J. C., Sum-Ping S. T., Moretti E. W., Young C. C., Wright D. R., Macleod D. B., Somma J. Dexmedetomidine pharmacodynamics: part I: crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology 2004; 101: 1066-1076.

Huupponen E., Maksimow A., Lapinlampi P., Särkelä M., Saastamoinen A., Snapir A., Scheinin H., Scheinin M., Meriläinen P., Himanen S. L., Jääskelainen S. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. Acta Anaesthesiol Scand 2008; 52: 289-294.

Iannuzzi M., Iannuzzi E., Rossi F., Berrino L., Chiefari M. Relationship between Bispectral Index, electroencephalographic state entropy and effect-site EC50 for propofol at different clinical endpoints. Br J Anaesth 2005; 94: 492-495.

Ibrahim A. E., Taraday J. K., Kharasch E. D. Bispectral index monitoring during sedation with sevoflurane, midazolam, and propofol. Anesthesiology 2001; 95: 1151-1159.

Iijima T., Nakamura Z., Iwao Y., Sankawa H. The epileptogenic properties of the volatile anesthetics sevoflurane and isoflurane in patients with epilepsy. Anesth Analg 2000; 91: 989-995.

Illman H., Antila H., Olkkola K. T. Reversal of neuromuscular blockade by sugammadex does not affect EEG derived indices of depth of anesthesia. J Clin Monit Comput 2010; 24: 371-376.

Imas O. A., Ropella K. M., Ward B. D., Wood J. D., Hudetz A. G. Volatile anesthetics disrupt frontal-posterior recurrent information transfer at gamma frequencies in rat. Neurosci Lett 2005; 387: 145-150.

Jiahai M., Xueyan W., Yonggang X., Jianhong Y., Qunhui H., Zhi L., Juan D., Xiuliang J. Spectral entropy monitoring reduces anesthetic dosage for patients undergoing off-pump coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2012; 26: 818-821.

John E. R., Prichep L. S. The anesthetic cascade: a theory of how anesthesia suppresses consciousness. Anesthesiology 2005; 102: 447-471.

John E. R., Prichep L. S., Kox W., Valdes-Sosa P., Bosch-Bayard J., Aubert E., Tom M., di Michele

F., Gugino L. D. Invariant reversible QEEG effects of anesthetics. Conscious Cogn 2001; 10: 165-183.

Johnson B. W., Sleigh J. W., Kirk I. J., Williams M. L. High-density EEG mapping during general anaesthesia with xenon and propofol: a pilot study. Anaesth Intensive Care 2003; 31: 155-163.

Jordan D., Stockmanns G., Kochs E. F., Pilge S., Schneider G. Electroencephalographic order pattern analysis for the separation of consciousness and unconsciousness: an analysis of approximate entropy, permutation entropy, recurrence rate, and phase coupling of order recurrence plots. Anesthesiology 2008; 109: 1014-1022.

Julliac B., Guehl D., Chopin F., Arne P., Burbaud P., Sztark F., Cros A. M. Risk factors for the occurrence of electroencephalogram abnormalities during induction of anesthesia with sevoflurane in nonepileptic patients. Anesthesiology 2007; 106: 243-251.

Jurcak V., Tsuzuki D., Dan I. 10/20, 10/10, and 10/5 systems revisited: their validity as relative head-surface-based positioning systems. Neuroimage 2007; 34: 1600-1611.

Jäntti V and Sloan T.B. Intraoperative monitoring of neural function. In: Nuwer M. eds. Handbook of Clinical Neurophysiology. Vol 8 Elsevier 2008: 2008: 77-93.

Jääskelainen S. K., Kaisti K., Suni L., Hinkka S., Scheinin H. Sevoflurane is epileptogenic in healthy subjects at surgical levels of anesthesia. Neurology 2003; 61: 1073-1078.

Kaisti K. K., Metsähonkala L., Teräs M., Oikonen V., Aalto S., Jääskelainen S., Hinkka S., Scheinin H. Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. Anesthesiology 2002; 96: 1358-1370.

Kang T. M. Propofol infusion syndrome in critically ill patients. Ann Pharmacother 2002; 36: 1453-1456.

Karamchandani K., Rewari V., Trikha A., Batra R. K. Bispectral index correlates well with Richmond agitation sedation scale in mechanically ventilated critically ill patients. J Anesth 2010; 24: 394-398.

Kellaway P. Orderly approach to visual analysis: elements of the normal EEG and their characteristics in children and adults. In: Ebersole JS and Pedley TA, eds. Current practice of Clinical Electroencephalography. 3rd ed. Lippincott Williams & Wilkins, Philadelphia, 2003: 100-158.

Kennealy J. A., Penovich P. E., Moore-Nease S. E. EEG and spectral analysis in acute hyperventilation. Electroencephalogr Clin Neurophysiol 1986; 63: 98-106.

Kennedy D., Norman C. What don't we know? Science 2005; 309: 75.

Kishimoto T., Kadoya C., Sneyd R., Samra S. K., Domino E. F. Topographic electroencephalogram of propofol-induced conscious sedation. Clin Pharmacol Ther 1995; 58: 666-674.

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

Kox W. J., von Heymann C., Heinze J., Prichep L. S., John E. R., Rundshagen I. Electroencephalographic mapping during routine clinical practice: cortical arousal during tracheal intubation? Anesth Analg 2006; 102: 825-831.

Kraaier V., Van Huffelen A. C., Wieneke G. H. Quantitative EEG changes due to hypobaric hypoxia in normal subjects. Electroencephalogr Clin Neurophysiol 1988; 69: 303-312.

Kreuzer M., Zanner R., Pilge S., Paprotny S., Kochs E. F., Schneider G. Time delay of monitors of the hypnotic component of anesthesia: analysis of state entropy and index of consciousness. Anesth Analg 2012; 115: 315-319.

Ku S. W., Lee U., Noh G. J., Jun I. G., Mashour G. A. Preferential inhibition of frontal-to-parietal feedback connectivity is a neurophysiologic correlate of general anesthesia in surgical patients. PLoS One 2011; 6: e25155.

Kuizenga K., Wierda J. M., Kalkman C. J. Biphasic EEG changes in relation to loss of consciousness during induction with thiopental, propofol, etomidate, midazolam or sevoflurane. Br J Anaesth 2001; 86: 354-360.

Kurita N., Kawaguchi M., Hoshida T., Nakase H., Sakaki T., Furuya H. The effects of sevoflurane and hyperventilation on electrocorticogram spike activity in patients with refractory epilepsy. Anesth Analg 2005; 101: 517-523.

Lakhlani P. P., MacMillan L. B., Guo T. Z., McCool B. A., Lovinger D. M., Maze M., Limbird L. E. Substitution of a mutant alpha2a-adrenergic receptor via "hit and run" gene targeting reveals the role of this subtype in sedative, analgesic, and anesthetic-sparing responses in vivo. Proc Natl Acad Sci U S A 1997; 94: 9950-9955.

Lambert I., Arthuis M., McGonigal A., Wendling F., Bartolomei F. Alteration of global workspace during loss of consciousness: A study of parietal seizures. Epilepsia 2012; 53: 2104-2110.

Landsness E., Bruno M. A., Noirhomme Q., Riedner B., Gosseries O., Schnakers C., Massimini M., Laureys S., Tononi G., Boly M. Electrophysiological correlates of behavioural changes in vigilance in vegetative state and minimally conscious state. Brain 2011; 134: 2222-2232.

Laureys S. The neural correlate of (un)awareness: lessons from the vegetative state. Trends Cogn Sci 2005; 9: 556-559.

Laureys S., Perrin F., Faymonville M. E., Schnakers C., Boly M., Bartsch V., Majerus S., Moonen G., Maquet P. Cerebral processing in the minimally conscious state. Neurology 2004; 63: 916-918.

Lee T. T., Galarza M., Villanueva P. A. Diffuse axonal injury (DAI) is not associated with elevated intracranial pressure (ICP). Acta Neurochir (Wien) 1998; 140: 41-46.

Leslie K., Skrzypek H., Paech M. J., Kurowski I., Whybrow T. Dreaming during anesthesia and anesthetic depth in elective surgery patients: a prospective cohort study. Anesthesiology 2007; 106: 33-42.

Leslie K., Sleigh J., Paech M. J., Voss L., Lim C. W., Sleigh C. Dreaming and electroencephalographic changes during anesthesia maintained with propofol or desflurane. Anesthesiology 2009; 111: 547-555.

Lesser R and Arroyo S Subdural electrodes. In: Niedermeyer E and da Silva F eds. Electroencephalography, basic principles, clinical applications and related fields. 5th ed. Lippincott Williams&Wilkins Philadelphia 2005:777-791

Lin F. H., McIntosh A. R., Agnew J. A., Eden G. F., Zeffiro T. A., Belliveau J. W. Multivariate analysis of neuronal interactions in the generalized partial least squares framework: simulations and empirical studies. Neuroimage 2003; 20: 625-642.

Litscher G., Friehs G., Maresch H., Pfurtscheller G. Electroencephalographic and evoked potential monitoring in the hyperbaric environment. J Clin Monit 1990; 6: 10-17.

Liu S. S. Effects of Bispectral Index monitoring on ambulatory anesthesia: a meta-analysis of randomized controlled trials and a cost analysis. Anesthesiology 2004; 101: 311-315.

Lobaugh N. J., West R., McIntosh A. R. Spatiotemporal analysis of experimental differences in event-related potential data with partial least squares. Psychophysiology 2001; 38: 517-530.

Lotto M. L., Banoub M., Schubert A. Effects of anesthetic agents and physiologic changes on intraoperative motor evoked potentials. J Neurosurg Anesthesiol 2004; 16: 32-42.

Lule D., Noirhomme Q., Kleih S. C., Chatelle C., Halder S., Demertzi A., Bruno M. A., Gosseries O., Vanhaudenhuyse A., Schnakers C., Thonnard M., Soddu A., Kubler A., Laureys S. Probing command following in patients with disorders of consciousness using a brain-computer interface. Clin Neurophysiol 2013; 124: 101-106.

Lysakowski C., Elia N., Czarnetzki C., Dumont L., Haller G., Combescure C., Tramer M. R. Bispectral and spectral entropy indices at propofol-induced loss of consciousness in young and elderly patients. Br J Anaesth 2009; 103: 387-393.

Långsjö J. W., Alkire M. T., Kaskinoro K., Hayama H., Maksimow A., Kaisti K. K., Aalto S., Aantaa R., Jääskelainen S. K., Revonsuo A., Scheinin H. Returning from oblivion: imaging the neural core of consciousness. J Neurosci 2012; 32: 4935-4943.

Maksimow A., Snapir A., Särkelä M., Kentala E., Koskenvuo J., Posti J., Jääskelainen S. K., Hinkka-Yli-Salomaki S., Scheinin M., Scheinin H. Assessing the depth of dexmedetomidine-induced sedation with electroencephalogram (EEG)-based spectral entropy. Acta Anaesthesiol Scand 2007; 51: 22-30.

Mapleson W. W. Effect of age on MAC in humans: a meta-analysis. Br J Anaesth 1996; 76: 179-185.

Maquet P., Peters J., Aerts J., Delfiore G., Degueldre C., Luxen A., Franck G. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 1996; 383: 163-166.

Marsh B., White M., Morton N., Kenny G. N. Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth 1991; 67: 41-48.

Mashour G. A., Shanks A., Tremper K. K., Kheterpal S., Turner C. R., Ramachandran S. K., Picton P., Schueller C., Morris M., Vandervest J. C., Lin N., Avidan M. S. Prevention of intraoperative awareness with explicit recall in an unselected surgical population: a randomized comparative effectiveness trial. Anesthesiology 2012; 117: 717-725.

Mason K. P., O'Mahony E., Zurakowski D., Libenson M. H. Effects of dexmedetomidine sedation on the

EEG in children. Paediatr Anaesth 2009; 19: 1175-1183.

Maze M., Angst M. S. Dexmedetomidine and opioid interactions: defining the role of dexmedetomidine for intensive care unit sedation. Anesthesiology 2004; 101: 1059-1061.

McIntosh A. R., Bookstein F. L., Haxby J. V., Grady C. L. Spatial pattern analysis of functional brain images using partial least squares. Neuroimage 1996; 3: 143-157.

McIntosh A. R., Lobaugh N. J. Partial least squares analysis of neuroimaging data: applications and advances. Neuroimage 2004; 23 Suppl 1: S250-263.

McIntosh A. R., Rajah M. N., Lobaugh N. J. Functional connectivity of the medial temporal lobe relates to learning and awareness. J Neurosci 2003; 23: 6520-6528.

Mesnil M., Capdevila X., Bringuier S., Trine P. O., Falquet Y., Charbit J., Roustan J. P., Chanques G., Jaber S. Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. Intensive Care Med 2011; 37: 933-941.

Miller G. What is the biological basis of consciousness? Science 2005; 309: 79.

Morris L. E., Knott J. R., Pittinger C. B. Electro-encephalographic and blood gas observations in human surgical patients during xenon anesthesia. Anesthesiology 1955; 16: 312-319.

Murphy M., Bruno M. A., Riedner B. A., Boveroux P., Noirhomme Q., Landsness E. C., Brichant J. F., Phillips C., Massimini M., Laureys S., Tononi G., Boly M. Propofol anesthesia and sleep: a high-density EEG study. Sleep 2011; 34: 283-291A.

Mustonen R and Salo A Säteily ja solu. In: Paile W, eds. Säteilyn terveysvaikutukset. 1st ed. Säteilyturvakeskus, Helsinki, 2002: 27-40

Myles P. S., Leslie K., McNeil J., Forbes A., Chan M. T. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet 2004; 363: 1757-1763.

Nagele P., Metz L. B., Crowder C. M. Xenon acts by inhibition of non-N-methyl-D-aspartate receptor-mediated glutamatergic neurotransmission in Caenorhabditis elegans. Anesthesiology 2005; 103: 508-513.

Nelson L. E., Lu J., Guo T., Saper C. B., Franks N. P., Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 2003; 98: 428-436.

Neukirchen M., Hipp J., Schaefer M. S., Brandenburger T., Bauer I., Winterhalter M., Kienbaum P., Werdehausen R. Cardiovascular stability and unchanged muscle sympathetic activity during xenon anaesthesia: role of norepinephrine uptake inhibition. Br J Anaesth 2012; 109: 887-896.

Niedhart D. J., Kaiser H. A., Jacobsohn E., Hantler C. B., Evers A. S., Avidan M. S. Intrapatient reproducibility of the BISxp monitor. Anesthesiology 2006; 104: 242-248.

Noreika V., Jylhankangas L., Moro L., Valli K., Kaskinoro K., Aantaa R., Scheinin H., Revonsuo A. Consciousness lost and found: subjective experiences in an unresponsive state. Brain Cogn 2011; 77: 327-334.

Oda Y., Toriyama S., Tanaka K., Matsuura T., Hamaoka N., Morino M., Asada A. The effect of dexmedetomidine on electrocorticography in patients with temporal lobe epilepsy under sevoflurane anesthesia. Anesth Analg 2007; 105: 1272-1277.

Ovadia-Caro S., Nir Y., Soddu A., Ramot M., Hesselmann G., Vanhaudenhuyse A., Dinstein I., Tshibanda J. F., Boly M., Harel M., Laureys S., Malach R. Reduction in inter-hemispheric connectivity in disorders of consciousness. PLoS One 2012; 7: e37238.

Owen A. M. Detecting consciousness: a unique role for neuroimaging. Annu Rev Psychol 2013; 64: 109-133.

Ozcan M. S., Thompson D. M., Cure J., Hine J. R., Roberts P. R. Same-patient reproducibility of state entropy: a comparison of simultaneous bilateral measurements during general anesthesia. Anesth Analg 2009; 108: 1830-1835.

Paile W. Säteilyn haittavaikutusten luokittelu. In: Paile W, eds. Säteilyn terveysvaikutukset. 1st ed. Säteilyturvakeskus, Helsinki, 2002: 43-46.

Parker R. M., Bentley K. R., Barnes N. M. Allosteric modulation of 5-HT3 receptors: focus on alcohols and anaesthetic agents. Trends Pharmacol Sci 1996; 17: 95-99.

Patel S. S., Goa K. L. Sevoflurane. A review of its pharmacodynamic and pharmacokinetic properties and its clinical use in general anaesthesia. Drugs 1996; 51: 658-700.

Patterson J. R., Grabois M. Locked-in syndrome: a review of 139 cases. Stroke 1986; 17: 758-764.

Pfister H. W., Feiden W., Einhaupl K. M. Spectrum of complications during bacterial meningitis in adults. Results of a prospective clinical study. Arch Neurol 1993; 50: 575-581.

Pfurtscheller G and da Silva F. EEG event-related desynchronization and event-related synchronization. In: Niedermeyer E and da Silva F eds. Electroencephalography, basic principles, clinical applications and related fields. 5th ed. Lippincott Williams&Wilkins Philadelphia 2005: 1003-1016

Pilge S., Zanner R., Schneider G., Blum J., Kreuzer M., Kochs E. F. Time delay of index calculation: analysis of cerebral state, bispectral, and narcotrend indices. Anesthesiology 2006; 104: 488-494.

Radtke RA. Sleep disorders: laboratory evaluation. In: Ebersole JS and Pedley TA, eds. Current practice of Clinical Electroencephalography. 3rd ed. Lippincott Williams & Wilkins, Philadelphia, 2003: 803-832.

Rampil I. J. A primer for EEG signal processing in anesthesia. Anesthesiology 1998; 89: 980-1002.

Ramsay M. A., Luterman D. L. Dexmedetomidine as a total intravenous anesthetic agent. Anesthesiology 2004; 101: 787-790.

Rau J., Roizen M. F., Doenicke A. W., O'Connor M. F., Strohschneider U. Propofol in an emulsion of long- and medium-chain triglycerides: the effect on pain. Anesth Analg 2001; 93: 382-384.

Revonsuo A. Can functional brain imaging discover consciousness in the brain? Journal of Consciousness studies 2001; 3: 3-23.

Rochat P., Broesch T., Jayne K. Social awareness and early self-recognition. Conscious Cogn 2012; 21: 1491-1497.

Russell I. F., Wang M. Absence of memory for intraoperative information during surgery under adequate general anaesthesia. Br J Anaesth 1997; 78: 3-9.

Saatman K. E., Duhaime A. C., Bullock R., Maas A. I., Valadka A., Manley G. T. Classification of traumatic brain injury for targeted therapies. J Neurotrauma 2008; 25: 719-738.

Sackey P. V., Radell P. J., Granath F., Martling C. R. Bispectral index as a predictor of sedation depth during isoflurane or midazolam sedation in ICU patients. Anaesth Intensive Care 2007; 35: 348-356.

Salmi E., Kaisti K. K., Metsähonkala L., Oikonen V., Aalto S., Nagren K., Hinkka S., Hietala J., Korpi E. R., Scheinin H. Sevoflurane and propofol increase 11C-flumazenil binding to gamma-aminobutyric acidA receptors in humans. Anesth Analg 2004; 99: 1420-1426.

Salmi E., Laitio R. M., Aalto S., Maksimow A. T., Långsjö J. W., Kaisti K. K., Aantaa R., Oikonen V., Metsähonkala L., Nagren K., Korpi E. R., Scheinin H. Xenon does not affect gamma-aminobutyric acid type A receptor binding in humans. Anesth Analg 2008; 106: 129-134.

Sanders R. D., Tononi G., Laureys S., Sleigh J. W. Unresponsiveness not equal unconsciousness. Anesthesiology 2012; 116: 946-959.

Sandin R. H., Enlund G., Samuelsson P., Lennmarken C. Awareness during anaesthesia: a prospective case study. Lancet 2000; 355: 707-711.

San-juan D., Chiappa K. H., Cole A. J. Propofol and the electroencephalogram. Clin Neurophysiol 2010; 121: 998-1006.

Sato K., Shamoto H., Kato M. Effect of sevoflurane on electrocorticogram in normal brain. J Neurosurg Anesthesiol 2002; 14: 63-65.

Sayer M., Ross J. A., Wilson C. M. Analyses of treatment for divers with actual or suspected decompression illness. Diving Hyperb Med 2009; 39: 126-132.

Schaefer W., Meyer P. T., Rossaint R., Baumert J. H., Coburn M., Fries M., Rex S. Myocardial blood flow during general anesthesia with xenon in humans: a positron emission tomography study. Anesthesiology 2011; 114: 1373-1379.

Scheinin H, Alkire M, Kaskinoro K, Långsjö. Method for changing an individual's state of consciousness. US Patent Application 20120083647, 5 April 2012

http://www.freepatentonline.com/y2012/0083647.html

Scheinin M., Lomasney J. W., Hayden-Hixson D. M., Schambra U. B., Caron M. G., Lefkowitz R. J., Fremeau R. T., Jr. Distribution of alpha 2-adrenergic receptor subtype gene expression in rat brain. Brain Res Mol Brain Res 1994; 21: 133-149.

Scheinin M., Schwinn D. A. The locus coeruleus. Site of hypnotic actions of alpha 2-adrenoceptor agonists? Anesthesiology 1992; 76: 873-875.

Schlunzen L., Vafaee M. S., Cold G. E., Rasmussen M., Nielsen J. F., Gjedde A. Effects of

subanaesthetic and anaesthetic doses of sevoflurane on regional cerebral blood flow in healthy volunteers. A positron emission tomographic study. Acta Anaesthesiol Scand 2004; 48: 1268-1276.

Schmidt G. N., Bischoff P., Standl T., Hellstern A., Teuber O., Schulte Esch J. Comparative evaluation of the Datex-Ohmeda S/5 Entropy Module and the Bispectral Index monitor during propofol-remifentanil anesthesia. Anesthesiology 2004; 101: 1283-1290.

Schneider G., Gelb A. W., Schmeller B., Tschakert R., Kochs E. Detection of awareness in surgical patients with EEG-based indices--bispectral index and patient state index. Br J Anaesth 2003; 91: 329-335.

Schommer K., Menold E., Subudhi A. W., Bartsch P. Health risk for athletes at moderate altitude and normobaric hypoxia. Br J Sports Med 2012; 46: 828-832.

Schrouff J., Perlbarg V., Boly M., Marrelec G., Boveroux P., Vanhaudenhuyse A., Bruno M. A., Laureys S., Phillips C., Pelegrini-Issac M., Maquet P., Benali H. Brain functional integration decreases during propofol-induced loss of consciousness. Neuroimage 2011; 57: 198-205.

Schultz B., Otto C., Schultz A., Osthaus W. A., Krauss T., Dieck T., Sander B., Rahe-Meyer N., Raymondos K. Incidence of epileptiform EEG activity in children during mask induction of anaesthesia with brief administration of 8% sevoflurane. PLoS One 2012; 7: e40903.

Shafiq F., Naqvi H. I., Ahmed A. Effects of bispectral index monitoring on isoflurane consumption and recovery profiles for anesthesia in an elderly asian population. J Anaesthesiol Clin Pharmacol 2012; 28: 348-352.

Sinclair S. E., Altemeier W. A., Matute-Bello G., Chi E. Y. Augmented lung injury due to interaction between hyperoxia and mechanical ventilation. Crit Care Med 2004; 32: 2496-2501.

Sinkovic A., Smolle-Juettner F. M., Krunic B., Marinsekz M. Severe carbon monoxide poisoning treated by hyperbaric oxygen therapy--a case report. Inhal Toxicol 2006; 18: 211-214.

Sleigh J. W., Galletly D. C. A model of the electrocortical effects of general anaesthesia. Br J Anaesth 1997; 78: 260-263.

Smith J. D., Shields W. E., Washburn D. A. The comparative psychology of uncertainty monitoring and metacognition. Behav Brain Sci 2003; 26: 317-339; discussion 340-373.

Smith M. Anesthestic agents and status epilepticus. Epilepsia 2011; 52 Suppl 8: 42-44.

Smith W. D., Dutton R. C., Smith N. T. Measuring the performance of anesthetic depth indicators. Anesthesiology 1996; 84: 38-51.

Sneyd J. R. Recent advances in intravenous anaesthesia. Br J Anaesth 2004; 93: 725-736.

Song D., Joshi G. P., White P. F. Titration of volatile anesthetics using bispectral index facilitates recovery after ambulatory anesthesia. Anesthesiology 1997; 87: 842-848.

Sonkajärvi E., Alahuhta S., Suominen K., Hakalax N., Vakkuri A., Löppönen H., Ohtonen P., Jäntti V. Topographic electroencephalogram in children during mask induction of anaesthesia with sevoflurane. Acta Anaesthesiol Scand 2009; 53: 77-84.

Sonner J. M., Antognini J. F., Dutton R. C., Flood P., Gray A. T., Harris R. A., Homanics G. E., Kendig J., Orser B., Raines D. E., Rampil I. J., Trudell J., Vissel B., Eger E. I., 2nd. Inhaled anesthetics and immobility: mechanisms, mysteries, and minimum alveolar anesthetic concentration. Anesth Analg 2003; 97: 718-740

Stamatakis E. A., Adapa R. M., Absalom A. R., Menon D. K. Changes in resting neural connectivity during propofol sedation. PLoS One 2010; 5: e14224.

Talke P., Lobo E., Brown R. Systemically administered alpha2-agonist-induced peripheral vasoconstriction in humans. Anesthesiology 2003; 99: 65-70.

Tarvainen M. P., Hiltunen J. K., Ranta-aho P. O., Karjalainen P. A. Estimation of nonstationary EEG with Kalman smoother approach: an application to event-related synchronization (ERS). IEEE Trans Biomed Eng 2004; 51: 516-524.

Tarvainen M. P., Georgiadis S., Laitio T., Lipponen J. A., Karjalainen P. A., Kaskinoro K., Scheinin H. Heart rate variability dynamics during low-dose propofol and dexmedetomidine anesthesia. Ann Biomed Eng 2012; 40: 1802-1813.

Teasdale G., Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974; 2: 81-84.

Trapani G., Altomare C., Liso G., Sanna E., Biggio G. Propofol in anesthesia. Mechanism of action, structure-activity relationships, and drug delivery. Curr Med Chem 2000; 7: 249-271.

Tsuneyoshi I., Boyle W. A., 3rd, Kanmura Y., Fujimoto T. Hyperbaric hyperoxia suppresses growth of Staphylococcus aureus, including methicillin-resistant strains. J Anesth 2001; 15: 29-32.

Vakkuri A., Jäntti V., Särkelä M., Lindgren L., Korttila K., Yli-Hankala A. Epileptiform EEG during sevoflurane mask induction: effect of delaying the onset of hyperventilation. Acta Anaesthesiol Scand 2000; 44: 713-719.

Vakkuri A., Yli-Hankala A., Sandin R., Mustola S., Hoymork S., Nyblom S., Talja P., Sampson T., van Gils M., Viertiö-Oja H. Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol-nitrous oxide-alfentanil anesthesia. Anesthesiology 2005; 103: 274-279.

Vakkuri A., Yli-Hankala A., Talja P., Mustola S., Tolvanen-Laakso H., Sampson T., Viertiö-Oja H. Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. Acta Anaesthesiol Scand 2004; 48: 145-153.

Vanluchene A. L., Struys M. M., Heyse B. E., Mortier E. P. Spectral entropy measurement of patient responsiveness during propofol and remifentanil. A comparison with the bispectral index. Br J Anaesth 2004a; 93: 645-654.

Vanluchene A. L., Vereecke H., Thas O., Mortier E. P., Shafer S. L., Struys M. M. Spectral entropy as an electroencephalographic measure of anesthetic drug effect: a comparison with bispectral index and processed midlatency auditory evoked response. Anesthesiology 2004b; 101: 34-42.

Vasella F. C., Frascarolo P., Spahn D. R., Magnusson L. Antagonism of neuromuscular blockade but not muscle relaxation affects depth of anaesthesia. Br J Anaesth 2005; 94: 742-747.

Venn R. M., Bradshaw C. J., Spencer R., Brealey D., Caudwell E., Naughton C., Vedio A., Singer M., Feneck R., Treacher D., Willatts S. M., Grounds R. M. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia 1999; 54: 1136-1142.

Venn R. M., Grounds R. M. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. Br J Anaesth 2001; 87: 684-690.

Vernon J. M., Lang E., Sebel P. S., Manberg P. Prediction of movement using bispectral electroencephalographic analysis during propofol/alfentanil or isoflurane/alfentanil anesthesia. Anesth Analg 1995; 80: 780-785.

Veselis R. A., Reinsel R. A., Feshchenko V. A., Dnistrian A. M. A neuroanatomical construct for the amnesic effects of propofol. Anesthesiology 2002; 97: 329-337.

Viertiö-Oja H., Maja V., Särkelä M., Talja P., Tenkanen N., Tolvanen-Laakso H., Paloheimo M., Vakkuri A., Yli-Hankala A., Meriläinen P. Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. Acta Anaesthesiol Scand 2004; 48: 154-161.

Violet J. M., Downie D. L., Nakisa R. C., Lieb W. R., Franks N. P. Differential sensitivities of mammalian neuronal and muscle nicotinic acetylcholine receptors to general anesthetics. Anesthesiology 1997; 86: 866-874.

Visser G. H., van Hulst R. A., Wieneke G. H., van Huffelen A. C. The contribution of conventional and quantitative electroencephalography during monitoring of exposure to hyperbaric oxygen. Undersea Hyperb Med 1996; 23: 91-98.

Walsh T. S., Ramsay P., Lapinlampi T. P., Särkelä M. O., Viertiö-Oja H. E., Meriläinen P. T. An assessment of the validity of spectral entropy as a measure of sedation state in mechanically ventilated critically ill patients. Intensive Care Med 2008; 34: 308-315.

Westmoreland PF. Electroencphalography: Adult, normal, and benign variants. In: Daube JR and Rubin DI, eds. Clinical Neurophysiology. 3rd ed. Oxford University Press, Oxford 2009: 119-136.

White P. F., Way W. L., Trevor A. J. Ketamine--its pharmacology and therapeutic uses. Anesthesiology 1982; 56: 119-136.

Wijdicks E. F., Bamlet W. R., Maramattom B. V., Manno E. M., McClelland R. L. Validation of a new coma scale: The FOUR score. Ann Neurol 2005; 58: 585-593.

Yaman F., Ozcan N., Ozcan A., Kaymak C., Basar H. Assesment of correlation between bispectral index and four common sedation scales used in mechanically ventilated patients in ICU. Eur Rev Med Pharmacol Sci 2012; 16: 660-666.

Yasuda N., Lockhart S. H., Eger E. I., 2nd, Weiskopf R. B., Liu J., Laster M., Taheri S., Peterson N. A. Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg 1991; 72: 316-324.

Yildiz S., Aktas S., Cimsit M., Ay H., Togrol E. Seizure incidence in 80,000 patient treatments with

hyperbaric oxygen. Aviat Space Environ Med 2004; 75: 992-994.

Yli-Hankala A., Jäntti V., Pyykkö I., Lindgren L. Vibration stimulus induced EEG bursts in isoflurane anaesthesia. Electroencephalogr Clin Neurophysiol 1993; 87: 215-220.

Yli-Hankala A., Vakkuri A., Särkelä M., Lindgren L., Korttila K., Jäntti V. Epileptiform electroencephalogram during mask induction of anesthesia with sevoflurane. Anesthesiology 1999; 91: 1596-1603.

Young G. B. The EEG in coma. J Clin Neurophysiol 2000; 17: 473-485.

Zanner R., Pilge S., Kochs E. F., Kreuzer M., Schneider G. Time delay of electroencephalogram index calculation: analysis of cerebral state, bispectral, and Narcotrend indices using perioperatively recorded electroencephalographic signals. Br J Anaesth 2009; 103: 394-399.

Zare M. A., Ahmadi K., Zadegan S. A., Farsi D., Rahimi-Movaghar V. Effects of brain contusion on mild traumatic brain-injured patients. Int J Neurosci 2013; 123: 65-69.

Zeman A. Consciousness. Brain 2001; 124: 1263-1289.

Zeman A. Consciousness: concepts, neurobiology, terminology of impairments, theoretical models and philosophical background. Handb Clin Neurol 2008; 90: 3-31.