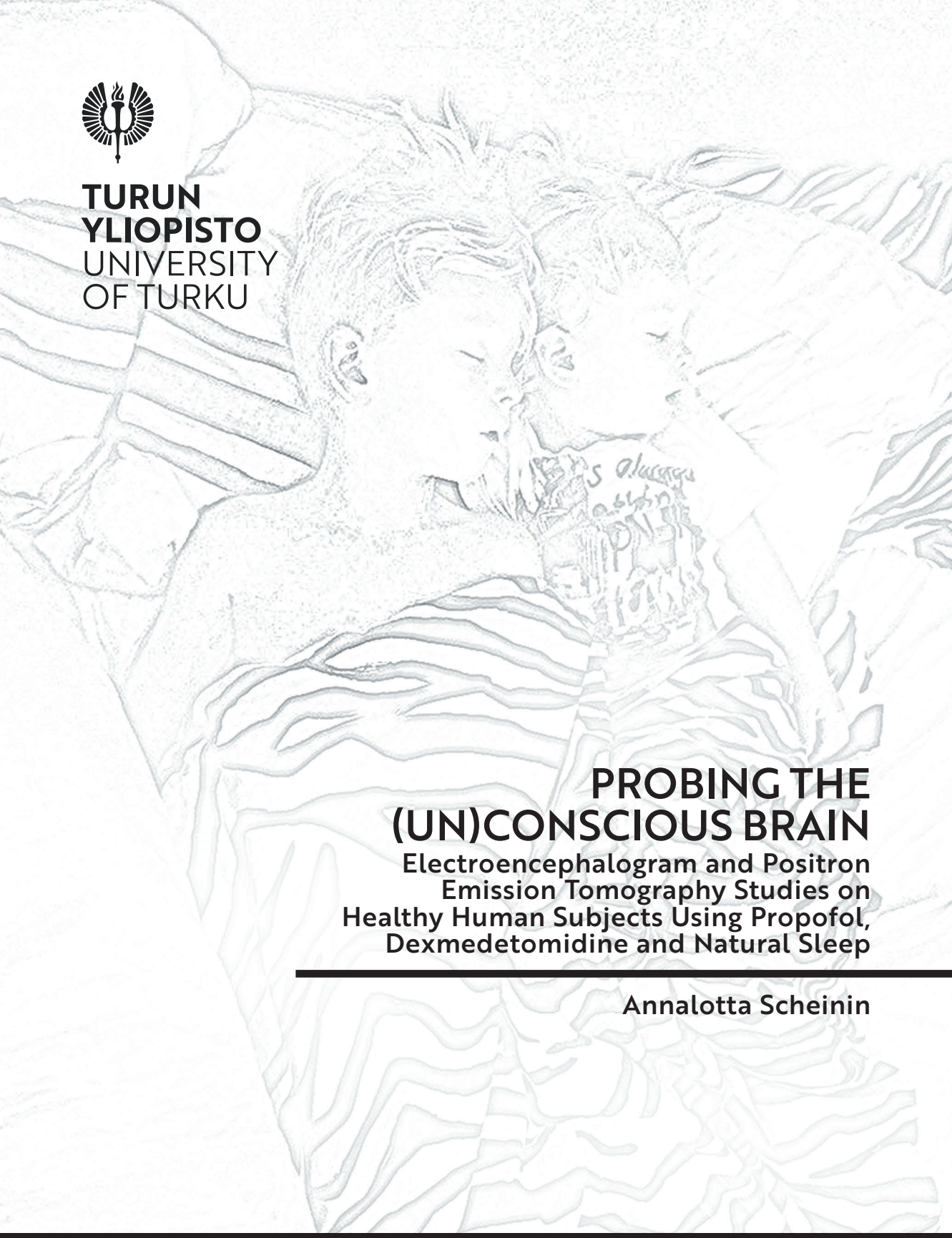

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PROBING THE (UN)CONSCIOUS BRAIN

Electroencephalogram and Positron Emission Tomography Studies on Healthy Human Subjects Using Propofol, Dexmedetomidine and Natural Sleep

Annalotta Scheinin

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1652 | MEDICA – ODONTOLOGICA | TURKU 2022

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University of Turku

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To my family

UNIVERSITY OF TURKU
Faculty of Medicine
Anesthesiology, Intensive Care, Emergency Care and Pain Medicine and Turku PET Centre
ANNALOTTA SCHEININ: Probing the (Un)Conscious Brain – EEG and PET Studies on Healthy Human Subjects Using Propofol, Dexmedetomidine and Natural Sleep.
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ABSTRACT

Consciousness cannot be objectively measured. By employing anesthesia and neurophysiologic measurements to study human consciousness, unconsciousness has been found to associate with suppression of regional brain activity and with breakdown of communication between different brain areas. However, due to conceptual and methodological heterogeneity, a unified theory on the "mechanisms" of (un)consciousness is lacking. Many anesthesia studies have employed arbitrary dosing schemes and disregarded the pharmacologic effects of the used drugs. Thus, many inferences on human consciousness have been premature.

The aim of this study was to use rigorous experimental protocols to study human consciousness in healthy subjects. Two anesthetics (propofol and dexmedetomidine) and natural sleep were used. First, we explored EEG changes in association to different states of consciousness during increasing doses and a steady-state infusion of two anesthetics. Second, by measuring N400 event related potentials, we explored whether or not sematic processing persists during an unresponsive state induced by the two drugs. Finally, positron emission tomography (PET) imaging was conducted to reveal brain activity alterations between connected and disconnected states (confirmed by subjective reports of mental content) induced by anesthesia and sleep.

Based on EEG and PET findings, we discovered that the state-related changes were distinct and separable from the overall effects of the different interventions. At awakening from steady-state anesthesia, spectral EEG patterns only partially reverted towards baseline values despite a restored conscious state, illustrating the multifaceted nature of anesthesia-EEG. PET imaging revealed that activity of a core brain network correlated best to the connected state *per se*. Furthermore, unresponsiveness and sleep rarely depicted unconsciousness (i.e., complete absence of subjective experiences) and semantic processing was partly preserved during dexmedetomidine-induced unresponsiveness. This study highlights the multi-dimensional nature of human consciousness and the related experimental challenges.

KEYWORDS: Consciousness, unconsciousness, propofol, dexmedetomidine, electroencephalography, positron emission tomography, event-related potentials, N400 ERP, connected consciousness, disconnected consciousness

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TIIVISTELMÄ

Tietoisuutta ei voi mitata objektiivisesti. Anestesia- ja neurofysiologiset tutkimukset ovat osoittaneet tajuttomuuden liittyvän eri aivoalueiden aktiivisuuden vaimenemiseen sekä niiden välisten yhteyksien heikkenemiseen. Käsitteellisen ja metodologisen monimuotoisuuden vuoksi yhtenäinen tajuttomuuden ”mekanismi” on kuitenkin vielä löytämättä. Monissa anestesiatutkimuksissa lääkkeiden annostelu on umpimähkäistä ja lääkkeiden farmakologiset vaikutukset on jätetty huomiotta. Näin ollen monet johtopäätökset tietoisuudesta ovat olleet ennenaikaisia.

Tämän työn tavoitteena oli käyttää tarkkoja koeasetelmia ja terveitä koehenkilöitä ihmisen tietoisuuden tutkimiseen. Tutkimuksessa käytettiin kahta anestesia-ainetta (propofoli ja deksmedetomidiini) sekä luonnollista unta. Ensimmäiseksi tutkimme aivosähkökäyrämuutoksia eri tajunnantiloissa nousevien ja tasaisten lääkepitoisuuksien aikana. Toiseksi tutkimme aivojen kielellistä prosessointia (N400 herätevasteet) kahdella lääkkeellä aiheutetun reagoimattoman tilan aikana. Lopuksi, aivojen aktiivisuusmuutoksia tutkittiin positroniemissiotomografia (PET) -kuvauksilla, erityisesti vertaamalla kytkeytyneitä sekä lääkkeellisesti ja fysiologisesti aiheutettuja irtikytkeytyneitä tiloja keskenään. Tajunnantilat varmistettiin subjektiivisin haastatteluin.

EEG ja PET tulokset osoittivat että tajunnantilan vaihteluun liittyvät aivotoiminnan muutokset ovat erillisiä ja eroteltavissa eri interventioiden kokonaisvaikutuksista. Koehenkilön herättäminen tasaisen lääkeannostelun aikana palautti vain osittain EEG:n spektrimuutokset, ja tämä osoittaa anestesia-EEG:n moniulotteisen luonteen. PET-kuvaukset osoittivat että aktiivisuusmuutokset aivojen syvien rakenteiden verkostossa korreloivat parhaiten tajunnantilan vaihteluun. Lisäksi, reagoimaton tila ja luonnollinen uni merkitsi vain harvoin tajuttomuutta (subjektiivisten kokemusten puuttumista). Kielellinen prosessointi säilyi osittain deksmedetomidiinin aiheuttaman reagoimattomuuden aikana. Tutkimuksemme havainnollistaa ihmisen tietoisuuden moniulotteisuuden ja kokeellisen tietoisuustutkimuksen sudenkuopat.

AVAINSANAT: Tietoisuus, tajuttomuus, propofoli, deksmedetomidiini, elektroenkefalografia, positroniemissiotomografia, herätevaste, N400 herätevaste, kytkeytyneisyys, irtikytkeytyneisyys

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Abbreviations

ACC	Anterior Cingulate Cortex
AG	Angular Gyrus
ASA	American Society of Anesthesiologists Physical Status Classification
AWR	Awareness with Explicit Recall
BIS	Bispectral Index
BOLD	Blood Oxygen Level Dependent
CBF	Cerebral Blood Flow
CLT	Central Lateral Thalamus
CMR	Cerebral Metabolic Rate
CSM	Cerebral State Monitor
DG	Deoxyglucose
DMN	Default Mode Network
dMPFC	Dorsomedial Prefrontal Cortex
daTT	Dorsal Attentional System
DoA	Depth of Anesthesia -monitor
DoC	Disorder(s) of Consciousness
EEG	Electroencephalogram
ECN	Executive Control Network
EMG	Electromyogram
EOG	Electro-oculogram
ERP	Event Related Potential
FDG	Fluorodeoxyglucose
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma Amino Butyric Acid
GNW	Global Neuronal Workspace
GWT	Global Workspace Theory
HRRT	High Resolution Research Tomograph
IIT	Integrated Information Theory
IPL	Inferior Parietal Lobule
LFA	Low-Frequency Activity
LFP	Local Field Potential

LOC	Loss of Consciousness
LOR	Loss of Responsiveness
MCS	Minimally Conscious State
N400	N400 Event related potential
NCC	Neural Correlates of Consciousness
NMDA	N-methyl D-aspartate
NREM	non-Rapid Eye Movement
OEF	Oxygen Extraction Fraction
PAC	Phase–Amplitude Coupling
PCC	Posterior Cingulate Cortex
PCI	Perturbational Complexity Index
PCun	Precuneus
PET	Positron Emission Tomography
PHG	Parahippocampal Gyrus
PLS	Partial Least Squares
PSG	Polysomnography
rCBF	Regional Cerebral Blood Flow
R	Responsive State
RE	Response Entropy
REM	Rapid Eye Movement
ROR	Return of Responsiveness
R-test	Responsiveness Test
RSN	Resting State Network
SE	State Entropy
SED	Sedative state
SD	Standard Deviation
SDW	Sleep Deprived Wakefulness
SN	Salience Network
SWA	Slow Wave Activity
SWS	Slow Wave Sleep
TCI	Target Controlled Infusion
TMN	Tuberomamillary Nucleus
TMS	Transcranial Magnetic Stimulation
UR	Unresponsive State
UWS	Unresponsive Wakefulness Syndrome (former “vegetative state”)
VLPO	Ventrolateral Preoptic Nucleus
vMPFC	Ventromedial Prefrontal Cortex
VS	Vegetative State (or Unresponsive Wakefulness Syndrome, UWS)
VTA	Ventral Tegmental Area
2PK	Two-pore potassium

List of Original Publications

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

I Scheinin A, Kallionpää RE, Li D, Kallioinen M, Kaisti K, Långsjö J, Maksimow A, Vahlberg T, Valli K, Mashour G, Revonsuo A, Scheinin H. Differentiating drug-related and state-related effects of dexmedetomidine and propofol on the electroencephalogram. *Anesthesiology,* 2018; 129: 22–36

II Kallionpää RE, Scheinin A, Kallionpää RA, Sandman N, Kallioinen M, Laitio R, Laitio T, Kaskinoro K, Kuusela T, Revonsuo A, Scheinin H, Valli K. Spoken words are processed during dexmedetomidine-induced unresponsiveness. *British Journal of Anaesthesia*, 2018; 121 (1): 270–280

III Scheinin A, Kantonen O, Alkire M, Långsjö J, Kallionpää RE, Kaisti K, Radek L, Johansson J, Sandman N, Nyman M, Scheinin M, Vahlberg T, Revonsuo A, Valli K, Scheinin H. Foundations of Human Consciousness - Imaging the Twilight Zone. *Journal of Neuroscience*, 2021; 41(8): 1769–1778

1 Introduction

In 2005, to celebrate their 125th anniversary, *Science* magazine published a special issue dedicated to the most important unanswered scientific questions. The first question was “What is the universe made of?”, followed by “What is the biological basis of consciousness?”. Since the mid 90’s, the latter question has had an essential role in neuroscience. In medical fields such as anesthesiology and neurology, consciousness has been investigated by exploring different states of consciousness during general anesthesia or during altered states of consciousness caused by, e.g., brain pathology. Methodological emphasis has been in functional brain imaging and electrophysiologic recordings.

The study of human consciousness is, however, facing a number of fundamental issues. These are, in part, explained by study design and conceptual differences, as well as methodological heterogeneity. It has traditionally been thought that the *neural correlates of consciousness* (NCC) are unveiled simply by comparing two distinct states of consciousness; an awake state and an anesthetized (and presumably unconscious) state. However, such comparisons reflect also other functional changes, such as the independent effects of the used drugs, drowsiness and the evident decline in cognitive capacities. Anesthetic agents have also very steep concentration-effect curves, and many studies employ arbitrary administration protocols with standard boluses at baseline. Individual susceptibility to anesthetics further disturbs the setup. We argue, that the aforementioned paradigm does not reveal the neural correlates of consciousness.

Nevertheless, anesthesia offers a unique possibility to study consciousness in experimental settings. Natural sleep can also be used, together enabling comparisons of conscious and unconscious states of different etiologies. Importantly, anesthetic-induced unresponsiveness may not be characterized by profound unconsciousness, but rather, by a disconnected state with subjective, dream-like experiences comparable to those during normal sleep. With this in mind, many previous studies have explored a heterogenous sample of phenomenal and pharmacological conditions. We introduce rigorous experimental protocols, which could unravel the mysteries of consciousness, unconsciousness and their different dimensions.

2 Review of the Literature

2.1 Consciousness – From Theories to Practice

2.1.1 Theoretical Frameworks

Human consciousness is one of the most mysterious phenomena in mankind. Despite major scientific breakthroughs in the past decades, a unified theory on the "mechanisms" of human consciousness has not been formed. It is yet to be explained which brain structures, functions or interconnections enable conscious experiences to emerge. Conversely, what happens in the brain when a person falls asleep or is anesthetized and finally becomes unconscious? Philosophers ask how purely physical substance and electrical activity give rise to the subjective experiences that is consciousness? This question has been referred to as the *hard problem of consciousness* by philosopher David Chalmers, implying that the problem persists even when the performance of all the relevant functions is explained (Chalmers, 1995). To be conscious is a purely subjective experience ("what it is like", Nagel, 1974), and due to that subjectivity, it is argued to be indescribable by any scientific approach. Some have consequently deemed human consciousness an unsolvable mystery.

In the 1990's, Francis Crick and Christof Koch argued that the time was ripe for neuroscience to take consciousness seriously as an experimental problem. They suggested that, for the time being, neuroscience can set aside the hard philosophical problem of consciousness, and instead focus on the search for the *neural correlates of consciousness* (NCC). According to them, the NCC can be defined as the minimally sufficient neural system or activity that invariably co-occurs together with a conscious experience of a specific kind (Koch, 2004). Their influential suggestion has led to the rise of the neuroscience of consciousness as a rapidly growing new field that has made great progress during the last 20 years (for reviews, see Koch et al 2004; Koch et al., 2016).

Modern experimental approaches have been inspired by the many contemporary theories on consciousness, and the *information integration theory of consciousness* (IIT) is possibly the most acknowledged theoretical framework. First developed by Giulio Tononi, the IIT argues that consciousness corresponds to the capacity of a

system to integrate information. Experience, i.e., consciousness, is determined by the informational relationships among its elements (Tononi and Edelman, 1998; Tononi, 2004; Tononi et al., 2016). The IIT has evolved to support that posterior regions of the brain are more crucial to consciousness *per se*, which is supported by empirical data using anesthesia and sleep (Boly et al., 2017; Siclari et al., 2017)). Another theoretical framework, *the global workspace theory* (GWT), was first described by Baars (Baars, 1988). The GWT argues that perceptual contents only become conscious when they are widely "broadcasted" across the brain; The wide accessibility of information is hypothesized to constitute conscious experience. The GWT is a cognitive architecture with special global workspace models, and these models have later been individually refined, such as the *global neuronal workspace* (GNW) by prof. Stanislas Dehaene. As opposed to the posterior hot zone theory inspired by the IIT (Ihalainen et al., 2021), the GNW is convinced of the importance of the prefrontal cortex (Dehaene and Changeux, 2011), as it suggests that this area, which controls higher order cognitive processes, collects and prioritizes information from sensory input. The IIT and GWT were recently revealed to be put against each other, i.e., tested experimentally on comatose patients (Reardon, 2019).

Other theoretical frameworks have also been introduced. *The recurrent processing theory* (Lamme and Roelfsema, 2000) suggests that a conscious process corresponds to any neural code that is shaped by recurrent loops from higher-order to lower-order areas and back. Accordingly, recurrent processing-induced network plasticity is a potential "missing ingredient" in many theories of consciousness (Lamme, 2018). This theory asks whether the real mystery of consciousness lies in the fact that we experience the world that surrounds us, or in the ability to reflect on it and cognitively manipulate what we perceive; is consciousness about seeing or about knowing what we see?

These theories have also received criticism. Some claim that these *causal structure* theories end up in an empirical impasse and are "either false or outside the realm of science" (Doerig et al., 2019), and such arguments illustrate some fundamental disagreements in the field. Nevertheless, contemporary consciousness research is largely inspired by the aforementioned theories. Modern neuroscience is blessed with numerous possibilities and state-of-the-art methodologies. These opportunities, problems as well as anesthetic mechanisms and how general anesthesia may unravel some of these mysteries, are reviewed and discussed here.

2.1.2 Defining Consciousness and Unconsciousness

Consciousness is a multi-dimensional phenomenon and covers a variety of concepts and impressions. What does one perceive as being conscious? Is it the ability to interact with the environment? Is it self-awareness? Is it the ability to dream?

Ultimately, the definition of consciousness is context-dependent and remains, thus, partly ambiguous.

Traditionally, two major components of consciousness are recognized, i.e., the *content* and *level* of consciousness (Laureys et al., 2004). The content of consciousness refers to the *quality* of experience itself, e.g., the sensation of pain, the color of the sky or the sound of a bird (i.e., awareness), whereas the level of consciousness refers to consciousness *as a state*, e.g., a wakeful state, an anesthetized state or coma (i.e., arousal). In the healthy brain, a simplified view is that the two components decrease or increase in parallel, such as during wakefulness, anesthesia or sleep (with the exception of rapid eye movement, REM, sleep). Importantly, there are pathological conditions where the two components may become dissociated. In *unresponsive wakefulness syndrome* (UWS, former vegetative state, VS), the cerebral cortex is severely injured, whereas brainstem functions can be relatively preserved. Thus, a patient may be wakeful (open eyes in reaction to a stimulus, grimace, tear and show intact sleep-wake cycle), yet be unaware of one's environment (see 2.1.4 Consciousness and Clinical Implications). Contrarily, locked-in syndrome is characterized by inability to move despite preserved awareness and arousal. Figure 1. portrays how awareness and arousal may manifest in selected clinical conditions.

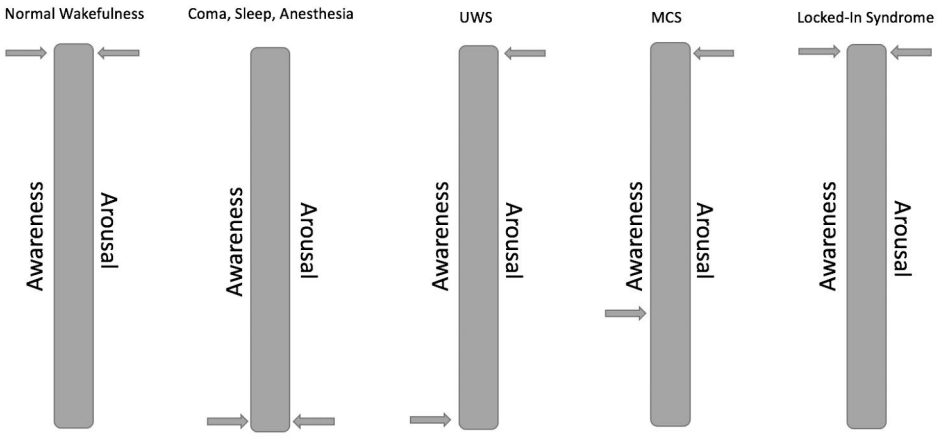

Figure 1. A simplification of the two components of consciousness, awareness and arousal, and some possible clinical manifestations. Unintended awareness during anesthesia may manifest similarly to locked-in syndrome. UWS = Unresponsive Wakefulness Syndrome, MCS = Minimally Conscious State. Modified from Laureys et al., 2004.

The aforementioned division is, however, a coarse simplification. A complementing and novel approach has tried to acknowledge the different

dimensions of consciousness by introducing the concepts of *local* and *global* states (Bayne et al., 2016). Accordingly, consciousness cannot be illustrated linearly on a single-dimension scale, but rather, is characterized as regions in a multidimensional space. Local states are defined in terms of their contents or phenomenal character, whereas the global state characterizes an organism's overall conscious condition. In summary, global states differ from each other in terms of how they gate conscious content and accordingly, consciousness is built up by the presence or absence of its key elements (Bayne et al., 2016; Bonhomme et al., 2019).

Other simplifications are also recognized. There is a fundamental agreement, that unresponsiveness is not a synonym for unconsciousness (Sanders et al., 2012). This is, however, overlooked in many experimental studies on consciousness, where a conscious state is indicated by behavioral responsiveness to a given stimulus. However, a person may be conscious and aware even in the absence of responsiveness. Figure 2 schematically illustrates the components of stimulus processing and motor readiness, all of which must be intact for a stimulus to eventually leads to a purposeful behavioral response.

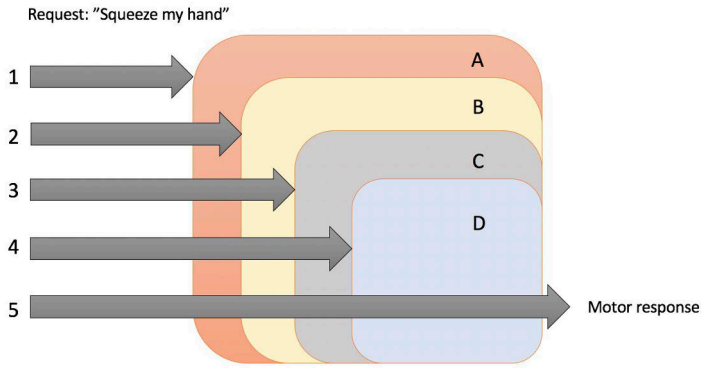

Figure 2. A schematic illustration of the components of stimulus processing and intact responsiveness. A= a conscious state, B= a connected state; comprehension of the stimulus, C= motor readiness; motivation and intention to respond, D= ability to respond. 1= Stimuli blocked from reaching consciousness (coma or brain death); 2= stimuli may (but not necessarily) affect conscious content (sleep, anesthesia); 3= deficient will to act (e.g., anterior cingulate lesion, Crick, 1995); 4= inability to respond regardless of total awareness (awareness during anesthesia, locked-in syndrome); 5= purposeful response (normal wakefulness). Modified, with permission, from Långsjö et al., 2012.

Scientists have only recently begun to acknowledge, that unresponsiveness does not unequivocally depict unconsciousness, but rather, is often accompanied by a variety of internal, *connected* or *disconnected*, experiences. In a *connected* state, stimuli from the surroundings modulate our experiences, such as during normal alert

wakefulness. Consistently, a *disconnected conscious* state would refer to a state where our experiences are not modulated by external stimuli, but we still continue to have internal subjective experiences, e.g., dreams. Also unconsciousness, i.e., complete absence of experiences, represents a disconnected state. Table 1 summarizes the cognitive and behavioral properties of connected conscious, disconnected conscious and unconscious states.

Table 1. Characteristics of connected and disconnected states of consciousness. Modified from Sanders et al., 2012; Bonhomme et al., 2019.

		Disconnectedness	
	Connected consciousness	Disconnected consciousness	Unconsciousness
Awareness of external stimuli	Yes	No	No
Behavioral responsiveness	Yes*	No	No
Subjective experiences	Yes	Yes	No

*Responsiveness may be absent in rare cases such as locked-in syndrome or unsuccessful general anesthesia.

2.1.3 Brain Networks and Consciousness

In recent years, increasing attention has been directed towards distinct neuroanatomical and functional networks that contribute to different behavioral and phenomenal conditions. Electrophysiological (such as EEG) or functional imaging (such as functional magnetic resonance imaging, fMRI, or positron emission tomography, PET) modalities can be used to study these brain networks.

Already in the 60's and 70's, cognitive brain functions could be visualized by single-photon emission tomography imaging, when Lassen and Ingvar utilized radiotracer ^{133}Xe to localize sensory, motor, and mental functions in a human brain (Lassen et al., 1978). Later on, Kety and Sokoloff developed the ^{14}C-DG and ^{18}F-FDG tracers, which facilitated direct mapping of neuroanatomical and functional pathways (Sokoloff, 1996). FMRI on the other hand, is a non-invasive method (no radioactive tracer is needed) developed in the 90's, and was first used in studies using visual tasks and imaging the activation on the visual cortex (Kwong et al., 1992; Ogawa et al., 1992). The fMRI is often used synonymously with fMRI blood-oxygenation-level-dependent (BOLD) methodology, which is based on the detection oxygen availability in the blood and the related local change in the magnetic field. In activated brain areas, the oxygen availability (paradoxically) increases (supply exceeds demand), and has been shown to reflect the changes in neuronal activity

(Logothetis et al., 2001; Raichle, 2001). The BOLD signal has also been found to fluctuate over time, revealing functionally coherent brain regions, i.e., networks in precence or absence of a task.

In the early 2000's, a PET study introduced that the resting brain is active "by default", prominently observed by coincidental fluctuation in the medial and lateral fronto-parietal areas (Raichle, 2001). Since then, there has been growing interest in so-called resting-state networks (RSN's), which have been investigated both with PET and fMRI methods. For instance, posterior cingulate and the precuneus, the posterior lateral cortices, the insular cortices, the cingulate, and aspects of both ventral and dorsal medial pre-frontal cortex have been described to associate with mind-wandering, which has been argued to be the brain's "psychological baseline" (Raichle et al., PNAS 2001; Mason et al., 2007). This functional network has also been named the default mode network (DMN), and it is attenuated when one is engaged in goal-directed actions (Shulman et al., 1997; Mazoyer et al., 2001) or when apparent consciousness is lost during sleep (Horovitz et al., 2009), anesthesia (Boveroux et al., 2010; Guldenmund et al., 2017) or as a result of brain pathology (Vanhaudenhuyse et al., 2010). Activity fluctuations in distinct RSN's at baseline have been shown to affect stimulus perception, suggesting a functional dissociation between self- and external awareness (Boly et al., 2008a). The DMN is mostly associated with self-awareness, the executive control network (ECN) with executive function and awareness of the environment (Boly et al., 2008a; Vanhaudenhuyse et al., 2011), and the salience network (SN) with the interplay between the DMN and ECN (Menon and Uddin, 2010; Demertzi et al., 2013). These systems have also been described as task-positive (dorsal attentional system, dATT, activates during a task) and task-negative (the DMN, deactivates during a task) systems (Fox et al., 2005). In the literature, the nomenclature may vary and the networks have partly overlapping regions, resulting in minor inconsistencies across publications. The main networks are illustrated in Figure 3.

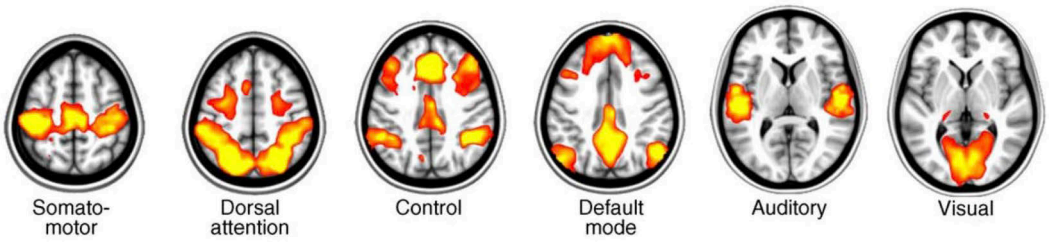

Figure 3. Six functional networks (somatomotor, dorsal attention, executive control, DMN, auditory and visual) visualized using fMRI BOLD data. The images portray patterns of spatial coherence within the brain, where a seed region is chosen and its activity is correlated with the rest of the brain. Reproduced, with permission, from Raichle, 2010.

Brain networks have also been implicated in consciousness science. Studies have utilized, e.g., general anesthesia to study network alterations in different conditions by using both functional brain imaging and electrophysiologic measurements. In general, there are four different types on connectivity that can be identified: 1) Structural, which refers to anatomical connections between brain regions. 2) Functional, which refers to the covariation of activities within different brain regions (e.g., coherence and phase lag index). 3) Directional, which acknowledges the direction of connectivity by identifying regional alterations that relate to alterations in another region in the past (e.g., transfer entropy, Granger causality). 4) Effective, which models the causal relationships between multiple brain regions over time (for a review, see (Mashour and Hudetz, 2018). Such connectivity measures have been calculated in numerous studies using general anesthesia, brain pathology and sleep, with somewhat heterogenous findings between studies and different drugs (see 2.4 Scientific Search for the Neural Correlates of Consciousness).

The most contemporary methodology rests on the mathematical technique of graph theory, where various properties of large-scale brain networks can be elucidated and visually presented. This analytical approach measures the capacity of a system to transfer information, and distinct network variables, e.g., centrality, efficiency and path length are used to describe the properties of these networks. In neuroscience, there is a fundamental premise that the brain is topologically organized to maximize information transfer within and between networks (Bullmore and Sporns, 2009, 2012). Graph theoretical examination is not restricted to the brain, but can be applied to various types of networks, e.g., the internet or the airport system.

2.1.4 Consciousness and Clinical Implications

The ability to detect or measure consciousness is a relevant clinical objective. At present, there is no method that could indisputably and individually detect the presence or absence of consciousness in a person. Disorders of consciousness (DoC) are a heterogeneous group of conditions, where the level of consciousness (awareness and/or arousal) is perturbed, most often as a result of diffuse or regional traumatic or anoxic brain injury. Unresponsive wakefulness syndrome (UWS, also known as vegetative state, VS) is the most severe form of DoC, where communication with the outside world is lost and no apparent awareness can be detected (Jennett 1972). Yet, patients may express intact sleep-wake cycle, open their eyes in reaction to tactile stimuli, grimace, tear and seem “awake” to the observer. Minimally conscious state (MCS) also manifests in this manner, but is distinguished from UWS/VS by partial preservation of cognitive and motor functions, such as simple command-following and delicate purposeful behavior

(Giacino et al., 2002). However, these conditions are susceptible to misdiagnose. A classic case report by Owen and colleagues describes a woman (falsely) diagnosed with UWS and no signs of awareness after a traumatic brain injury. Functional MRI scans yet showed patterns of brain activations, indistinguishable from those of healthy controls during mental imagery tasks (Owen et al., 2006). Similar task-related activations in DoC patients have later been observed by fMRI (Monti et al., 2010) and EEG (Cruse et al., 2012), as well as in a healthy volunteer during unresponsiveness induced with the anesthetic propofol (Huang et al., 2018). These results have, however, later been intensely debated (Nachev and Husain, 2007; Greenberg 2007; Goldfine et al., 2013).

Another important clinical implication is anesthesiology, where the assessment of the optimal level of general anesthesia is largely dependent on indirect measures such as the patient's blood pressure, heart rate and muscle movements. Fortunately, also frontal EEG-derived indices are also today used. Unintended awareness during surgery is an underdiagnosed condition, which can manifest in a variety of ways. For instance, the patient may hear sounds or feel something during the anesthesia period, without even experiencing pain or discomfort. There is also a possibility to be partially aware without remembering anything afterwards (Sanders et al., 2017). At the extreme, the patient is fully aware of the surgery and experiences pain but is unable to move or indicate awareness. This is a very traumatic experience and may lead to post-traumatic stress disorder and/or long-term psychological harms.

The incidence of awareness with explicit recall (AWR) has been reported to vary between 0.1-4% (Sandin et al., 2000; Sebel et al., 2004; Mashour and Avidan, 2015), with the aforementioned conceptual differences contributing to the variation of the estimates. Increased risk of AWR has been identified to be patient-related (Aranake et al., 2013), surgery-related (Dowd et al., 1998; Ghoneim, 2007) and iatrogenic such as underdosing or equipment malfunction (Ghoneim et al., 2009). In a recent study by Sanders et al, 4.6% of anesthetized patients showed meaningful response in form of hand-squeeze after tracheal intubation during the isolated forearm technique (Sanders et al., 2017). Subsequently 1.9% reported pain through a second hand-squeeze. Nonetheless, zero participants reported explicit recall of the events after the surgery. This study nicely illustrates the actual incidence of awareness (at time of intubation) and the strong subsequent suppression of memory traces.

As early as the 1930's, pharmacologic interventions were observed to affect electroencephalogram patterns (Gibbs et al., 1937) and it was also introduced, that EEG measures could be used to monitor depth of anesthesia. Despite the detailed characterization of the effects of different anesthetics on the electroencephalogram (see Effects of General Anesthesia on the Electroencephalogram Spectra), interpreting unprocessed or spectrogram-compressed EEG during surgery never became a part of standard anesthetic care.

Already in the 80's, there were aims to measure the depth of anesthesia in a clinical setting by recording scalp EMG and EEG (Tammisto et al., 1983; Edmonds and Paloheimo, 1985) during anesthetic administration. This was pursued by Finnish company Datex Oy (Now GE Healthcare, Helsinki, Finland) by developing the "Anesthesia and Brain Activity Monitor" among other anesthesia monitoring devices. Later on, the first available commercial depth of anesthesia (DoA) –monitor was the Bispectral Index (BIS) monitor, and it was introduced in 1994 by Aspect Medical Systems and later approved by the Food and Drug Administration in 1996. It is now the most common DoA –monitor worldwide, although also other devices, such as the Spectral Entropy monitor (GE Healthcare, Helsinki, Finland), Narcotrend (MonitorTechnik, Bad Bramstedt, Germany), or Cerebral State Monitor (CSM, Danmeter, Odense, Denmark) are used. The derived indices are based on online EEG recording, which is collected by electrodes placed on the patient's forehead and calculated in real time by different algorithms (Rampil, 1998; Bruhn et al., 2000; Vakkuri et al., 2004; Viertiö-Oja et al., 2004; Kreuer et al., 2001, Kreuer and Wilhelm, 2006). The BIS and entropy monitors are the most used techniques with distinct signal calculations. BIS is a weighted sum of three processed variables (Rampil, 1998), whereas the E-entropy monitor uses the irregularity of the EEG and frontal electromyogram for calculation of two indices, state entropy (SE) and response entropy (RE) (Viertiö-Oja et al., 2004). One value is created by BIS (from 100 to 0), and two values by E-entropy (RE from 100 to 0 and SE from 91 to 0), where high values represent normal wakeful state, and 0 represents suppressed, isoelectric EEG (and presumably profound unconsciousness). A level of anesthesia, that is considered appropriate for surgical procedures, is a BIS or entropy value of 40-(50)60, and they seem relatively reliable in day-to-day practice. On individual level, however, wide variation in BIS values have been reported at similar behavioral end points. Consequently, BIS is unreliable in individually detecting loss of responsiveness during increasing concentrations of propofol, sevoflurane and dexmedetomidine (Kaskinoro et al., 2011). A similar shortcoming has been shown to apply also to Narcotrend (Schneider et al., 2004) and CSM (Pilge et al., 2011) monitors during sevoflurane and propofol anesthesia. DoA –monitors were originally considered to decrease the risk of AWR during surgery, as they enable online assessment of the patient's brain activity during anesthesia. In a study by Myles et al (Myles et al., 2004), BIS monitoring seemed to reduce the incidence of accidental awareness in a high-risk surgical population. Based on later studies, the superiority of the BIS monitor to reduce the risk of awareness compared to traditional assessment methods has yet been challenged (Avidan et al., 2008, 2011; Mashour et al., 2012).

Importantly, even if DoA –monitors would fail to decrease the incidence of AWR, EEG monitoring during anesthesia has many other advantages. Indeed,

profound EEG suppression during surgery is often unnecessary and may impact the cognitive recovery of elderly or otherwise fragile patients (Fritz et al., 2016). This, in turn, leads to personal burden on patients, prolonged hospital stay and increased healthcare expenses. BIS-guided anesthesia has been associated with reduced anesthetic consumption (Gan et al., 1997; Shafiq et al., 2012) and a lower incidence of postoperative delirium and cognitive decline at three months after surgery (Chan et al., 2013; for a review and meta-analysis, see MacKenzie et al., 2018). Evidence for the contrary has also recently been published (Wildes et al., 2019).

2.2 Physiological Characteristics of General Anesthesia

The aim of general anesthesia is to provide optimal conditions for surgery to be performed and to maintain and support vital functions during a procedure or a critical illness. General anesthesia is traditionally divided to cover three main components: hypnosis, analgesia and muscle paralysis. Hypnotic drugs are administered to induce hypnosis, strong opioids for potent analgesia and muscle relaxants to optimize surgical circumstances and to prevent reflex-like muscle movements. These interventions result in ventilatory and circulatory suppression, which require mechanical ventilation and often also pharmacological hemodynamic support. Depending on the procedure, all three components are necessarily not targeted, or the doses are reduced or differently proportioned. The drugs also have partly overlapping effects on the central nervous system, allowing various anesthetic techniques based on individual patient needs.

2.2.1 Molecular Mechanisms of General Anesthetics

General anesthetics and their molecular mechanisms have been a target of intense research for decades. The mystery is, how can such a diverse group of pharmacologic agents induce such similar states of apparent unconsciousness? And what is the pharmacologic endpoint that enables the transition from a conscious to an unconscious state? It was once hypothesized, that anesthetics act in a non-specific way through perturbation of the nerve cell phospholipid bilayer. Later on, substantial evidence has demonstrated membrane proteins, i.e., receptors, as actual anesthetic targets (Franks and Lieb, 1988; Belelli et al., 1999; Franks, 2008)

The relevance of γ-aminobutyric acid, type A ($GABA_A$) -receptors in general anesthesia has been recognized for many years. GABA is the most widely distributed inhibitory neurotransmitter, which suppresses excitatory neuronal signaling in the CNS (Nutt, 2006). The $GABA_A$ -receptor consists of five receptor subunits, with

high heterogeneity of different assemblies. The most abundant $GABA_A$ receptor consists of two α, two β and one γ subunit (Whiting et al., 1999). The majority of different general anesthetics and sedatives, both intravenous and inhalational, exert their effects by potentiating GABA-induced Cl^- currents and directly activating GABA and its inhibitory effects in the central nervous system. Propofol, sevoflurane, desflurane, isoflurane, etomidate, thiopental, as well as benzodiazepines and alcohol act mainly through this mechanism to induce hypnosis, depression of spinal reflexes and amnesia (for a review, see Brohan and Goudra, 2017). Owing to the advancement of genetic manipulation in the 1990's, different GABAergic drugs have shown to preferentially target the distinct $GABA_A$ subunits, altering or attenuating anesthetic effects in rodents (Jurd et al., 2003; Reynolds et al., 2003; Sonner et al., 2007).

Other relevant targets of general anesthetics have also been demonstrated. The effects of volatile anesthetics have been found to be partially mediated through two-pore-domain K^+ (2PK) channels (Franks and Lieb 1988; Patel et al., 1999; Andres-Enguix et al., 2007) on the neuronal cell membrane. Functional 2PK channels are formed of dimers, and volatile anesthetics have been found to affect five members of this channel family, mediating an inhibitory synaptic K^+ -current in the CNS. Similar to $GABA_A$ -subunits, also the subunits of 2PK channels are preferentially affected by different volatile anesthetics.

N-methyl-D-aspartate (NMDA) receptors, which have a key role in functions like learning and memory, have also been recognized as anesthetic targets. NMDA receptors are formed of a variety of subunits with glutamate- and glycine binding sites, mediating excitatory neurotransmission. These receptors are found synaptically, presynaptically and extrasynaptically in the CNS, hence contributing heterogeneously to normal neuronal functions. Based on substantial research both in vitro and in vivo (Anis et al., 1983; Irifune et al., 1992; Petrenko et al., 2004, 2014; Sato et al., 2005; Dickinson et al., 2007), antagonization of NMDA receptors is thought to be the primary molecular mechanism of the intravenous anesthetic ketamine, as well as the inhalational anesthetics xenon and nitric oxide. Interestingly, also anesthetics recognized mainly as GABA-ergic (such as propofol and benzodiazepines) have been suggested to partially and/or indirectly affect the NMDA receptor (Flohr et al., 1998).

$Alpha_2$ adrenoceptor agonism is also a relevant molecular pathway in sedation and anesthesia (for a review, see Scheinin et al., 1989). Dexmedetomidine, which is a highly selective $alpha_2$ agonist, binds to the pre- and postsynaptic α_2 –receptors and leads to the hyperpolarization of locus coeruleus neurons, the decrease in norepinephrine release and ultimately, an increase in the inhibitory outputs in the major arousal centers in the brain (Segal et al., 1988; Savola et al., 1986; Correa-Sales et al., 1992; Jorm and Stamford, 1993; Nacif-Coelho et al., 1994). In fact,

dexmedetomidine has been found to activate endogenous sleep promoting pathways (Nelson et al., 2003) with the induced state having most resemblance to natural sleep. Recently, dexmedetomidine has been referred to as a "biomimetic anesthetic" (Akeju et al., 2018), recognizing its pharmacological and beneficial cognitive profile.

It is apparent that most anesthetics mediate their actions through several receptor units, as well as induce secondary, possibly concentration–dependent, effects on the different neurotransmitter systems. This conclusion can be derived from numerous pharmacological studies and behavioral observations. For instance, a subanesthetic dose of ketamine during isoflurane anesthesia has been seen to deepen the anesthetic level to burst-suppression, but paradoxically, accelerate recovery in rats, possibly through cholinergic mechanisms (Hambrecht-Wiedbusch et al., 2017). Interesting insights are also provided by animal studies using genetic manipulation. For instance, knockout of the NMDA GluN2A subunit has been found to reduce the hypnotic effects of NMDA antagonist ketamine, but to also reduce the hypnotic effects of GABAergic pentobarbital (Petrenko et al., 2004), as well as propofol and benzodiazepines (Sato et al., 2005). In another study using knockout mice, selective knockout of the α_{2A} adrenergic receptors from the locus coeruleus eliminated dexmedetomidine-induced loss of righting reflex, but not sedation (Zhang et al., 2015). These studies show that hypnotic drugs likely mediate their effects through multiple receptor systems.

Finally, physiologic sleep-wake nuclei in the brainstem, the hypothalamus and basal forebrain have been found critically involved in both anesthesia induction and emergence. Accounting for the regulation of circadian rhythm and sleep, the ventrolateral preoptic nucleus (VLPO), ventral tegmental area (VTA) and tuberomamillary nucleus (TMN), have all been implicated in anesthesia, interestingly applying for both GABAergic and non-GABAergic drugs (Nelson et al., 2002, 2003; Zecharia et al., 2009; Luo and Leung, 2011; Moore et al., 2012; Taylor et al., 2016).

2.2.2 Effects of Anesthesia on the Electroencephalogram Spectra

The electrical activity of the brain is significantly altered by anesthesia. In 1937, Gibbs et al introduced that electrical activity, reflected in recordings through the scalp, is altered during increasing doses of ether or pentobarbital (Gibbs et al., 1937). Later on, Dr Albert Faulconer (1911-1985), a pioneer in clinical anesthesiology, was among the first to systematically investigate this phenomenon. He introduced the effects of diethyl ether and thiopental on the raw EEG signal during surgical anesthesia (Courtin et al., 1950; Kiersey et al., 1951), as well as discovered that

diethyl ether and cyclopropane progressively affected EEG patterns in concordance with arterial concentrations (Faulconer, 1952, Possati et al., 1953). Significantly, Findeiss and colleagues introduced power calculation –a two dimensional graph of the relationship between power and frequency– to be more illustrative of spectral changes and thus, anesthetic effect (Findeiss et al., 1969).

The oscillations seen in the unprocessed EEG are thought to reflect the alterations in neural firing and functional circuitries induced by general anesthetics. Different anesthetics induce individual EEG patterns, and even within drug groups, such as the GABAergic agents propofol, etomidate, thiopental and volatile anesthetics, the EEG effects are partly heterogenous. Modern EEG recording (excluding intraoperative EEG with only frontal recording) is conducted by measurements from multiple sites, typically with 64 or 132 (or even 200+) electrode channels. As summarized in Table 2, the EEG waveforms are categorized by band width frequency to slow-delta (0.1–1), delta (1–4Hz), theta (4–8), alpha (8–14Hz), beta (14–25) and gamma (25–45Hz) waves.

Table 2. Frequencies of EEG waveforms

	slow delta	delta	theta	alpha	beta	gamma
FREQUENCY (Hz)	0.1–1	1–4	4–8	8–14	14-25	25-45

The electroencephalographic characteristics of GABAergic anesthetics are well described, with propofol probably being the most studied agent. Importantly, the EEG effects of especially (but not limited to) propofol are manifested in a multiphasic manner (Kuizenga et al., 2001), which can be correlated to the anesthetic level/ plasma concentration of the drug. At low doses, propofol induces an excitatory pattern, i.e., an increase in beta oscillations, which is referred to as “paradoxical excitation”. Despite being an unexpected pattern, this excitation can be behaviorally witnessed, as low doses are often associated with restlessness and dysphoria. The explanation for this is not completely understood, but striatothalamic modulation and interneuron antisynchrony have been suggested (McCarthy et al., 2008; Brown et al., 2010; Ching and Brown, 2014). When the concentration of propofol is increased, the sedative effects become more apparent and several typical patterns emerge: Slow-wave activity (SWA, slow delta and delta) increases in power and spreads across the scalp (Gugino et al., 2001), up to the point of slow-wave saturation (Mhuircheartaigh et al., 2013). Also, a shift from occipital to frontal alpha activity is a typical EEG pattern induced by propofol (Tinker et al., 1977; Gugino et al., 2001; Purdon et al., 2013). The neuronal mechanism behind alpha rhythms is also unclear, but

enhancement of rhythmic thalamocortical loops has been suggested as a possible cause (Ching et al., 2010). Both SWA saturation (Mhuircheartaigh et al., 2013) and alpha waves (Ching et al., 2010) have been suggested as signatures of unconsciousness during propofol administration. Propofol has also been found to induce a specific phase-amplitude relationship, where alpha oscillations are maximal either at low-frequency troughs (loss of responsiveness/consciousness), or at low-frequency peaks (profound unconsciousness). This is referred to as phase-amplitude coupling (PAC) and is observed during propofol exposure (Purdon et al., 2013; Mukamel et al., 2014). The clinical relevance of PAC is unknown, but it suggests distinct EEG signatures of light and profound sedation with propofol. Figure 4 illustrates a modulogram of alpha and low-frequency activity (LFA) during propofol-induces unresponsiveness.

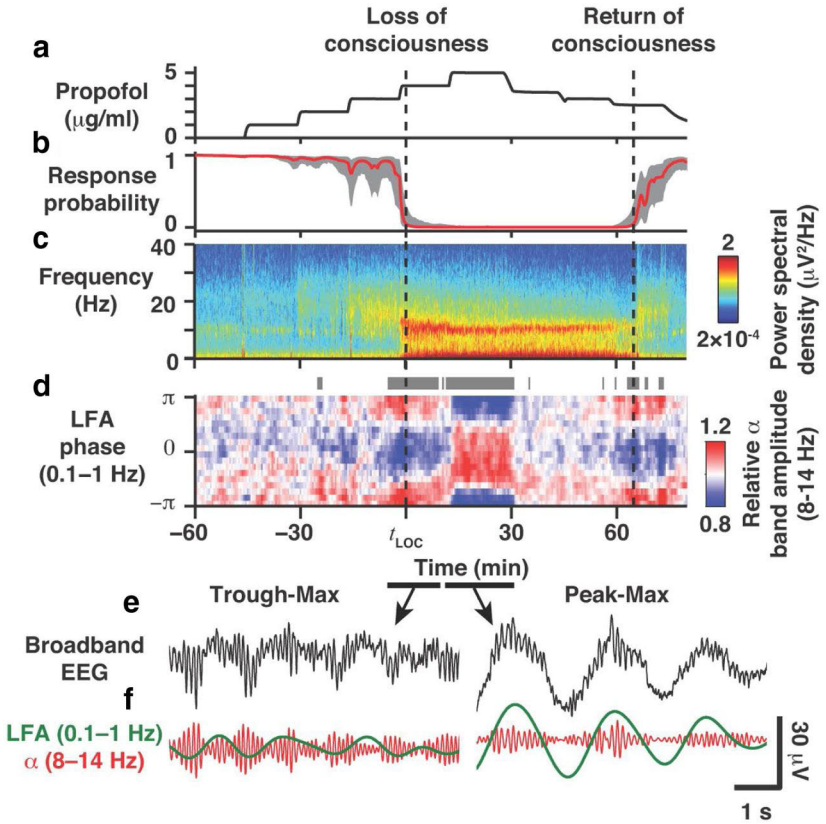

Figure 4. Two distinct patterns (trough-max and peak-max) have been reported in propofol anesthesia. a and b represent escalating effect-site concentration (a) and probability of response to command (b). c is the frontal power spectrum and d represents the modulation of alpha power by low frequency activity (LFA) phase. e is the raw EEG signal and f illustrates the relationships of alpha and LFA during trough-max and peak-max coupling. Reproduced, with permission, from Mukamel et al., 2014.

The effects of other GABAergic drugs, such as thiopental, etomidate, sevoflurane and GABA–mediated sedatives such as midazolam, resemble those of propofol. All except midazolam have been found to have biphasic effects in terms of alpha and beta activity (Kuizenga et al., 2001), followed by increase in slow activity. Sevoflurane, which is widely used in both induction and maintenance, induces frontal alpha predominance and global increase in beta and delta activity (Gugino et al., 2001). Ultimately, increasing concentrations of the described GABAergic anesthetics eventually lead to a burst suppression pattern (flat EEG combined with fast periods of alpha and beta waves) and finally, isoelectric EEG (Clark and Rosner, 1973). It must be emphasized, that the induced spectral EEG changes show large inter-individual variation, and no specific spectral pattern or processed EEG index can unambiguously be correlated to an unconscious state (Kuizenga et al., 2001; Kaskinoro et al., 2011).

The effects of dexmedetomidine on the EEG have been studied to a lesser extent. Before quantitative EEG experiments during dexmedetomidine exposure were made, it was introduced that this drug exerts its effects through endogenous sleep promoting pathways, thus mimicking physiological sleep (Nelson et al., 2003). The EEG changes seen during dexmedetomidine sedation corroborate these views. Sleep spindles, which are short-lasting bursts in the high α or low β frequency bands (11-14Hz) (Naitoh et al., 1982), are typically observed in non-REM stage 2 sleep (N2) (Jankel and Niedermeyer, 1985). They have also been observed during dexmedetomidine sedation: "Dex-spindles" are 9-15 Hz bursts, somewhat resembling the alpha oscillations induced by propofol. These have less power but are yet highly coherent in the frontal regions (Huupponen et al., 2008; Akeju et al., 2014; O Akeju et al., 2016). A profound decrease in beta oscillations is also typical for dexmedetomidine (Akeju et al., 2016), different from GABAergic drugs. Also increases in slow–delta and delta are characteristic for dexmedetomidine-induced unconsciousness, especially in the occipital regions (Akeju et al., 2014). Despite the somewhat similar EEG profiles of propofol and dexmedetomidine, these drugs induce notably different behavioral states, i.e., awakening from dexmedetomidine-induced sedation is feasible even during continuous administration of the drug. It has been suggested, that thalamocortical activities are more profoundly inhibited by propofol than by dexmedetomidine (Purdon et al., 2015), possibly explaining some of the differences. Also, the stronger delta waves induced by propofol suggest a more profound state of neuronal silence (Akeju et al., 2014).

The NMDA–antagonist ketamine has markedly different electroencephalographic signatures as compared to GABA mimetics. Despite its hypnotic effect, ketamine induces fast activity, followed by rhythmic theta and episodic delta waves (Corssen et al., 1969; Schwartz et al., 1974; Hering et al., 1994; Blain-Moraes et al., 2014). Also gamma spindles or "gamma bursts" have been

shown characteristic (Maksimow et al., 2006; Akeju et al., 2016). These properties illustrate the heterogeneous EEG characteristics of drug-induced unresponsive states, and that spectral patterns on the EEG are unreliable in individually defining the state of consciousness.

2.2.3 Effects of Anesthesia on Cerebral Blood Flow and Metabolism Measured with PET Imaging

The physiological changes in circulation or metabolism in a target organ/tissue can be quantitatively measured by PET imaging. PET is based on the use of short-lived positron emitting radioisotopes, which are to be synthesized (necessitating generation of isotopes in a cyclotron), purified, quality tested, and then injected to the study subject or patient. Different receptor- and enzyme-systems, malignancies or hormonal abnormalities can also be studied with PET. The imaging technique is based on the detection of the injected isotopes, where Geiger Counter-like detector crystals located in a ring outside the body are used to detect paired gamma rays, annihilated from the target tissue after encountering an electron. By using computed tomography reconstruction of the decay events, the anatomical distribution of the radiolabeled molecules can then be measured.

PET-imaging was used to measure metabolic alterations in the rat brain during thiopental anesthesia already in the 70's (Sokoloff et al., 1977), and later on during propofol anesthesia (Dam et al., 1990, Cavazzuti et al., 1991). The latter studies demonstrated that propofol was associated with global, dose-dependent suppression of metabolism with whole-brain suppression ranging between 15 and 55%. Later on, studies on humans revealed corroborating findings, where propofol and isoflurane globally suppressed metabolic activity in the human brain, as measured by cerebral metabolic rate of glucose (CMR_{glu}) using the ^{18}F-FDG radiotracer (Alkire et al., 1995, 1997). Preferential effects of propofol were observed in the frontal, parietal and occipital lobes and overall, a relatively low inter-individual variation was seen (Alkire et al., 1995). Isoflurane was associated with a fairly uniform metabolic reduction across brain areas (Alkire et al., 1997). In the late 90's, Fiset and co-workers used PET-imaging to measure cerebral blood flow (CBF) changes induced by propofol. Consistent with the metabolic profile, CBF suppression induced by propofol was global, albeit with pronounced effects in the medial thalamus, the cuneus and precuneus, the posterior cingulate and orbitofrontal gyri, and the right angular gyrus (Fiset et al., 1999). The aforementioned studies were the first to have used "threshold" levels of anesthesia, i.e., they aimed to target loss of responsiveness, as opposed to imaging brain activity during surgical levels of anesthesia. Thus, these experiments have been considered as pioneer studies of using anesthesia as a tool to explore human consciousness.

Studies employing deep anesthetic levels have also been conducted (Kaisti et al., 2002, 2003; Schlünzen et al., 2004, 2006; Långsjö et al., 2005; Laitio et al., 2007, 2009; Schlünzen et al., 2010, 2012). Most anesthetics in clinical use today, with the exception of ketamine, globally and/or regionally suppress both blood flow and metabolism, as shown by studies on GABA-mediated drugs (Alkire et al., 1995,1997,1999, Kaisti et al., 2002, 2003), alpha-agonists (Prielipp et al., 2002; Laaksonen et al., 2018; Akeju et al., 2014) and NMDA-antagonist xenon (Laitio et al., 2007, 2009). These studies have been clinically relevant, and they have provided important knowledge on anesthetic effects especially in regards to the neurosurgical and neurointensive patient population. Also, different sedatives, such as midazolam (Veselis et al., 1997) and lorazepam (Schreckenberger et al., 2004) have been investigated.

More specifically, volatile anesthetics, such as sevoflurane, induce a clear global reduction in metabolism with less distinct changes in perfusion (Kaisti et al., 2003; Laitio et al., 2009; Schlünzen et al 2004). I.e., during surgical levels of anesthesia with sevoflurane, the perfusion profile differs from that of metabolism, suggesting a disturbance of the flow-activity coupling (Kaisti et al., 2003; Schlünzen et al., 2004). Propofol has been considered more appropriate for neurosurgical patients, with a more favorable flow-metabolism profile; it reduces both blood flow, oxygen metabolism and glucose metabolism down to approximately 50% of the awake values, when surgical doses are used (Schlünzen et al., 2012). Propofol has also shown to maintain lower intracranial pressure (Petersen et al., 2003), although patient outcome has not robustly been shown to be affected by anesthetic choice (Todd et al., 1993; Chui et al., 2014). Despite some ongoing debate on the matter, intravenous anesthesia has become the basic anesthetic regimen for neurosurgical procedures (Hans and Bonhomme, 2006).

Importantly, as to assessing the effects on consciousness specifically, many studies have been heterogenous in study designs, administration protocols and the induced behavioral states, thus impeding direct comparability across different agents and studies. Nevertheless, thalamic suppression seems to be a common factor across several drug classes. In the early 2000's, Alkire and co-workers introduced the "thalamic switch"-theory, suggesting thalamocortical disruption as key mechanism of anesthetic-induced unconsciousness (Alkire et al., 2000). In this study using halothane and isoflurane, a conjoint effect of the two agents at loss of responsiveness centered in the thalamus, suggesting hyperpolarization of thalamocortical neurons as a common mechanism for narcosis. Analogous findings were observed a year earlier with propofol (Fiset et al., 1999) and later on with dexmedetomidine in an exploratory study setting (Prielipp et al., 2001).

Ketamine is distinct from other traditional anesthetics, as it is excitatory, rather than suppressive in nature. Ketamine can be used both as a racemate or as an isomeric

enantiomer S-ketamine, and they have both been shown to increase CBF and to decrease oxygen extraction fraction (OEF) (Långsjö et al., 2003, 2004, 2005). In fear of unfavorable effects on intracranial pressure and coupling, ketamine and S-ketamine were long considered unsuitable for neurotrauma and neurosurgical patients. This subject is, however, controversial, as ketamine has since been shown to maintain or sometimes lower intracranial pressure (Bar-Joseph et al., 2009; Zeiler et al., 2014) and, in fact, have numerous neuroprotective properties (Bell, 2017).

2.3 Cognitive, Behavioral and Phenomenal Characteristics of General Anesthesia

2.3.1 Cognitive Characteristics

Despite the distinct pharmacological and molecular profiles of different anesthetic agents, ultimately, a fairly similar state of apparent unconsciousness can be induced with these drugs. It is not clear, whether different anesthetics embark a common cascade of network alterations in the brain, nor if they induce a common cognitive end-point. Traditionally, anesthetics have been considered to induce their effects in a "bottom-up" manner, referring to a neurocognitive hierarchy based on molecular events and arousal pathways. This conception is justified, given the current knowledge on anesthetics and their molecular effects (Franks, 2008), and certain similarities between anesthesia and physiological sleep (Nelson et al., 2003). The "thalamocortical switch" theory can be seen as foundational in the study of anesthetic mechanisms and is in support of the "bottom-up" view on anesthetic effects (Alkire et al., 2000). The causality of events in not, however, entirely clear. It is also introduced that "top-down" processes could be more responsible for anesthetic-induced unconsciousness (Mashour, 2014), and this hypothesis suggests a more essential role of cortical disruptions as the root effect of anesthetic-induced unconsciousness.

Anesthesia is most often not, at concentrations enough to induce unresponsiveness, a state of profound unconsciousness. Anesthetic-induced unresponsiveness is often accompanied by subjective experiences, mostly characterized by pleasant dream-like mental content (Brice et al., 1970; Noreika et al., 2011; Radek et al., 2018). This could be possible even during surgical levels of anesthesia. As described earlier, the aim of anesthesia is to induce a *disconnected* state, where the contents of consciousness are not modulated by external stimuli, and surgery can be performed without pain, perception or explicit memory. During such conditions, the brain may continue to process external stimuli, as seen both by brain imaging and electrophysiologic data of the anesthetized brain. Indeed, activity and/or

functional connectivity in the visual and auditory networks seem to be maintained across sedative and unresponsive states (Plourde et al., 2006; Boveroux et al., 2010; Guldenmund et al., 2016), and multisensory stimuli (pain, words and tones) have been shown to elicit normal sensory fMRI BOLD responses during propofol-induced unresponsiveness (Warnaby et al., 2016). Interestingly, implicit (i.e., unconscious) memory traces after light and moderate anesthesia have been detected by using EEG and a postoperative reading speed task (Münte et al., 2003; for a review and meta-analysis, see Linassi et al., 2021). Together, these findings indicate that sensory information is received, relayed to and partly processed on the cortex, but fails to access conscious awareness. In other words, the stimulus is "received but not perceived" by the brain (Hudetz, 2006). Consistently, there is evidence on preferential suppression of the *non-specific* thalamocortical circuitries during unresponsiveness induced by propofol (Liu et al., 2013). This network is thought to have an integrative role in information processing, which is responsible for the integration of the stimuli into a meaningful experience. Conversely, the *specific circuits* are responsible for lower-order information transfer, i.e., transmission of sensory and motor information to the cortex (Llinas et al., 1998). The term *cognitive unbinding* (Mashour, 2013) denotes that cognitive processing persists while the binding of this activity into a meaningful conscious representation is inhibited, and it can be seen as a framework strengthened by the aforementioned findings. The information integration theory of consciousness (Tononi, 2004) is also theoretically related to this paradigm (see 2.1.1 Theoretical Frameworks). It is noteworthy, that the distinct functions and circuitries are affected in a dose-dependent manner, and deep levels of any anesthetic has profound global effects on the brain. For example, high concentrations of propofol have been shown to suppress also the primary sensory areas, and stimulus-evoked activations in these regions are lost (Mhuircheartaigh et al., 2013).

2.3.2 Event-Related Potentials

Task-related activations and the associated cognitive functions can also be measured from the EEG. Electrophysiologic recording has certain advantages, such as the non-invasive nature of the technique and better time resolution compared to imaging modalities such as PET and fMRI. Electrophysiologic responses to specific cognitive, auditory or sensory stimuli measured by EEG are referred to as event-related potentials (ERP's). These are positive or negative deflections on the EEG recording, seen at specific sites after a characteristic latency period between 0 and 400ms. The basic principle is to use repeated stimuli and then compute amplitude averages of the elicited responses over the selected time period. Compared to fMRI,

ERP's are more sensitive to detect subtle cognitive functions, as witnessed in a study using simultaneous ERP and fMRI BOLD measurements (Geukes et al., 2013).

It has been proposed that the latency of an ERP is associated to consciousness (Cul et al., 2007), i.e., early potentials are considered to reflect more primary processing, whereas late potentials reflect more integrative activity and perhaps, conscious perception. Brainstem evoked potentials, somatosensory evoked potentials and visual evoked potentials are short-latency potentials, which reflect intact function of the primary somatosensory system. These potentials estimate the integrity of ascending pathways and are preferentially preserved during anesthesia (Hudetz, 2009). To specify, they do not denote subjective perception of the stimuli. Early cognitive potentials, such as mismatch negativity, N100 and P300 reflect more integrative activity beyond the primary sensory cortex, as they are associated to cognitive auditory functions and discrimination of sounds. The presence of these potentials has been shown to associate to better prognosis in brain injured, unresponsive patients (Daltrozzo et al., 2007; Qin et al., 2008; Cavinato et al., 2009), and are even argued to possibly indicate consciousness (Faugeras et al., 2011). In comparison, preserved brainstem- and primary somatosensory potentials in such disorders seem to be weak predictors of recovery. Absent brainstem potentials, however, predict poor outcome (Robinson et al., 2003).

The N400 ERP is a late cognitive potential, characterized by a negative deflection measured in the centroparietal electrodes on the EEG that peaks around 400ms post-stimulus (Kutas and Hillyard, 1980, 89). This ERP is related to processing of meaning, where the amplitude of the N400 is inversely associated to the meaningfulness of a stimulus in a context. It is suggested to reflect the activation of such cognitive processes, that retrieve the representation of the stimulus and integrate it into the context (Kutas and Federmeier, 2011). A frequent method to test the N400 ERP is by the congruency, i.e., meaningfulness, of spoken words, and this is most robustly found by examining the last word of a sentence. For example, "The bear walks in the forest" is a semantically congruent sentence, i.e., the last word has a high expectancy with respect to the preceding sentence. In contrast, "The bear walks in the tomato" is an incongruent sentence where the word "tomato" has low expectancy with respect to the preceding sentence. The last word of the latter sentence would, thus, be associated to a larger N400 amplitude. The difference between the N400 components elicited by expected and unexpected stimuli is called the N400 effect.

Given the specific cognitive qualities measured by the N400, it has been argued to associate more specifically to consciousness. The N400 requires language comprehension, which is a critical component of awareness. This could offer a better methodology to detect covert consciousness in unresponsive, brain injured patients. Indeed, some UWS and MCS patients have preserved electrophysiologic N400

responses (Schoenle and Witzke, 2004; Balconi et al., 2013; Beukema et al., 2016), raising questions about the accuracy of such, behavior-based, diagnoses. It has also been suggested to independently predict recovery from such states (Steppacher et al., 2013). The N400 could also have potential in detecting anesthesia awareness, as accurate bedside assessment methods are still lacking. Awareness during unresponsive states induced by propofol has been detected using fMRI method and imaging brain activations to specific mental imagery tasks (Hudetz et al., 2018). In the future, perhaps intraoperative EEG recordings could be used to detect comparable task-related activations. Such measurements could be made at the bedside and in real-time.

2.3.3 Phenomenal and Behavioral Characteristics

In the clinical setting, the phenomenal state(s) induced by anesthesia often remain a mystery. It is likely that during profound, surgical levels of anesthesia the patients are –at least periodically– unconscious. Dreaming has traditionally been considered to mainly manifest during the recovery period, when the concentrations of anesthetic agents have decreased, and the patients start to recover. However, it has recently been shown that subjective experiences are common also during the administration phase (Noreika et al., 2011; Radek et al., 2018), and they are mostly characterized as being pleasant and unrelated to one's surroundings. To emphasize, such conditions are *conscious* states, where one is *disconnected* from the external world (see Defining Consciousness). Indeed, this may even be considered as an appropriate target of general anesthesia. The only method to access subjective mental content during an unresponsive period is retrospective reports. As anesthetic agents have strong amnestic effects, reports collected at moment of or immediately after awakening do not, however, explicitly specify the phenomenal state during the preceding anesthetic condition. Consistently, the lack of a dream report does not unequivocally indicate unconsciousness (Windt et al., 2016). It has not largely been investigated whether or not the prevalence of dreaming differs between different anesthetic agents. The NMDA-agonist ketamine is, however, associated with vivid dreaming and hallucinations, separating it from the traditional, suppressive anesthetics.

Behaviorally, increasing doses of anesthetics seem to induce a fairly common end-point of unresponsiveness. Some significant differences in behavioral characteristics can, however, be highlighted; GABAergic drugs, e.g., propofol, thiopental and volatile anesthetics affect in a concentration-dependent manner, and at sufficient concentrations induce profound unconsciousness, which cannot be reversed during administration. Dexmedetomidine has a unique quality in inducing a sedated state, from which a person can be easily aroused by mild auditory or tactile

stimuli. Such clear restoration of a conscious state has not been considered possible during administration of traditional anesthetics at clinically relevant doses. In this sense, dexmedetomidine induces a "sleep-like" state, which is observable both by behavioral and phenomenal qualities (Radek et al., 2018), as well as by electroencephalogram measures (Huupponen et al., 2008). Dexmedetomidine has, in addition, less effects on the respiratory function as opposed to other intravenous anesthetics. Despite its' reversible hypnotic effect, dexmedetomidine has been shown to –somewhat surprisingly– suppress glucose metabolism more than propofol or sevoflurane at equipotent anesthetic levels (Laaksonen et al., 2018).

When assessing phenomenal and behavioral features related to distinct anesthetic drugs, the NMDA-antagonist ketamine needs to be highlighted. Ketamine is a hypnotic drug, which can be used to achieve anesthesia without compromising respiratory function or hemodynamic stability. Interestingly, clinical significance has been witnessed also in treatments of depression and pain (Pribish et al., 2020). Depending on the administered dose, ketamine is known to induce a phenomenally distinct state, characterized by vivid hallucinations and distorted self-perceptions, such as out-of-body experiences and restlessness. The property of ketamine to maintain and even increase global brain activity, indicated by increased CBF and CMR_{glu} at subanesthetic and anesthetic concentrations (Långsjö et al., 2003, 2004, 2005; Laaksonen et al., 2018), could partly explain the distinct phenomenal conditions induced by this drug. In a study by Sarasso and colleagues (Sarasso et al., 2015) using propofol, xenon and ketamine, only ketamine subjects reported subjective experiences after unresponsiveness, and these states were associated to TMS-elicited EEG responses comparable to wakefulness. This observation is, however, inconsistent with other studies indicating high incidence of subjective experiences during both xenon and propofol sedation (Noreika et al., 2011; Radek et al., 2018).

2.4 Scientific Search for the Neural Correlates of Consciousness

2.4.1 The Classical Paradigm – Unresponsiveness as a Surrogate Measure for Unconsciousness

Identifying the neural correlates of consciousness is one of the greatest challenges in neuroscience. General anesthesia allows manipulation of consciousness in a controllable and reversible way, and thus opens a unique possibility to explore human consciousness. Varying administration protocols and study setups have,

however, led to somewhat heterogenous data, creating a difficult basis for comparisons across studies.

The pharmacologic challenges related to anesthesia studies are of great significance. The inter-individual variability in response to most anesthetics is large, complicated by the relatively steep concentration-effect curves. After a standard bolus, one person may become sedated and maintain responsiveness to external stimuli, whereas another might become unresponsive or even unconscious. Most investigators have therefore assessed the state of consciousness by behavior, where unresponsiveness to a pre-defined stimulus depicts the "unconscious" state which is then compared to the wakeful state. A comparison of the obtained neurophysiologic or brain imaging data has then been considered to reveal those brain functions that separate the conscious from the unconscious brain. This paradigm has been the cornerstone of anesthesia-based studies on consciousness for decades, and there is a great body of work based on this paradigm together with EEG and brain imaging modalities. Despite the opportunities offered by general anesthetics to experimental study of consciousness, many previous studies have disregarded the explicit characterization of the explored states and the independent effects of different interventions on brain functions. Thus, the optimal study setup and the administration protocol have not yet been introduced (see Study Design Challenges).

2.4.2 Anesthetic-Induced Unresponsiveness and EEG

As described earlier, the effects of different anesthetics on EEG spectra are well known (see 2.2.2 Effects on the Electroencephalogram Spectra). Nevertheless, the state of consciousness cannot be specified based on these drug-induced patterns or on processed EEG indices. The spectral changes seen during anesthesia are not merely explained by local neuronal firing or silence, but rather, by interactions within and between cortico-cortical and thalamo-cortical networks (Boly et al., 2012; Akeju et al., 2016). Thus, the most recent experimental EEG studies have focused on characterizing spatiotemporal dynamics in the brain, and measured disruptions or alterations in connectivity between distinct brain regions in concordance with anesthetic-induced unconsciousness (unresponsiveness).

Network dynamics can be assessed by analyses of functional, directional and/or effective connectivity. Typically, these measures are calculated in different task-independent conditions, and comparisons between (apparent) conscious and unconscious states are then conducted to reveal the changes related to consciousness. Coherence, which is the most "simple" form of EEG-based functional connectivity, refers to synchronous oscillations between spatially separate brain regions. This

measure lacks directionality and causality and thus, is rarely inferred in mechanisms of consciousness *per se*.

Causal alterations in connectivity are assessed by directional connectivity measurements. Such studies have been conducted using numerous intravenous and inhalational anesthetics. EEG studies have strongly associated disruption of frontal-parietal communication to loss of responsiveness induced by propofol, sevoflurane and ketamine, with net directionality depending on the chosen methodology, e.g., symbolic transfer entropy, phase lag index or Granger causality (Jordan et al., 2013; Lee et al., 2013; Maksimow et al., 2014; Ranft et al., 2016). Consistently, analyses based on directed effective connectivity have shown similar results (Boly et al., 2012). Interestingly, the changes or disruptions in connectivity are not simply result of metabolic and/or circulatory depressions. Ketamine is particularly demonstrative in this respect. Ketamine has a molecular effect of blocking NMDA-receptors and it does not strongly suppress metabolism or blood flow. Rather, it has a maintaining or even increasing effect on these measures at anesthetic and sub-anesthetic concentrations (Långsjö et al., 2003, 2004, 2005). Nevertheless, ketamine has shown to disrupt frontoparietal and frontal-to-parietal connectivity in the alpha and theta bandwidths (Blain-Moraes et al., 2014; Vlisides et al., 2017), demonstrating network-level similarities behind unresponsiveness induced by GABAergic and non-GABAergic anesthetics.

Despite somewhat uniform alterations in connectivity during unconsciousness of different etiologies, direct inferences on human consciousness based on these studies are not entirely warranted. In a recent study on isoflurane anesthesia, connectivity was revealed to be dynamic, despite a stable anesthetic level over time (Li et al., 2019). During procedural anesthesia with different anesthetic regimens, transitions between different connectivity patterns were present throughout anesthesia without apparent change in the state of consciousness (Vlisides et al., 2019). These observations imply that a single measure of EEG-based functional connectivity may not be a reliable measure of anesthetic depth (or consciousness) in the clinical setting. Recent graph-theoretical approaches emphasize, that anesthetic-induced unresponsive or unconscious states reduce the number of connectivity configurations that can be accessed, rather than preferentially disrupt any specific neuronal circuit

(Lee et al., 2010, 2017; Mashour and Hudetz, 2018). This is referred to as a reduced spatial repertoire of brain networks and can be witnessed also by perturbational approaches, such as cortical reactivity to transcranial magnetic stimulation (TMS). During a wakeful, vigilante state, perturbing the cerebral cortex with TMS produces a sequence of waves moving to connected cortical areas. This phenomenon, i.e., cortical effective connectivity, was first shown to be attenuated during non-rapid eye movement -sleep (Massimini et al., 2005) and later on, during midazolam-induced unconsciousness (Ferrarelli et al., 2010). The perturbational

complexity index (PCI) is a mathematically calculated index, derived from the reactivity of the EEG signal, and has been introduced to reliably measure consciousness (Casali et al., 2013). In a study by Sarasso et al, PCI values discriminated different phenomenal states during unresponsiveness induced by propofol, xenon and ketamine. Propofol and xenon were observed to correlate with low PCI values (low complexity and no post-anesthesia reports), whereas ketamine with complex spatiotemporal activation (high complexity and post-anesthesia reports describing vivid dreams). In ketamine subjects, PCI values resembled those of wakefulness and REM-sleep (Sarasso et al., 2015).

In addition to spectral and connectivity characteristics during anesthetic-induced unresponsiveness, also other EEG measures and their associations to (un)consciousness have been investigated. For instance, a distinct relationship of slow wave- and alpha bands have been shown to differentiate moderate and deep sedation with propofol, despite apparent unconsciousness in both groups (Mukamel et al., 2014). EEG connectivity has also been calculated at baseline to identify inter-individual differences, which could explain the variation in susceptibility to different anesthetics. It has been shown that weak alpha-band connectivity at baseline is related to higher susceptibility for propofol, i.e., subjects are more likely to become unresponsive during sedation(Chennu et al., 2016).

2.4.3 Anesthetic-Induced Unresponsiveness and Functional Brain Imaging

Similar to electrophysiologic changes seen on the EEG, the primary interest in imaging studies has shifted from the physiology of the anesthetized brain, to the specific changes related to consciousness per se. These studies have used the described paradigm, where comparisons of brain imaging data are made between conscious and unresponsive (and thus, presumable unconscious) states. High concentrations and rapid boluses of anesthetics have been avoided in order to isolate and investigate the subtle state transitions between different pre-defined conditions.

After the first investigations on cerebral glucose metabolism during isoflurane-, halothane- and propofol anesthesia (Alkire et al., 1995, 1997, 1999), the study by Fiset and colleagues (Fiset et al., 1999) was the first to use ^{15}O-H_2O PET method to measure cerebral blood flow during propofol-induced unresponsiveness in humans. This study was designed to reveal those brain regions/functions, associated with loss of responsiveness specifically, and drug dosing was carefully titrated to this pre-defined behavioral end point. PET imaging revealed suppression of blood flow globally, but preferentially in the thalamus, cuneus and precuneus and the posterior cingulate, orbitofrontal cortex, and right angular gyri, having best association to unresponsiveness. Importantly, functional relationships between the thalamus and

the midbrain were observed, and this was the first imaging study to focus on consciousness being regulated by alterations in neuronal networks, as opposed by local suppression in blood flow or metabolism. Propofol has become the most commonly used anesthetic agent in consciousness research, possibly due to its' wide clinical use, easy administration method and beneficial pharmacologic properties.

Functional MRI has established a strong status in the study of human consciousness, and it is often combined with single-agent administration protocols and connectivity analyses of the obtained data. Resting-state fMRI analyses have been performed using various anesthetics in clinical use, where imaging data of unresponsive states has been compared to the wakeful state. Many distinct functional rearrangements associated with (presumed) loss of consciousness has been found using this paradigm. For instance, brain imaging data of propofol-induced unresponsiveness suggests disruptions in both cortico-cortical (Jordan et al., 2013; Monti et al., 2013) as well as thalamo-cortical (Boveroux et al., 2010; Liu et al., 2013; Guldenmund et al., 2017) connectivity, applying especially to those circuits that account for the higher-order associative functions. Also, a suppression of frontal resting-state connectivity (Guldenmund et al., 2016) has been characterized. In stimulus paradigms, propofol has been shown to induce a disruption of thalamo-regulatory systems (functional disconnection of basal ganglia to the cortex) (Mhuircheartaigh et al., 2010) and to disrupt circuits that mediate higher-order processing (Liu et al., 2012). Sevoflurane, which is suitable for mask-induction and thus, step-wise administration increments, has also been associated to similar circuit disruptions, e.g., decrease in interhemispheric resting-state connectivity (Peltier 2005), in DMN connectivity (Deshpande et al., 2010; Palanca et al., 2015), in thalamic connectivity to frontoparietal cortex (Ranft 2016) and in memory- and pain-related higher-order circuits (Martuzzi 2010). The DMN has also been observed to maintain its' connectivity during 1% end-tidal concentration of sevoflurane (Martuzzi 2010).

Dexmedetomidine, which has a unique property to induce a reversible state of unresponsiveness, has been studied by brain imaging to a lesser extent. This is somewhat conflicting, as its behavioral properties could entail the key elements needed to unfold the mysteries of human consciousness. Without making alterations in drug administration, the state of consciousness can be manipulated multiple times. With this method, the imaging data between wakeful and unresponsive states are not confounded by altering drug levels. Physiologically, dexmedetomidine has a suppressive effect on cerebral blood flow, and was first witnessed in humans by functional brain imaging in 2002 (Prielipp et al., 2002). The interest was then preferentially on the physiological effects of the relatively novel sedative. The first study to exploit the unique property of dexmedetomidine and to focus on consciousness specifically was the study by Långsjö and colleagues (Långsjö et al.,

2012): During a constant-rate TCI, return of consciousness from an unresponsive state induced by dexmedetomidine was associated with the reactivation of deep core brain structures, especially the thalamus and ACC, as well as the inferior parietal cortex. Concomitant restoration of connectivity between the parietal cortex and ACC was observed (Långsjö et al., 2012). More recently, a multi-modal study that simultaneously measured the changes in CMR_{glu} (measured with the 18F-FDG method) and CBF (measured with the fMRI arterial spin labelling method) observed suppressions especially in the thalamus and frontoparietal cortices (the default mode network) when comparing dexmedetomidine-induced unresponsiveness to the awake state (Akeju et al., 2014). Connectivity results from the same data suggested functional connectivity in the thalamocortical networks to have most consistent association to the state of consciousness. A study by Guldenmund and colleagues (Guldenmund et al., 2017) compared natural sleep to propofol- and dexmedetomidine-induced sedation and explored the associating connectivity alterations. All three interventions disrupted resting-state functional connectivity in the higher-order resting state networks, the DMN, ECN and SN, while thalamic connectivity to the lower-order RSN's was relatively preserved.

Recently, increasing interest has been placed in more refined analytical approaches and graph-theoretical presentations (see Consciousness and Brain Networks). Propofol has been shown to decrease global information-processing efficiency, i.e., increase the path length of brain networks (Monti et al 2013) and reduce whole-brain spatiotemporal integration (Schröter et al., 2012). Similar findings have been discovered using dexmedetomidine, where unresponsiveness has been associated with significantly reduced local and global efficiencies, reduced mean strength of network connectivity, sustained degree distribution and modulated functional connectivity within and between all resting-state networks (Hashmi et al., 2017). Such findings suggest that consciousness is reliant on intact information transfer across multiple brain regions, and that decreased efficiency of brain networks is the main feature that dissociates the conscious from the unconscious brain.

2.4.4 Pathological Brain States and the Study of Human Consciousness

Disorders of consciousness (DoC) are a diverse group of conditions involving profound disruption of awareness and/or arousal. Most often resulting from diffuse traumatic or anoxic brain injury, DoC patients create a considerable burden on the society and individual families challenged by multiple medical and ethical questions. In recent years, numerous studies have been carried out to better understand these conditions and to improve diagnostics and therapy for this patient group. The

different clinical manifestations and nomenclature of the conditions are characterized in Consciousness and Clinical Implications.

The first functional imaging studies conducted on DoC patients were made almost forty years ago. They were carried out on patients in vegetative state (VS) or persistent vegetative state (PVS), depending on the duration of the condition (>12 months in traumatic injury, >3 months in non-traumatic, Laureys et al., 2004). These PET studies demonstrated that cortical metabolism was globally declined to approximately 40-50% of normal healthy values (Levy et al., 1987, Tommasino et al., 1995; Rudolf et al., 1999). Now termed unresponsive wakefulness syndrome (UWS), the condition is characterized by preserved arousal and autonomic functions, which is explained by the relatively intact subcortical structures and brainstem. However, individual metabolic values cannot unambiguously define whether a patient is conscious or unconscious, as some healthy volunteers have shown values of low metabolism comparable to patients in vegetative state (Laureys et al., 1999a). Conversely, some VS patients may have close to normal brain metabolism in cortical areas (Schiff et al., 2002). Furthermore, a recovery from VS is not always accompanied by full restoration of metabolic activity (Laureys et al., 1999a).

In 1999, a preliminary study reported a significant dysfunction of the prefrontal, premotor, posterior cingulate and higher-order association areas in PVS patients, accompanied by impaired frontoparietal connectivity (Laureys et al., 1999b). It has also been demonstrated that in non-communicative brain injured patients, the connectivity within the DMN is significantly decreased in proportion to the severity of the clinical condition (Vanhaudenhyuse et al., 2010). Similar to experiments using anesthesia, activation studies on VS and MCS patients have convincingly shown preserved sensory processing (Laureys et al., 2000; Boly et al., 2008b; Schoenle et al., 2004; Balconi et al., 2013; Beukema et al., 2016), suggesting intact function of certain sensory pathways in these patients. The higher-order areas, which represent associative functions are, however, perturbed (Boly et al., 2008b, Boly et al., 2011). While the clinical relevance of preserved evoked potentials is under debate, some studies have shown a correlation between intact long-latency potentials and subsequent recovery (Boly et al., 2011; Daltrozzo et al., 2007; Qin et al., 2008; Cavinato et al., 2009).

In recent years, studies on pathological brain states have tried to identify sites of structural damage that would correlate to poor recovery, thus enlighten prognostic factors and pinpoint brain areas crucial to consciousness. E.g., early thalamic hypometabolism has been shown to predict poor outcome after TBI (Lull et al., 2010). Conversely, recovery of consciousness after acute severe TBI has recently been associated with partial preservation of DMN correlations in the ICU, followed by long-term normalization of DMN correlations and anticorrelations (Threlkeld et al., 2018).

2.4.5 Physiologic Sleep, Dreaming and the Study of Human Consciousness

Physiologic sleep is not a state of profound unconsciousness, but rather, a dynamic state with periodic subjective experiences, i.e., dreams. Thus, sleep offers a unique possibility to study consciousness and its dimensions in a purely physiological setting. In the 1930's, it was first demonstrated that sleep alters the brain's electrical activity, as recorded with scalp electrodes (Loomis et al., 1935). Later, it was observed that periods of distinct electrical potentials divided physiological sleep to a cycle of different stages (Loomis et al., 1937). REM sleep was characterized in the 1950's, when it was demonstrated that periods of ocular movements preceded sleep with dream reports (Dement and Kleitman, 1957). Subsequently, physiological sleep was divided to REM and non-REM sleep, non-REM being further subcategorized to four nREM stages 1 through 4 (stages 3 and 4 termed slow-wave sleep, SWS).

In the 1990's, the first functional imaging studies on humans during REM and non-REM sleep were carried out using PET. For the time being, there was no specific focus on dreaming or consciousness *per se*, as the interest was mainly in discovering the physiological changes manifested during a normal sleep cycle. In a thorough study by Braun et al (Braun et al., 1997), it was demonstrated that non-REM and REM sleep were characterized by distinct patterns of CBF suppression; During non-REM sleep, CBF is decreased, with the most significant global reduction occurring during SWS. This was shown to be followed by CBF/activity increase in association with REM sleep. Sustained CBF suppression was observed in post-sleep wakefulness and interestingly, this state associated with comparable CBF levels as those observed during REM sleep (Braun et al., 1997). The differences between light and deep non-REM sleep are also noteworthy; when compared to wakefulness, deep sleep is characterized by widespread cortical and subcortical suppressions (Maquet et al., 1997), whereas light non-REM sleep shows less prominent cortical changes and sustained activity of the midbrain reticular formation (Kajimura et al., 1999).

As to metabolic alterations during sleep, the FDG-PET method has been the most used. This PET tracer has a relatively long half-life and thus, rapid changes in the state of consciousness cannot be detected using this tracer. Nevertheless, global suppression of metabolism is characteristic for non-REM sleep, observed especially in the frontal-parietal association cortices and the thalamus (Nofzinger et al., 2002). During REM sleep, the metabolic rate of glucose is comparable to values during wakefulness, which is in line with results from CBF studies. Interestingly, regional metabolic values have been shown to even exceed waking levels, especially in the basal forebrain (Nofzinger et al., 1997).

More recently, increasing emphasis has been placed in discovering alterations in network level perturbations during sleep. In this sense, analysis methods parallel the recent experimental studies on anesthesia and disorders of consciousness and

ultimately, have shown corroborating results. For instance, physiological deep sleep in relation to wakefulness has been shown to associate with reduced DMN connectivity, especially in connectivity of the frontal cortex to posterior regions (Horovitz et al., 2009) and thalamic connectivity to the higher-order resting-state networks (Guldenmund et al., 2017). In concordance, graph theoretical analyses have also found network modularity (a measure of functional segregation) to increase during deep sleep (Tagliazucchi et al., 2013). As already discussed, cortical effective connectivity is significantly reduced during non-REM sleep, as assessed by cortical reactivity to TMS (Massimini et al., 2005). These findings strengthen the conception of disrupted connectivity along "decreasing" level of consciousness and suggest network level similarities between physiological and pharmacological states of apparent unconsciousness.

However, when relating findings from sleep studies to human consciousness *per se*, the presence and absence of dreams becomes relevant. After the description of REM sleep, it was considered that dreaming occurs exclusively during this sleep stage (Dement and Kleitman, 1957), whereas non-REM sleep was thought to represent dreamless sleep, i.e., unconsciousness. This was rapidly disproved, as dream reports were soon found to associate also with non-REM stages 1 and 2, and even SWS (Foulkes, 1962). There is a tendency of slightly higher report frequency and length after REM sleep, although there has been debate about the robustness of such findings (Stickgold et al., 2001). It has been shown, however, that memory traces are predominantly processed during REM sleep (Maquet et al., 2000; Eichenlaub et al., 2018), which applies especially for experiences with higher emotional intensity. Importantly, neither dreaming nor unconsciousness during sleep are uniform states, where the phenomenal state would unambiguously represent one of the two options. There are different dimensions of experiences and perceptual activity throughout the sleep cycle, which makes the interpretations about possible mentation during sleep much more complex. The related challenges have been nicely summarized in a recent review (Windt, 2016).

Some studies have already pursued to separate dreaming from dreamless sleep based on cortical brain activity. As described earlier, NREM and REM sleep have shown to exhibit distinct EEG responses to transcranial magnetic stimulation (See 2.4.2 Anesthetic-Induced Unresponsiveness and EEG). This paradigm has later been used to discriminate different phenomenal states within NREM sleep; Nieminen et al demonstrated that subjects who did not report dreaming after NREM sleep showed a larger negative deflection and a shorter phase- locked response to TMS compared to subjects who reported a dream (Nieminen et al 2016). These findings illustrate that cortical activity may discriminate different states of consciousness within the same physiologic condition.

Demonstrably, dreaming can occur during all stages of sleep (Nielsen, 2000). The lack of a dream report does not, however, unequivocally indicate unconsciousness (Windt, 2016), as delayed interviews are subject to amnesia (Schwartz and Maquet, 2002). The only way to access subjective experiences are, thus, retrospective reports. In a recent study on dreaming, an awakening paradigm with immediate interviews was used. Based on individual EEG patterns, it was possible to predict with 87% total prediction accuracy across all states whether a subsequent report from NREM and REM sleep included dreaming (Siclari et al., 2017). This study provided important validation for the report-based state classification.

2.4.6 Study Design Challenges

There are several challenges related to experimental studies on human consciousness. One fundamental challenge is related to whether studies approach consciousness in terms of conscious *contents* or overall conscious *states* (or *levels)*. As described earlier, the study of consciousness has mostly been directed towards one of these two dimensions of consciousness (see Introduction). This is, however, somewhat problematic, as both approaches seem to disregard one another. As reviewed by e.g., Searle (Searle, 2005) and Hohwy (Hohwy, 2009), both experimental approaches have some fundamental limitations. The content-based approaches seem to set aside the fact that whenever any particular content of consciousness is investigated, the subject is already in a conscious state. On the other hand, state-based approaches tend to be over-inclusive, i.e., interpret all findings to be state-related (Hohwy, 2009). It has recently been emphasized, that the two experimental approaches need to be combined (Hohwy 2009, Bachmann and Hudetz, 2014).

Some other fundamental issues also persist. In state-based studies, the matter of the most relevant contrasts is still largely disregarded. In studies using anesthesia, it is a common practice to compare two distinct states of consciousness; an awake state and an anesthetized (and presumed unconscious) state. The difference in neurophysiological measurements between these states has then been considered to reflect the correlates of consciousness. However, pharmacological agents have independent effects on the brain even when no change in the state of consciousness can be witnessed. Before consciousness is lost, the subject becomes drowsy, sedated and there is a decline in attention and other cognitive functions. With this in mind, using normal wakefulness as reference oversees such, probably concentration-dependent effects on brain functions and leads to false interpretations about state-related effects. Similar confounding effects may manifest, when consciousness is studied using natural sleep, and the effects related to drowsiness are not accounted

for. In an ideal setting, the compared states would be rigorously selected, and minimal differences in drug concentration and other confounding elements should be present. It should be bared in mind, that the concentration-effect curves of many general anesthetics are relatively steep, and many previous studies have employed standard boluses at baseline to achieve the desired state(s). Finally, a shift in the state of consciousness also entails the prerequisites and aftereffects of the transition (Aru and Bachmann, 2017), a matter that is mostly not acknowledged in state-based studies.

Some experimental studies have attempted to overcome the pharmacological shortcomings. One elegant method has been to maintain anesthetic exposure constant, and pursue reversal of anesthesia with external stimulation. Measuring brain activity during awakening would thus reveal brain regions crucial to restoration of consciousness, without confounding effects of varying anesthetic concentration. This was first pursued by Långsjö and colleagues (Långsjö et al., 2012) by exploiting the unique property of dexmedetomidine, and awakening subjects from an unresponsive state during steady-state anesthesia. In this PET study, return of consciousness was associated with activation of subcortical structures such as the thalamus and ACC and restoration of connectivity between inferior parietal cortex and ACC and other frontal regions (Långsjö et al., 2012). A propofol-group was also studied, but steady-state awakening was not attempted.

Importantly, abrupt awakenings during steady-state anesthesia may not be feasible with the majority of anesthetics. Thus, awakenings have also been carried out by stimulating arousal pathways with other pharmacological agents, while keeping the anesthetic exposure constant. For instance, propofol has been thought to partly mediate its' effects through cholinergic mechanisms. Physostigmine, an anticholinesterase inhibitor, has been witnessed to partly antagonize the sedative effects of propofol (Meuret et al., 2000), as well as enhance recovery from ketamine (Toro-Matos et al., 1980) and midazolam sedation (Caldwell and Gross, 1982). PET data of abrupt awakening from constant rate propofol anesthesia with the use of physostigmine has been associated to activations of the thalamus and precuneus, suggesting a crucial role of these brain regions to consciousness (Xie et al., 2011). Some other agents have also shown to reverse anesthetic actions; In a rat model, general anesthesia induced by isoflurane (Solt et al., 2011) and propofol (Chemali et al., 2012) have been shown to be partially reversed by methylphenidate (a dopamine and norepinephrine reuptake inhibitor), whereas sevoflurane anesthesia (Kenny et al., 2015) by dextroamphetamine (a dopamine and norepinephrine agonist). Hence, dopaminergic nuclei, especially ventral tegmental area (VTA), seem critical to the regulation of consciousness. Indeed, electrical and optogenic stimulation of VTA has shown to induce reanimation from general anesthesia in a rat model (Solt et al., 2014,

Taylor et al., 2016). Table 3 summarizes consciousness studies using anesthesia, which have targeted to eliminate drug-related effects with different methods.

Table 3. Anesthesia studies, which have targeted to eliminate confounding drug-related effects in consciousness research.

Authors	year	anesthetic	method	species	intervention	conclusions
Meuret et al.	2000	propofol	EOG	humans	i.v physostigmine	Unconsciousness is mediated via interruption in central cholinergic muscarinic transmission.
Xie et al.	2011	propofol	PET	humans	i.v physostigmine	rCBF changes in the thalamus and precuneus independently associate to propofol-induced unconsciousness
Solt et al.	2011	isoflurane	EEG	Rats	i.v methylphenidate	Consciousness is restored through activation of dopaminergic and adrenergic arousal circuits
Långsjö et al.	2012	dexmedetomidine	PET	humans	constant-dose awakening	Recovery of consciousness involves activation of the brainstem, thalamus and the ACC arousal networks, as well as restores functional connectivity within the frontoparietal network.
Chemali et al.	2012	propofol	EEG	Rats	i.v methylphenidate	Methylphenidate induces emergence from propofol general anesthesia in rats. This supports the hypothesis that monoaminergic arousal pathways play a critical role in restoration of consciousness
Solt et al.	2014	isoflurane	VTA Electrodes	Rats	Electrical stimulation of the VTA and SN	Dopaminergic activation induces reanimation from general anesthesia
Kenny et al.	2015	sevoflurane	EEG	Rats	i.v dextroamphetamine and atomoxetine	dopaminergic stimulation promotes behavioral arousal, whereas noradrenergic stimulation does not.
Taylor et al.	2016	isoflurane	VTA Electrodes	Mice	Optogenic stimulation of the VTA	VTA DA neurons play an important role in recovery of consciousness after general anesthesia.
Pal et al.*	2018	sevoflurane	EEG	Rats	Reverse dialysis delivery of carbachol and norepinephrine to prefrontal and parietal cortices	Cholinergic mechanisms in prefrontal cortex regulate the level of consciousness.
Pal et al.*	2020	sevoflurane	EEG	Rats	charbacol delivery to prefrontal cortex	Level of consciousness is dissociable from electroencephalographic measures of cortical connectivity, slow oscillations, and complexity
Redinbaugh et al.	2020	NREM sleep, isoflurane, propofol	linear multi-electrode arrays (spikes and LFP's)	Macaques	(Gamma-frequency) Electrical stimulation of the central lateral thalamus	Consciousness is reliant on the reciprocal interaction between central lateral thalamus and deep cortical layers

Abbreviations: Electro-oculogram (EOG), Local Field Potentials (LFP's), Substantia Nigra (SN), Ventral Tegmental Area (VTA)
*same data

Another study design issue related to consciousness research is the (in)stability of the achieved states and the associated neurophysiological measures. It has been argued that conscious and unconscious states are dynamic processes that involve continuous shaping of brain activities (for reviews, see Tononi, 1998; Cavanna et al., 2018). Accordingly, any static measure of brain activity or connectivity is an ambiguous reflection of the state of consciousness. This is supported also clinically;

As opposed to a monotonic path from an unconscious to a conscious state, recovery of consciousness during isoflurane anesthesia has been found to be mediated by a sequence of distinct, metastable functional states in a rat model (Hudson, 2017). Such metastability has also been found in humans using EEG; despite a stable anesthetic level, functional connectivity fluctuates dynamically and nonrandomly over time (Untergehrer et al., 2014; Li et al., 2019). A similar finding has also been seen during surgical levels of anesthesia (Vlisides et al., 2019).

Finally, the definition of unconsciousness in anesthesia studies has been somewhat arbitrary for decades. In experimental state-based studies, unconsciousness has mostly been defined by behavior, i.e. by responsiveness to external stimuli. As already thoroughly discussed, unresponsiveness does not equal unconsciousness (see 2.1.2 Defining Consciousness). The phenomenal states induced by anesthetic agents and physiological sleep are much more diverse, which calls for proper characterization of the explored states. It is justified to argue, that anesthesia dreaming, i.e., disconnected consciousness, has been largely overlooked in experimental studies on human consciousness.

3 Aims

The aim of this study was to investigate human consciousness in rigorous experimental paradigms using healthy subjects studied with EEG and PET methods. Two distinct anesthetic agents and natural sleep were used.

The specific aims of these studies were:

1. To characterize spectral EEG changes manifested during increasing and constant concentrations of propofol and dexmedetomidine and different pre-defined behavioral conditions. (Study I)
2. To differentiate drug–related and state–related effects of the drugs on EEG measures with a carefully designed study protocol and by rigorous statistical analyses between the pre-defined states. (Study I)
3. To explore whether or not semantic processing, as indicated by N400 ERP, is preserved during propofol- and dexmedetomidine-induced unresponsive states. (Study II)
4. To discover the overall effects different interventions have on relative rCBF by performing PET imaging during increasing concentrations of propofol and dexmedetomidine and during deepening physiologic sleep. (Study III)
5. To explicitly characterize the induced unresponsive states beyond behavioral properties. (Study III)
6. To delineate the changes related specifically to the connected state *per se*, i.e., separate them from the overall effects of the interventions. (Study III)

4 Materials and Methods

4.1 Experimental Designs

This was an open, parallel-group and randomized study using healthy subjects. Five separate study sessions were conducted (parts 1–5, ClinicalTrials identifier NCT01889004), and all study sessions were conducted between February 2014 and November 2015 in Turku PET Centre and the intensive care unit in Turku University Hospital, Turku, Finland. Same subjects were used in the subsequent sessions. Data from parts 2–4 formed this thesis. Studies **I** and **II** report EEG and N400 ERP results, respectively, from part 2 ("Dose Finding"), and study **III** reports PET results from parts 3 and 4 ("Experiment 1" and "Experiment 2"). The nomenclature of the experiments aims to parallel the terminology in the original publications. Dose Finding refers to our objective to determine individual plasma concentrations for loss of responsiveness (LOR). These concentrations were to be used to guide the anesthetic dosing in the subsequent PET study.

Dose Finding and Experiment 1 were anesthesia experiments, where anesthesia (propofol or dexmedetomidine) were used to manipulate the state of consciousness. Experiment 2 was a sleep study, where only natural sleep was used. Table 4 clarifies the structure of this study entity and the different experiments and the respective methods and measured variables. In all experiments (parts 1–5), also other variables (immunologic markers, EEG connectivity, experiences, fMRI BOLD) were collected and the results from these data are reported separately (for clarification, see Table 4.)

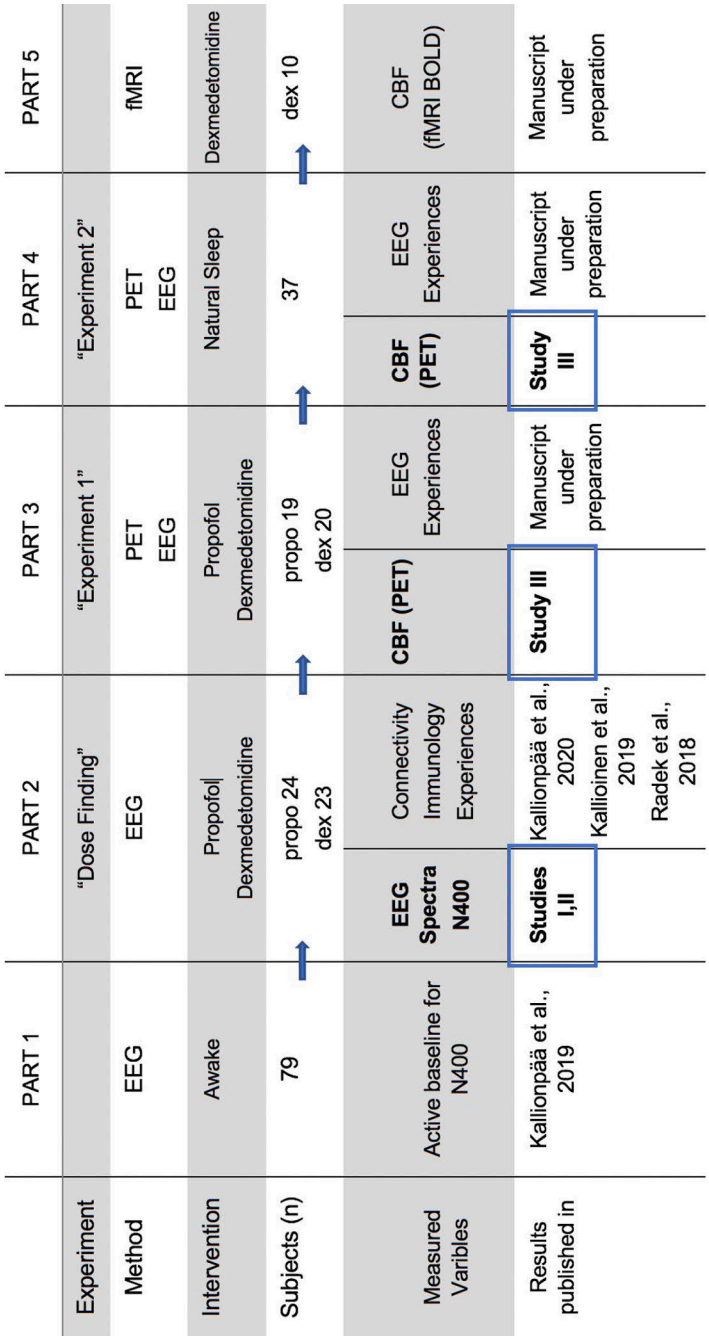

Table 4. Clarification of the different parts and experiments of the study entity. Studies I and II report the findings from Dose Finding. Study III reports the findings Experiment 1 and Experiment 2.

4.2 Study Subjects

Altogether, 79 right-handed, healthy (American Society of Anesthesiologists physical status I), non-smoking, 20−30 years old male subjects were recruited to participate in this open-label, randomized, parallel-group study entity. Subjects were recruited from universities in Turku, Finland. Female subjects were ineligible due to radiation exposure related to the subsequent PET scans. Other exclusion criteria were history of psychiatric disorder, somatic illness of clinical relevance, cardiac arrhythmias, substance abuse or drug allergies. Ongoing medications and hearing impairment were also considered as reasons for exclusion. Interview and laboratory tests were acquired from all subjects, including hearing test, drug screening and an electrocardiogram recording was performed. All subjects sustained from using alcohol or medications for 48 hours prior to study sessions and they fasted overnight before anesthesia. A written informed consent was acquired from all participants according to the Declaration of Helsinki.

In Part 1 (n=79), the eligibility of the N400 paradigm was tested. Those subjects, who showed apparent N400 effect in the awake state (n=47), continued to Dose Finding (Studies I and II) and they were randomized to receive either propofol (n=24) or dexmedetomidine (n=23) as target-controlled infusion (TCI). Subsequently, the same subjects continued to Experiments 1 and 2 (Study III). In Experiment 1, the drugs were administered using the individually determined concentrations for LOR, measured in Dose Finding

Because of 3 exclusions (mild apnea in Dose Finding [n=2] and abnormal MRI scan [n=1]) and 5 withdrawals, 39 subjects participated in Experiment 1. Two more subjects withdrew after Experiment 1, and 37 subjects participated in Experiment 2.

4.3 Randomization

Randomization was conducted by the principal investigator (H.S), who did not participate in the recruitment of the subjects nor the execution of the experiments. In the Dose Finding, permuted blocks (block size 20) were used to randomize the subjects to receive either propofol or dexmedetomidine. The same anesthetic agent was used in the subsequent Experiment 1.

4.4 Anesthesia Protocols (Studies I, II, III)

Similar anesthesia protocols were used in Dose Finding (Studies I and II) and Experiment 1 (Study III). In these experiments, subjects received either propofol (Propofol-Lipuro, 10mg/ml, B. Braun) or dexmedetomidine (Dexdor 100 µg/ml; Orion Pharma, Espoo, Finland), and the anesthetics were delivered using target-controlled infusion (TCI) by a Harvard 22 syringe pump (Harvard Apparatus, South Natick, MA) and a portable computer running Stanpump software (by Steven L. Schafer, MD, www.opentci.org/code/stanpump). The pharmacokinetic parameters by Marsh (Marsh et al., 1991) and Talke (Talke et al., 2003) were used for propofol and dexmedetomidine, respectively.

4.4.1 Dose-Finding (Studies I and II)

Consciousness was manipulated with step-wise increasing concentrations of either propofol (1.0–1.5–1.75–2.0–2.25–etc. µg/ml) or dexmedetomidine (1.0–1.5–1.75–2.0–2.25–etc. ng/ml), until loss of responsiveness (LOR). LOR was defined as participant's inability to respond to a standardized pre-recorded responsiveness test (see below). Both drugs were administered as step-wise escalating pseudo-steady state plasma concentrations at approximately 7 min intervals. The last responsive sedative state before LOR was denoted SED. Once LOR was achieved, the respective target concentration was maintained for approximately 25 min as a pseudo steady-state infusion, during which EEG and ERP data was collected. The last two minutes of the steady-state phase was designated as LOR_{late}. After the steady-state phase, an attempt was made to awaken the subject with verbal or mild tactile stimulation without terminating or changing the target concentration (see 4.6.2 Responsiveness Testing and Awakening Procedure). After successful awakening (return of responsiveness, ROR), the TCI was continued and subjects were allowed to return to unresponsiveness (LOR2) and then again awakened (ROR2). To clarify, two cycles of LOR, each followed by awakenings were attempted (LOR–ROR–LOR2–ROR2). Depending on the arousability of the subjects (see below), the steady-state infusion lasted from 25 min up to two hours. After ROR2 (or any unsuccessfully targeted state) the drug concentration was increased by 50% (1.5x LOR) to achieve (presumable) unconsciousness (loss of consciousness, LOC). If the subject remained responsive after this final increment, an additional 0.25 concentration increase was made. The outline of the study is illustrated in Figure 5

and the assessments made during the drug administration are specified in "Measured Variables and Data Processing".

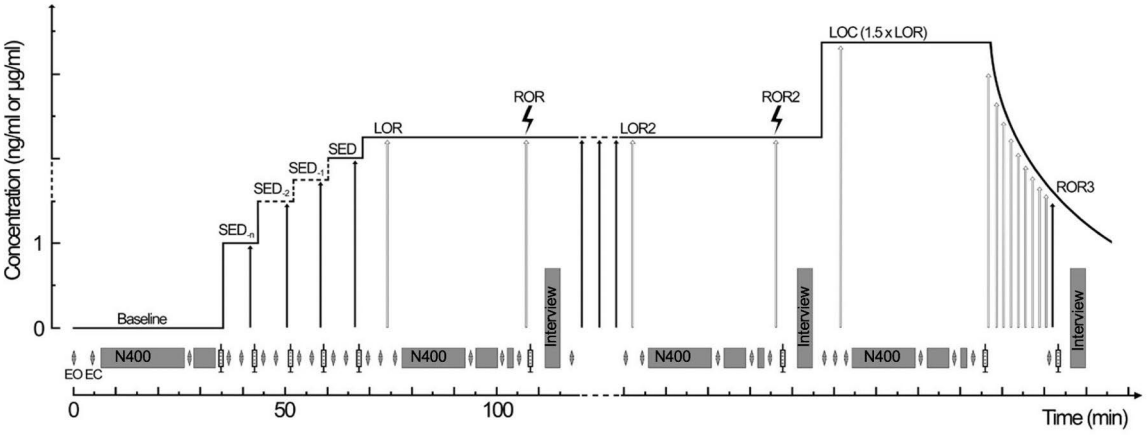

Figure 5. Schematic outline of the Dose-Finding study design. Modified from Original Publication I, see text for details. Black arrows= R-test, responsive; Grey arrows= R-test, unresponsive; Lightning= awakening, Syringe= Blood sample. Abbreviations: EC= Eyes closed, EO= Eyes open, SED= Sedative state, LOR= Loss of responsiveness, ROR= Return of responsiveness, LOC= Loss of consciousness, N400= N400 ERP Paradigm.

4.4.2 Experiment 1 (Study III)

The same subjects were exposed to the same anesthetic as in Dose Finding, and the estimated plasma concentrations for LOR were used as reference for each subject individually. The drug administration started from 0.5xLOR, then 0.75xLOR–1.0xLOR until unresponsiveness (UR) was reached. UR was defined as participant's inability to respond to a standardized pre-recorded responsiveness test (see below). If UR was not reached with 1.0xLOR, additional 0.25–0.5–fold increments (relative to the preceding target) were applied at approximately 7 min intervals until UR was reached in every subject. "Moderate sedation" (SED_{mod}) was defined as the last responsive anesthetic level before UR and "light sedation" (SED_{light}) the preceding sedative level. Once UR was achieved, the respective target was maintained for approximately 25 min as a pseudo steady-state infusion. Identically to Dose Finding study, two cycles of UR followed by awakenings (R) were attempted (UR-R-UR2-R2). Finally, a 1.5xUR concentration increment was applied for a more profound anesthetic effect, after which the infusion was terminated and the subjects were left to recover spontaneously. The outline of the study is illustrated in Figure 6. The

assessments made during the drug administration are specified in “Measured Variables and Data Processing”.

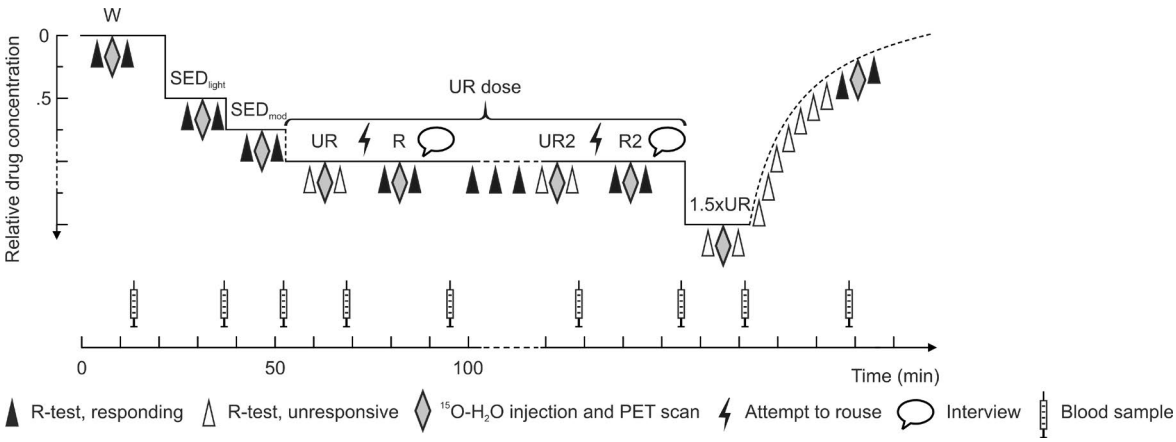

Figure 6. Schematic outline of Experiment 1 study design. Modified from Original Publication III, see text for details. Abbreviations: W= Wakefulness, SEDlight= Light Sedation, SEDmod= Moderate Sedation, UR= Unresponsiveness, R=Responsive during UR-dose, 1.5xUR= 1.5fold UR-concentration.

4.5 Sleep Study Protocol (Study III)

Subjects from Experiment 1 (anesthesia) continued to Experiment 2 (sleep). An at-home 30-hour sleep deprivation was conducted, to maximize the likelihood of sleep onset in the scanner. Vigilance through the preceding night was monitored with ZEO sleep monitor (ZEO Inc, Boston, MA). Subjects were instructed to use ZEO monitor from 10 pm to at least 8 am, or until departure to study unit. A tablet computer, with pre-programmed alarms every 20–40 min, was also provided. The alarm volume increased until it was turned off. The alarm could also not be turned off until the subject had solved a mathematical problem correctly. Participants were also asked to fill in a log throughout the night.

Same EEG equipment as in the anesthesia studies was used to record EEG signal and monitor sleep stages during the scanning session. For complete polysomnography (PSG), four bipolar electrodes were used to measure horizontal and vertical eye movements, two bipolar electrodes were attached on mentalis and submentalis muscles to measure EMG, and ECG was monitored similarly to anesthesia experiments.

PET scan onsets were determined by visual sleep staging, which was done by inspection of online PSG by an experienced sleep technician using The Academy of American Sleep Medicine 2013 sleep scoring manual guidelines. We aimed to scan each subject awake (sleep deprived state) and then in as many different sleep stages

as possible. The total amount of scans was restricted to five to restrict the radiation exposure related to the study entity. If the subject successfully fell asleep in the scanner, second emission scan was attempted immediately (non-REM stage N1), the third one during light (non-REM stage N2) sleep and fourth one during deep (on-REM stage N3) sleep. The outline of the study is illustrated in Figure 7. The assessments made during the sleep study are specified in "Measured Varibles and Data Processing".

Final sleep staging from the 90 s scan time used for PET data analysis, was conducted by two experienced sleep technicians applying the Academy of American Sleep Medicine 2013 guidelines with a strong inter-rater agreement of 93.1% (Cohen's kappa = 0.908, $p<0.001$).

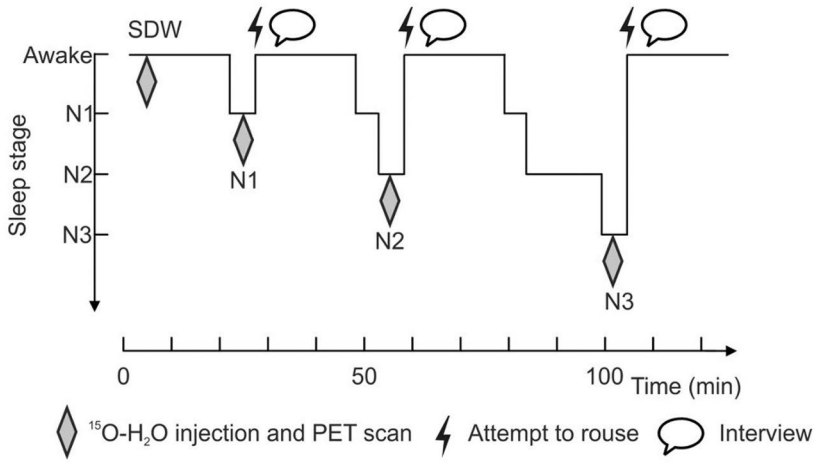

Figure 7. Schematic outline of the sleep study design. Modified from Original Publication III, see text for details. Abbreviations: SDW= Sleep Deprived Wakefulness, N1, N2, N3= Non-REM Sleep Stages 1, 2 and 3, respectively.

4.6 Measured Variables and Data Processing

4.6.1 Drug Concentration Measurements (Studies I, III)

Blood samples for concentration measurements were collected in Dose Finding and Experiment 1. The samples were drawn at the end of each drug concentration level, and whenever the state of consciousness was thought to have changed (see study outlines in Figures 5 and 6). Plasma concentrations of dexmedetomidine and propofol were determined using high-performance liquid chromatography with tandem mass spectrometry and fluorescence detection (Yeganeh and Ramzan, 1997)

4.6.2 Responsiveness Testing and Awakening Procedure (Studies I, II, III)

The subjects responsiveness guided the execution of the anesthesia studies. Responsiveness was tested with a responsiveness test (R-test), and it was presented through headphones with Presentation 17.0 stimulus delivery and experimental control software system (Neurobehavioral Systems Inc, Berkeley, CA, USA). All instructions and stimuli were also delivered via headphones.

The R-test was a pre-recorded set of 10 sentences with a semantically congruent (n = 5) or incongruent (n = 5) last word. The response was instructed to be carried out by left or right handle press according to the congruency of the sentence. The hand corresponding congruous sentences (left or right) was balanced in both groups. In Dose-Finding, a standard R-test was presented at every drug concentration level and whenever responsiveness was lost. In Experiment 1, only novel sentences were used, and the R-test was played at every drug concentration level and whenever the state of consciousness was thought to have changed. Loss of responsiveness (LOR, Dose Finding) and unresponsiveness (UR, Experiment 1) were defined as zero responses out of ten (both abbreviations denote unresponsiveness, but nomenclature aim to parallel the terminology used in the original publications). In Experiments 1 and 2, the actual state of consciousness (connected, disconnected, unconscious) was later assessed based on individual reports of mental content (see 4.6.4 Assessment of the state of consciousness).

The awakening procedure (also the term “arouse” is used) was carried out after the LOR and LOR2 states in Dose Finding, after the UR and UR2 states in Experiment 1 and after each sleep stage in Experiment 2 (see Figures 5, 6 and 7 for illustrative images). The awakening procedure was made by the sessions main anesthesiologist by first addressing the subject by name and a request was made to open ones’ eyes. After that, a mild tactile stimulation (shake in the shoulder) was added. If needed, the subject was again addressed by name and a more forceful shake in the shoulder was conducted. If the awakening was unsuccessful, i.e., the subject was non-arousable, he was left unstimulated and the awakening(s) were abandoned. Most often, the awakening was performed by the same person (A.S), but in case of absence also by two others (M.K and J.L).

4.6.3 EEG Recording and Data Processing (Studies I, II)

Online EEG data was collected in all experiments. The results of the collected EEG data is, however, reported only from Dose Finding, as EEG data from Experiments 1 and 2 are to be reported separately (see Table 4). The data were collected with NeurOne 1.3.1.26 software and Tesla no. MRI 2013011 and no. MRI 2013012

amplifiers (Mega Electronics Ltd, Finland). The EEG tracing was recorded using 64-channel EasyCap Active electrode cap (EasyCap GmbH, Germany) with sintered silver/silver chloride active electrodes, placed according to international 10-10 electrode placement system. Four additional electrodes were placed to record horizontal and vertical eye movements and two to record ECG. EEG data were collected with a sampling rate of 1,000 Hz with amplifier low-pass filter having half-amplitude threshold of 360 Hz (transition band, 250 to 498 Hz) and high-pass filter of 0.16 Hz (6 dB/octave). Data were referenced to the fronto-central site, and the ground electrode was placed at the medial prefrontal site. The EEG signal quality was monitored online by a technician, specialized in clinical neurophysiology.

Continuous electroencephalogram data for spectral and phase-amplitude coupling (PAC) analyses were collected from stimulus- and response-free 2 min periods, segmented from raw EEG using EEGLAB toolbox for MATLAB (version 2015a; MathWorks, Inc., USA). The states of interest were BL, SED, LOR, LOR_{late}, ROR and LOC (see Figure 5 for study outline). The segments were visually inspected, noisy channels were interpolated, and a maximum of 10 seconds of artifacts (resulting from, e.g., head or eye movements) were removed. Each segment was shortened to 110 s, and the sampling frequency was reduced to 250 Hz. Fifty-nine scalp channels were processed using custom-written functions in MATLAB.

To improve spatial localization and to mitigate the effect of volume conduction, The EEG signals were re-montaged to Laplacian reference. Spectrograms were computed using the multitaper method, implemented in Chronux analysis software (http://chronux.org) (Mitra, 2007) with window length of 4 seconds at a 2 second overlap, time–bandwidth product = 2, number of tapers = 3, and spectral resolution = 1 Hz. For statistical comparisons, the mean spectral distribution was obtained by taking the average across all the windows at each of the studied segments, and the electroencephalogram powers were calculated for delta (1 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 14 Hz), beta (14 to 25 Hz), and gamma (25 to 45 Hz). EEG power for slow–delta was calculated in temporal domain by applying a bandpass filter (passband edges: 0.1 to 1 Hz; –6 dB cutoff frequencies at 0.05 and 1.05 Hz) to the electroencephalogram signals, using the eeg-filtnew function in the EEGLAB toolbox. The topographic maps of group-level spectral power for each studied segment and frequency band were constructed using the topoplot function in the EEGLAB toolbox. (Delorme A, 2004)

The phase-amplitude coupling analysis was performed according to recent literature (Mukamel et al., 2014). Each 110-second EEG segment was bandpass-filtered and Hilbert- transformed to obtain the slow-delta (0.1 to 1 Hz, eegfiltnew parameters, same as above) phase and alpha (passband edges 8 to 14 Hz, –6 dB cutoff frequencies at 7 and 15 Hz) power component, thereafter divided into windows of 60 seconds, with an overlap of 55 seconds. For each window, the modulogram was

constructed by assigning each sample of alpha power to one of the equally spaced slow-delta phase bins (N = 18 bins), then averaging the power values in each bin, and applying entropy index to quantify this distribution (Tort et al., 2008) which was deemed significant if it exceeded 95% of the surrogate values generated by shuffling the power series (Canolty et al., 2006; Onslow et al., 2011). The coupling type (trough-max or peak-max as defined by Mukamel and colleagues (Mukamel et al., 2014; Purdon et al., 2013) was combined into the entropy index by assigning a negative or positive sign, respectively. For statistical comparisons, the phase-amplitude coupling values across all windows were averaged and set to zero if insignificant (Bonferroni-corrected $P < 0.05$) at each of the studied segments. The topographic maps of group-level phase-amplitude coupling for each studied segment were constructed using the topoplot function in the EEGLAB toolbox.

4.6.4 N400 ERP Data Collection and Processing (Study II)

The ERP stimuli were 620 Finnish auditory high-cloze-probability sentences. The sentences were constructed with the help of twenty psychology students, who were asked to fill a missing last word in the sentences, using a word that first comes to mind and fits the context. Cloze probability ≥ 50% was required (which means that the same word had to be selected by at least half of the participants). Thereafter, half of the sentences were randomly selected and the expected (congruous) last word was replaced with an unexpected (incongruous) word, which matched on inflection, word class, number of syllables, and word lemma frequency (Laine and Virtanen, 1999). The resulting congruous and incongruous sentences did not differ in terms of last-word lemma frequency, the number of syllables in the last word, or sentence word count (Mann-Whitney U; $P>0.05$ for all). A female native Finnish speaker recorded the sentences. There was a 1 s silence before and after the last word of each sentence. The sentence was followed by a response cue (a 100 ms sine sound) and 2.3 s was left for the response. The stimuli were organized into blocks with 50% incongruous sentences. Congruous and incongruous sentences were randomly ordered, and their presentation sequence was the same to all subjects. The blocks of stimuli did not differ in terms of last-word lemma frequency, the number of syllables in the last word, or sentence word count (KruskaleWallis H; $P>0.05$).

Headphones were used to deliver all instructions and stimuli via Presentation 17.0 software (Neurobehavioral Systems Inc., Berkeley, CA, USA). One stimulus block per condition was presented, and each block was presented only once.

In the active baseline (Kallionpää et al 2019, see Experimental designs, Table 4) and in the Dose-Finding Study, the subjects were instructed to distinguish between

congruous and incongruous sentences by pressing the right or left response handle after hearing the response cue. Instruction to respond were given before each R-test.

The EEG signal was pre-processed using MATLAB R2013b (MathWorks Inc., Natick, MA, USA) and EEGLAB 13_4_4b-toolbox (Swartz Center for Computational Neuroscience, University of California San Diego, La Jolla, CA, USA). The signal was down-sampled to 250 Hz and re-referenced to the mastoid average. Filtering was performed using half-amplitude passband of 0.5–20 Hz with non-causal Blackman-windowed sinc FIR filter with transition bandwidth of 1 Hz for high pass and 4 Hz for low pass (passband ripple 0.02%; stopband attenuation –74 dB).

The N400 component elicited by the first and last words of the sentence stimuli was analyzed. The trials were segmented from –1000 to 1000 ms respective to the onset of the word. The baseline was corrected using the pre-stimulus period, –1000 to 0 ms. Noisy channels were visually identified and interpolated (mean: 0.23; standard deviation: 1.05 channels per subject in the anesthesia experiment). Epochs with absolute value of amplitude exceeding 150 mV or amplitude changes greater than 100 mV in 80 ms were excluded using an automated algorithm. The median number of epochs excluded per stimulus block was 3 (range: 0–77) in the awake experiment and 9 (range: 0–100) in the anesthesia experiment.

To analyze the N400 ERP component and effect, amplitude averages in the presumed time window of the N400 component (300–600 ms) were computed (Kutas and Hillyard, 1980). They were also computed from the pre-stimulus baseline in a corresponding control time window (–600 to –300 ms), which was chosen to account for baseline variation of the signal in segments of 300 ms. For each subject, the amplitudes were averaged over trials within each stimulus block, and it was made separately for congruous and incongruous stimuli. Cases with data from less than 20 congruous or incongruous trials were excluded. The analysis was restricted to 13 centroparietal channels (Cz, C1, C2, C3, C4, Pz, P1, P2, P3, P4, CPz, CP1, and CP2).

4.6.5 PET Imaging (Study III)

PET imaging was conducted using an ECAT HRRT (Siemens CTI, Knoxville, TN, USA) brain scanner. The HRRT is a dual-layer, LSO (lutetium oxyortho-silicate) /LYSO (lutetium yttrium oxyortho-silicate) crystal-detector scanner with a nearly isotropic 2.5 mm intrinsic spatial resolution. In the reconstructed images, spatial resolution varies from 2.5 to 3 mm in the radial and tangential directions and from 2.5 to 3.5 mm in the axial direction in the 10 cm field-of-view covering most of the brain (de Jong et al., 2007). In the scanner, subjects were positioned in supine

position using a standard headrest, and a Velcro band was tightened over the forehead to minimize any head movements. Head motion was monitored with a high-precision, stereotaxic tracking device (Polaris Vicra, Northern Digital, Waterloo, ON, Canada), which was attached to the subject's head.

To assess regional cerebral blood flow (rCBF), ^{15}O -labelled O_2 ($[^{15}O]O_2$) was produced with a low-energy deuteron accelerator Cyclone 3 (IBA, Ion Beam Applications Inc., Louvain-la-Neuve, Belgium) at Turku University Hospital. The target gas with $[^{15}O]O_2$ was mixed with pure H_2 to produce water vapor in a hot (700 °C) quartz furnace. Radiopharmaceutical-grade $[^{15}O]H_2O$ was produced according to good manufacturing practices using an automated Hidex Radiowater Generator (Hidex Oy, Turku, Finland). Whenever imaging was initiated, a 300 MBq dose of $[^{15}O]H_2O$ was administered by an automated infusion system (Rad Injector, Tema Sinergie, Faenza, Italy) in approx. 15 seconds. Emission data in list-mode format were recorded over the duration of the $[^{15}O]H_2O$ administration and the subsequent 120 s. Point of departure (PoD) for emission data was determined offline as the time point where the count rate of "trues" exceeded the count rate of "randoms". By default, the list-mode data were histogrammed in two (60 s and 30 s) 3D sinograms from PoD onwards. In case the external motion recordings indicated significant (>2.5 mm) within-frame motion, sub-frames were formed until sub-threshold level motion was assured (Johansson et al., 2016). In most cases, sub-framing was not needed; yet, 91 sub-frames in 31 (out of 302) sessions were generated for Experiment 1, and 10 sub-frames in 6 (out of 116) sessions were generated for Experiment 2, and some sub-frames were discarded (in 29 sessions in Experiment 1 and in 2 sessions in Experiment 2) due to shortage of data. There were no marked differences in the number of incidences between the two drugs in Experiment 1. Transmission data acquired just before the first $[15O]H_2O$ administration were used to generate photon attenuation maps, while a single-scatter simulation algorithm was used to estimate the proportion of scattered events and randoms were estimated from the block singles. All corrections were included in an iterative image reconstruction procedure including resolution modelling (PSF-OP-OSEM, 12 iterations, 16 subsets) (Comtat et al., 2008) and motion compensation of the attenuation maps (Johansson et al., 2016). Motion compensated frame-wise data were summed to form a 90 s sum-image for subsequent analysis.

Image preprocessing was performed with standard PET techniques. For each subject, an average image of the summed PET images was formed for each condition. Across-subject image alignment, registration, and normalization were performed using statistical parametric mapping software (SPM8 and 12, Wellcome Institute). A reference frame from the baseline scan was used as a target to obtain initial between-sessions realignment and motion correction. The mean PET image was co-registered with the skull-stripped anatomic MRI and the session images were

resliced accordingly into MRI voxel size (1 x 1 x 1 mm). Nonlinear mapping from the MRI to the MNI standard space was estimated using unified segmentation in SPM8, and the deformations were subsequently applied to the MRI and co-registered PET images. All normalized PET images were smoothed using an isotropic Gaussian kernel of 12 mm FWHM. Proportional scaling was used in the PET analyses.

4.6.6 Assessment of the State of Consciousness (Study III)

Explicit characterization of the explored states is often missing in consciousness research. After classification of the investigated conditions to responsive and unresponsive categories and non-REM sleep stages, the state of consciousness was subsequently assessed beyond behavioral properties (Experiments 1 and 2). We have previously demonstrated that the used anesthetics and concentrations are efficient in inducing a disconnected state, defined as either an unconscious state or as a disconnected conscious state involving internally generated experiences (Noreika et al., 2011; Radek et al., 2018). Thus, all behaviorally unresponsive states and verified sleep stages were assessed in detail to define the phenomenal state (connected/disconnected/unconscious) in the investigated conditions. All behaviorally responsive and awake sleep-deprived states before verified sleep onset indicated a connected state.

In both experiments, each evoked awakening was followed by an initial question, where the subjects were asked whether dreaming had been present during the unresponsive period/ sleep stage. Response options were “yes”, “no” and “uncertain”. In Experiment 1, a PET scan was then performed to attain a scan from

Table 5. The interview questions in Experiments 1 and 2. If the participant answered ‘yes’ to any question, he was asked to describe the experience in as much detail as possible

Did you dream during the unresponsive period?
Did you experience anything related to the research environment during the unresponsive period?
Did you hear anything during the unresponsive period?
Did you sense anything (else) during u the unresponsive period?
Do you remember anything else that you have not already mentioned?
What is the last thing you remember before falling asleep for the first time? (Asked only after recovery.)
What is the first thing you remember after awakening? (Asked only after recovery.)

the evoked awakening (R-state). A more detailed interview followed the scan, where the subjects were requested to continue the report by specifying any subjective experiences they might have had during the unresponsive period, including possible awareness of the study surroundings (similar to Radek et al., 2018). In Experiment 2, the detailed interview immediately followed the evoked awakening. The interview questions are specified in Table 5.

The interviews and reports were recorded digitally on-line, and transcribed off-line for systematic content analysis, conducted by two independent judges. In the content analysis, the judges first divided the interview reports into three main categories: 1) no recall of any subjective experiences, 2) white reports, i.e., strong impression of some experiences, but no recall of any specific content, and 3) reports including specific content. The reports in the third category were further divided to internally and externally generated experiences. Internally generated experiences involved hallucinatory contents of consciousness, either dreaming or memory incorporation of the research environment (i.e., experiences related to details/people in the study surroundings without awareness of any specific event, or events that occurred before unresponsiveness ensued). Externally generated experiences referred to awareness of the environment (experiences related to verifiable stimuli that the participant could not have expected to occur during the experimental session). Reports including no recall of any experiences, white reports, and reports including internally generated experiences were considered to verify a disconnected state, whereas reports of awareness were considered as suggesting a (perhaps partly) connected state.

4.7 Statistical Analyses

4.7.1 Drug Concentration Measurements

Concentration measurements were made in the anesthesia studies (Dose Finding, Experiment 1). In these studies, unpaired and paired t tests were used to compare measured drug concentrations between the arousable and non-arousable, and between the disconnected and connected conditions, respectively.

4.7.2 EEG Spectra (Study I)

As this study was exploratory in nature, no predefined statistical plan was applied, and part of the groupings of the data was made *post hoc*. For the statistical comparisons, four regions of interest were chosen and mean spectral power values were calculated for frontal, central, temporal and posterior regions (see Figure 2 in

Study I). The states of interest were represented by EEG segments chosen for statistical analyses. Because not all subjects were arousable during the constant infusion, two separate overall analyses were performed. In the first analysis, the following states of consciousness were included: BL (eyes closed), SED, LOR, and LOC; and in the second analysis: LOR, LOR_{late}, and ROR (See Table 6 and Figure 5). Thus, two LOR segments were included (LOR and LOR_{late}), as the LOR state was relatively long (approximately 25 min) and the EEG features were found to be unstable. Electroencephalogram power values at each frequency band were first analyzed using three-way repeated-measures ANOVA with two within-factors (state and region) and one between-factor (treatment; SAS/STAT, PROC MIXED; SAS Institute Inc., USA).

If significant region, state–by–region, and/or treatment–by–region interactions were found, the analyses were continued for each region separately using two-way repeated-measures ANOVAs with one within-factor (state) and one between-factor (treatment) followed by paired comparisons of different states and drugs using Bonferroni correction for multiple comparison. Unstructured covariance structure was used in the analyses. Data from the second cycle of different states (i.e., LOR2 and ROR2) were also not included in the statistical analyses because most of the arousable propofol subjects did not achieve LOR2. The alpha band power at SED, LOR, and LOR_{late} was compared between arousable and non-arousable subjects using two-way ANOVA. Because of positively skewed distributions, decadic (common) logarithm values of the absolute spectral powers were used in statistical analyses.

Frontal and posterior phase-amplitude coupling at BL, SED, LOR, and LOC were analyzed similarly to spectral variables, followed by paired comparisons using Bonferroni correction. Chi-square was used to compare arousability between groups. A two-tailed probability level of 5% ($P < 0.05$) was considered statistically significant. Results are given as means (SD) or model-estimated marginal means (SE) if not otherwise stated. Statistical analyses were performed with SAS System for Windows, version 9.4 (SAS Institute Inc.).

4.7.3 Event-Related Potentials (Study II)

Linear mixed-effects regression was used for the statistical analysis. The regression models included random slopes for subject and channel to take into account the repeated measures within each subject and channel. In the case of non-convergence, the random slope for channel was reduced to random intercept. The N400 component was examined by comparing the N400 time window with the control time window, whereas the presence of the N400 effect was established by comparing data from congruous and incongruous trials. $P<0.05$ was considered as evidence of the N400

component or effect. The active awake baseline was compared with the unresponsive conditions, and the resulting P-values were multiplied by the number of comparisons (Bonferroni correction). The latency of the N400 component was determined as the most negative value observed in the time window 200–800 ms using the jackknife method (Miller et al Psychophysiology 1998). The 13 centroparietal electrodes were combined by averaging for latency measurements.

Sentence recognition was analyzed using discriminability measure d' and response bias criterion c. (Wickens, 2002; Hautus, 1995). Cases with missing recognition response to >50% of stimuli from a single condition were excluded. Two-tailed t-tests were used to determine whether the d' and c values differed significantly from zero indicating sentence recognition or response bias, respectively. The reaction time was measured from response cue to response, and values <100 ms were excluded. The natural logarithm of the reaction time was analyzed using linear mixed-effects regression with random intercept for subject. All analyses were conducted using the R software (version 3.3.2, www.r-project.org) with lmerTest package (version 2.0–33, http://cran.r-project.org/package=lmerTest).

4.7.4 PET Data (Study III)

Partial least-squares (PLS) software was used to analyze relative rCBF data over state transitions. PLS is a multivariate statistical analysis technique that analyzes associations between two sets of data. Here, brain activity patterns were identified using PLS, in order to identify rCBF differences between selected experimental conditions. The PLS output consists of a set of latent variables (LVs), which are linear combinations of initial variables that maximally covary with the corresponding conditions. Permutation tests were used to calculate the statistical significance of each LV. Bootstrapping was used to assess the reliability of voxels contributing to the LV. The bootstrap ratio is the ratio of the weights to the SEs estimated from bootstrapping. Therefore, the larger the magnitude of a bootstrap ratio, the larger is the weight (i.e., contribution to the LV) and the smaller the SE (i.e., higher stability; McIntosh and Lobaugh, 2004; Mišic et al., 2016).

Five thousand permutations were computed to determine the significance of each LV, and 5000 bootstrap iterations were run to assess the reliability of identified saliences. Voxels with saliences >2.575 times their SE, corresponding to approximately $p < 0.01$, were considered statistically significant. All comparisons yielded two LVs of which LV1 explained 100% of the cross-block covariance and was significant with $p < 0.001$, while LV2, representing the residuals, was not significant. In the original publications, all figures are bootstrap ratio figures with thresholds of $p < 0.01$ for voxels significantly contributing to the pattern. Since PLS

analyzes the data in a multivariate fashion, there is thus only one statistical test and no need to correct for multiple comparisons.

Two sets of analyses were carried out. First, a mean-centered task PLS analysis was conducted to establish the patterns of relative blood flow changes between the relative activity seen in the normal wakeful state (baseline acquired in experiment 1 for all subjects) and the gradually deepening levels of anesthesia (dexmedetomidine or propofol) and sleep, using separate pairwise analyses. Next, we conducted an analysis to seek for those patterns of brain activity alterations that were exclusively related to changes in the state of consciousness (from connected to disconnected states during constant-dose anesthesia and sleep, and from disconnected to connected states during constant-dose anesthesia). The achieved states and successful PET scans are specified in 5.1 Realization of Experimental Designs.

The normality of variables was checked using the Shapiro–Wilk test. The Fisher's exact test was used to compare arousability and responsiveness between the treatments.

5 Results

5.1 Realization of Experimental Designs

5.1.1 Dose-Finding

All targeted states were not achieved in every subject, but LOR was reached by all 47 subjects. During the steady-state infusion, 10 subjects in the propofol group (42%) and 18 subjects in the dexmedetomidine group (78%) were arousable, i.e., reached ROR during a pseudo steady-state infusion (p= 0.011 between the drugs).

After the awakening, propofol subjects tended to become restless and only 4 subjects reached LOR2. In the dexmedetomidine group, all 18 subjects reached LOR2. In the propofol group, two subjects had snoring and mild apnea during the drug administration, and the study had to be terminated prematurely. Both subjects reached LOR, but LOC was not attempted. In both groups, two subjects required additional drug concentration increments to reach LOC. In the dexmedetomidine group, LOC data (1 subject) is missing due to technical difficulties, and due to insufficient data on ROR2, this state was not used in the analyses. The numbers of successful EEG epochs were thus [n=propofol (obtained from % subjects), n=dexmedetomidine (%)]: wakeful baseline [n=24 (100%), n=23 (100%)], SED [n=24 (100%), n=23 (100%)], LOR [n=24 (100%), n=23 (100%)], LOR_{late} [n=24 (100%), n=23 (100%)], ROR [n=10 (42%), n=18 (78%)], LOC [n=22 (92%), n=22 (96%)] (Table 6).

Table 6. The states and the respective EEG epochs selected for statistical analyses.

Abbreviation	State	N
BL	Awake baseline with eyes closed	P 24, D 23
SED	The last sedative state before LOR	P 24, D 23
LOR	Loss of responsiveness	P 24, D 23
LOR_{LATE}	Loss of responsiveness immediately before awakening	P 24, D 23
ROR	Return of responsiveness (during constant-dose anesthesia)	P 10, D 18
LOC	Loss of consciousness (1.5x concentration for LOR)	P 22, D 22

P=Propofol, D=Dexmedetomidine

5.1.2 Experiment 1

All targeted states, interviews and scans were not obtained from every subject, but all subjects reached the UR state. From the 19 propofol and 20 dexmedetomidine subjects, 13 (68 %) and 16 subjects (80 %) reached R-state (i.e., were arousable) during the steady-state drug infusion (Fisher exact test, p=0.480). Four awakened propofol subjects were not scanned in the R-state due to fluctuations in behavior (3 subjects) or intravenous line malfunction (1 subject). The numbers of successful rCBF PET scans were thus [n=propofol (obtained from % subjects), n=dexmedetomidine (%)]: wakeful baseline [n=19 (100 %), n=20 (100 %)], light sedation [n=14 (74 %), n=6 (30 %)], moderate sedation [n=19 (100 %), n=20 (100 %)], UR [n=19 (100 %), n=20 (100 %)], R [n=9 (47 %), n=16 (80 %)], UR2 [n=2 (11 %), n=15 (75 %)], R2 [n=2 (11 %), n=14 (70 %)], 1.5 x UR [n=15 (79 %), n=16 (80 %)].

As stated in 4.7 Statistical Analyses, two analyses were performed. The first analysis used all obtained scans, whereas the second analysis used only within-subject image pairs of connected and disconnected subjects, and thus, required successful within-subject scans from both states. In the 2nd analysis, comparisons were made during constant-dose anesthesia, i.e., UR, R and UR2 (see Figure 6 for clarification) states. However, since only 2 of 13 previously awakened propofol subjects achieved UR2, this state could not be used in the propofol group due to lack of statistical power. Thus, we used the condition with the least confounding drug effect (i.e., SED_{mod} versus UR) to examine brain activity changes related to transition from a responsive (and connected) to an unresponsive (and disconnected) state. Finally, successful scans (where unresponsive states were successfully assessed as disconnected) for comparisons were obtained from 19 and 14 subjects (“becoming disconnected”) and from 9 and 16 subjects (“becoming connected”), in the propofol and dexmedetomidine, respectively, groups. The states and the respective PET scans used in the PLS analyses are specified in Table 7.

Table 7. The achieved states and respective PET scans chosen for comparisons (two analyses).

Abbreviation	State	N (1st analysis)	N (2nd analysis) connected → disconnected	N (2nd analysis) disconnected → connected
BL	Awake baseline with eyes closed	39		
SED_{LIGHT}	Light sedation	P 14, D 6		
SED_{MOD}	Moderate sedation	P 19, D 20	P 19*	
UR	Unresponsiveness	P 19, D 20	P 19*	P 9, D 16
R	Responsive state (during constant UR-dose)	P 9, D 16	D 14	P 9, D 16
UR2	2nd unresponsiveness		D 14	
LOC	(presumed) Loss of consciousness (1.5x concentration for UR)	P 15, D 16		
SDW	Sleep deprived wakefulness	22	9	
N1	non-REM stage 1 sleep	14		
N2	non-REM stage 2 sleep	24	9	
N3	non-REM stage 3 sleep	14		

P= propofol, D= dexmedetomidine.

*Because only 2 subjects reached UR2 in the propofol group (thus lacking statistical power to perform the R→UR2 PLS analyses, *SED_{MOD} and UR states were used in the connected → disconnected analysis in the propofol group (see 6.3 Limitations).

5.1.3 Experiment 2

Two participants fell asleep during the sleep deprivation period despite alarms, one of them sleeping for a total of 26 min and the other 1 hour 47 min.

All targeted states and scans were not obtained from every subject. Altogether, 32 subjects fell asleep at least once (86 %). While some subjects reached the same sleep stage and were awakened from it several times, only the first successful scan obtained from each sleep stage was used. The numbers of first successful rCBF PET scans were [n= state, (obtained from % subjects)]: Sleep deprived wakefulness [n=22 (59 %)], N1 [n=14 (38 %], N2 [n=24 (65 %)], N3 [n=14 (38 %)]. The baseline scan (SDW) was not obtained from all subjects because of inability to stay awake during the scan.

As stated in 4.7 Statistical Analyses, two analyses were performed. The first analysis used all obtained scans, whereas the second analysis used only within-subject image pairs of connected and disconnected subjects, and thus, required successful within-subject scans from both states. In the 2nd analysis, comparisons were made during SDW and N2 (see Figure 7 and Table 7 for clarification) states. Successful scans (where unresponsive states were successfully assessed as disconnected) for comparisons were obtained from 9 ("becoming disconnected") subjects. The states and the respective PET scans used in the PLS analyses are specified in Table 7.

5.2 Drug Concentration Measurements (Studies I, III)

5.2.1 Dose-Finding (Study I)

The mean (SD) measured drug concentrations for LOR was 1.67 (0.62) μg/ml for propofol and 2.06 (0.66) ng/ml for dexmedetomidine. (The target concentration for LOR varied between 1.0 and 2.75 μg/ml for propofol and between 1.0 and 3.25 ng/ml for dexmedetomidine.) The measured concentrations of dexmedetomidine at LOR and LOC were somewhat higher than targeted. In those subjects who could be aroused (i.e., reached ROR), the measured concentrations in LOR were significantly lower in the propofol group, i.e., 1.36 (0.68) μg/ml in arousable versus 1.93 (0.50) μg/ml in non-arousble subjects ($p = 0.036$). In the dexmedetomidine group, there was no statistical difference in LOR concentrations between arousable and non-arousble subjects. The concentration measurements in both anesthesia studies are summarized in Table 8.

5.2.2 Experiment 1 (Study III)

The mean (SD) measured drug concentrations for UR was 1.48 (0.60) for propofol and 1.80 (0.66) for dexmedetomidine. In those subjects who could be awakened (i.e., reached R), the measured concentrations for UR were significantly lower in both groups ($p<0.05$).

In those subjects who could be aroused (i.e., reached R), the measured concentrations in UR were significantly lower in both drug groups. In the propofol group, the measured concentrations were 1.06 (0.25) μg/ml in arousable versus 1.81 (0.60) μg/ml in non-arousble subjects ($p = 0.005$). In the dexmedetomidine group, the respective concentrations were 1.48 (0.40) ng/ml in arousable versus 3.10 (0.92) in non-arousable subjects ($p <0.001$). The concentration measurements in both anesthesia studies are summarized in Table 8.

Table 8. Targeted and measured concentrations in the Dose-Finding study and Experiment 1.

Dose-finding (n=47)

Drug	SED_{-n}		SED		LOR and unresponsive		LOR Dose and responsive		LOC		Recovery	
	Targeted	Measured	Targeted	Measured	Targeted	Measured	Targeted	Measured	Targeted	Measured	Estimated	Measured
All subjects												
Propofol (µg/ml)	1.40 (0.39) n=13	1.07 (0.52) n=12	1.46 (0.44) n=21	1.14 (0.53) n=19	1.71 (0.41) n=24	1.67 (0.62)	1.58 (0.41) n=10	1.21 (0.60)	2.58 (0.63) n=22	2.63 (0.79) n=21	0.95 (0.23) n=20	1.31 (0.51) n=21
Dexmedetomidine (ng/ml)	1.58 (0.60) n=9	1.38 (0.76) n=6	1.43 (0.58) n=19	1.36 (0.86) n=16	1.67 (0.54) n=23	2.06 (0.66) n=21	1.67 (0.60) n=18	2.04 (0.74)	2.53 (0.82) n=23	3.13 (0.94) n=22	1.92 (0.85) n=21	2.16 (0.91) n=22
Subjects awakened during constant infusion												
Propofol (µg/ml)					1.58 (0.41) n=10	1.36 (0.68)	1.58 (0.41) n=10	1.21 (0.60)#				
Dexmedetomidine (ng/ml)					1.67 (0.60) n=18	2.04 (0.72) n=17	1.67 (0.60) n=18	2.04 (0.74)°				

Experiment 1 (n=39)

Drug	SEDlight		SEDmod		UR Dose and disconnected		UR Dose and connected		1.5x UR Dose		Recovery	
	Targeted	Measured	Targeted	Measured	Targeted	Measured	Targeted	Measured	Targeted	Measured	Estimated	Measured
All subjects												
Propofol (µg/ml)	1.13 (0.37) n=13	0.73 (0.39)	1.37 (0.49) n=18	1.01 (0.51)	1.78 (0.56) n=18	1.48 (0.60)	1.47 (0.42) n=8	1.13 (0.31)	2.74 (0.81) n=15	2.46 (0.77)	1.14 (0.37) n=15	1.16 (0.35)
Dexmedetomidine (ng/ml)	1.19 (0.38) n=6	0.98 (0.54)	1.06 (0.54) n=20	1.10 (0.58)	1.50 (0.56) n=20	1.80 (0.66)	1.24 (0.33) n=16	1.54 (0.37)	2.38 (1.05) n=16	3.27 (1.32)	1.38 (0.51) n=17	1.60 (0.64)
Subjects awakened during constant infusion												
Propofol (µg/ml)					1.47 (0.42) n=8	1.06 (0.25)	1.47 (0.42) n=8	1.13 (0.31)*				
Dexmedetomidine (ng/ml)					1.24 (0.33) n=16	1.48 (0.40)	1.24 (0.33) n=16	1.54 (0.37)§				

Mean (SD) targeted or estimated and measured drug concentrations in plasma during light and moderate sedation (i.e., next last and last responsive anesthetic levels before losing responsiveness), unresponsive or disconnected and responsive or connected states of consciousness during constant infusion titrated to unresponsiveness (LOR/ UR Dose), deep unresponsive state (LOC/ 1.5x UR Dose) and responsive state after terminating the drug infusion (Recovery) in the propofol and dexmedetomidine groups in the Dose-finding study and Experiment 1. No statistically significant differences in the measured concentrations between the unresponsive or disconnected and responsive or connected states in subjects who could be awakened (#p=0.271; °p=0.234; *p=0.880; §p=0.203; paired t-tests after Bonferroni correction). The numbers vary because not all states were achieved in every subject and because of few missing blood samples or data.

5.3 Effects of propofol and dexmedetomidine on EEG Spectra and Phase-Amplitude Coupling (Study I)

Statistically significant region, state–by–region, and/or treatment–by–region interactions were found in all spectral bands in both overall analyses ($P < 0.05$ for all). Therefore, the analyses were continued for each region separately. Spectral changes were strongly state- and drug-dependent, as revealed by significant differences between the states in all, and between the treatments in many bands and regions, and significant interactions between state and treatment (see Tables 9 and 10). Then, these statistical analyses were finalized by calculating paired comparisons (using contrasts in two-way repeated-measures ANOVA models) of different states for both drugs separately (within-drug analyses) and between the drugs (between-drug analyses). In summary, the interindividual variability of spectral powers (both at baseline and during the drug administration) was large. Figure 8 illustrates average spectrograms from the frontal and posterior regions during the study session and the

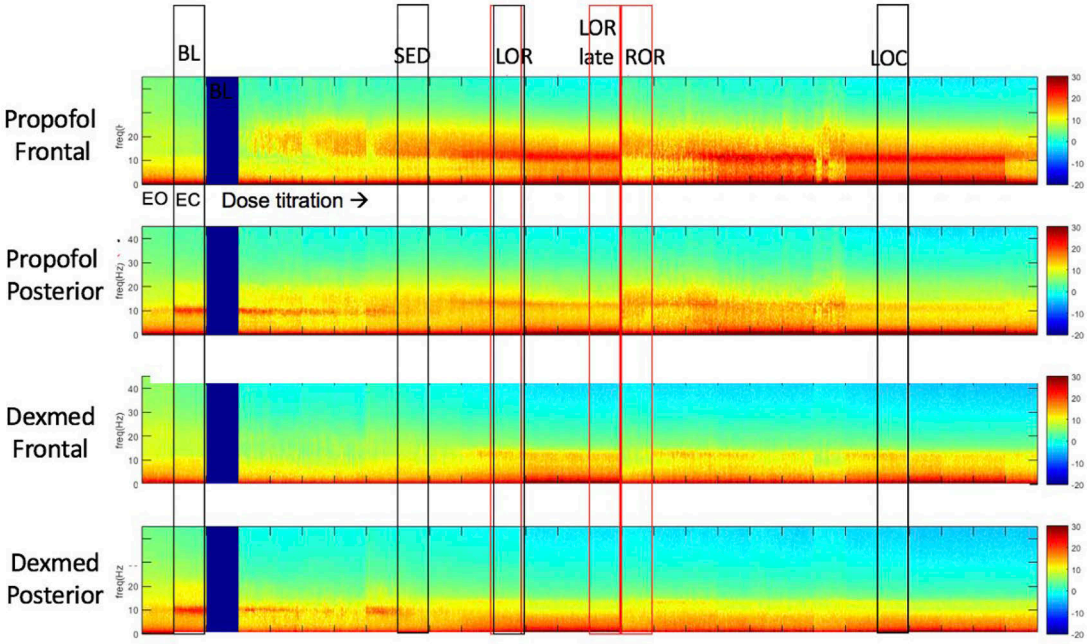

Figure 8. Spectrograms (absolute power) of frontal and posterior regions throughout Dose Finding study in the propofol (upper) and dexmedetomidine (lower) groups. Two separate overall statistical analyses were performed (see Statistical Analyses and Table 6 for details). Specific time points selected for these analyses are marked, black boxes indicating the first and red boxes the second analysis. Modified from Original Publication I. BL = baseline; EC = eyes closed; EO = eyes open; SED = last responsive state before LOR; LOR = loss of responsiveness; LORlate= last LOR segment before awakening; ROR = return of responsiveness; LOC = loss of consciousness

selected EEG epochs chosen for statistical comparisons. Topographic scalp images for each band and state separately are illustrated in figure 9. Spectral powers at baseline did not show any relation to target concentration needed for loss of responsiveness.

5.3.1 Comparison of BL, SED, LOR and LOC (Study I)

Both drugs induced profound changes of the spectral powers in all regions and all frequency bands (state effect $P < 0.01$ for all, Table 9). The drugs affected the band powers differently in all areas except the central, temporal, and posterior delta power and the temporal and posterior theta power (state–by–treatment interaction $P > 0.05$, table 9). In summary, propofol induced an increase in slow-delta, delta, and alpha power, especially in the frontal regions, as well as an initial increase followed by a decrease in beta power. Dexmedetomidine induced a similar increase in slow-delta and delta power (maximal slow-wave activity already at LOR_{late}), and a more subtle increase in frontal alpha power. Yet, a clear alpha-anteriorization (alpha dominance shifting from posterior to frontal regions) was observed. With propofol, frontal alpha power increased along escalating drug concentration, whereas with dexmedetomidine, a plateau-effect of frontal alpha power occurred already at LOR. A consistent decrease in beta power in all regions along deepening levels of anesthesia was induced by dexmedetomidine. Statistically significant decreases in the gamma band were observed across the entire scalp in both groups. For detailed results, see table 9 and figures 8 and 9.

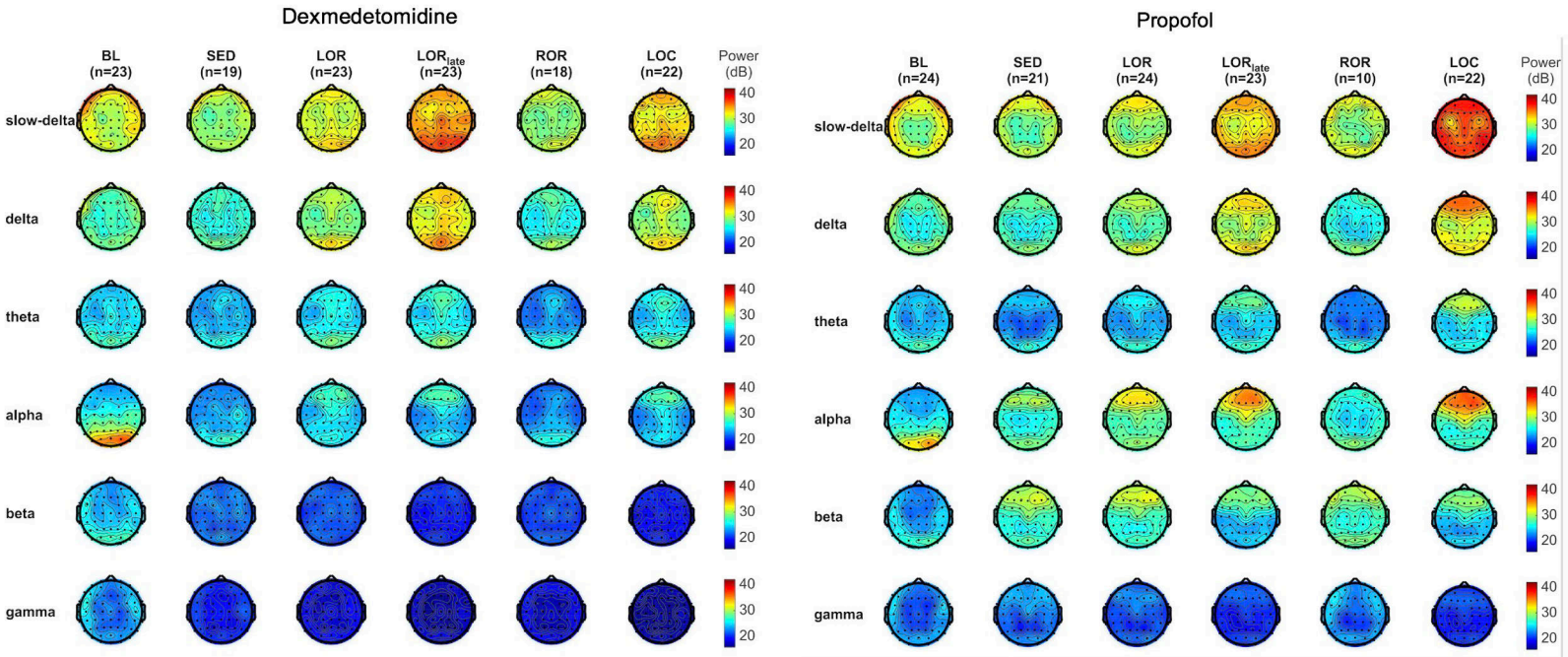

Figure 9. Spatial distribution of average slow-delta (0.1−1 Hz), delta (1−4 Hz), theta (4−8 Hz), alpha (8−14 Hz), beta (14−25 Hz), and gamma (25−45 Hz) band powers at distinct pre-defined states during propofol and dexmedetomidine infusions. At LOR, a clear alpha anteriorization was seen in both groups, although greater absolute power values were evident in the propofol group. With both treatments, the frontal alpha dominance separated SED from LOR, and the pattern was disrupted when the subjects were awakened during the constant infusion (ROR). An increase in slow-wave activity (slow-delta and delta) was observable in both groups along increasing concentrations. These features reverted upon ROR. A clear difference between the treatments was observed in the behavior of the beta bandwidth. See text for more details. For abbreviations, see Figure 8 Legend.

5.3.2 Comparison of LOR, LOR_{late} and ROR (Study I)

Despite a pseudo steady-state drug level in the selected conditions, the spectral powers were not stable. The changes induced by the drugs tended to intensify from LOR to LOR_{late} in both groups, which was evident especially in the dexmedetomidine group, excluding the alpha power, which plateaued at LOR (figures 6 and 7, table 10). At ROR, drug-induced spectral changes partially reverted toward awake baseline or sedation in most regions and bandwidths. Especially the widespread increases of slow-delta and delta power and the frontal increase of alpha power strongly reverted when subjects were awakened (table 10). In contrast, the drug- induced changes in beta power (increase with propofol and decrease with dexmedetomidine) did not revert in ROR state in either treatment group. For detailed results, see table 10 and figures 8 and 9.

Table 9. Estimated means and standard errors (SE) of absolute (10log) spectral powers of slow delta (0.1−1 Hz), delta (1−4 Hz), theta (4−8 Hz), alpha (8−14 Hz), beta (14−25 Hz) and gamma (25−45 Hz) bands in four cortical areas (see Figure 2 in **I**) in four pre-defined states, BL, SED, LOR and LOC, during propofol (n=24) and dexmedetomidine (n=23) infusions.

	Baseline				SED				LOR				LOC				2-way RM ANOVA (p-value)		
	Dexmedetomidine		Propofol		Dexmedetomidine		Propofol		Dexmedetomidine		Propofol		Dexmedetomidine		Propofol		State	Treatment	State × Treatment
	Mean	SE	Mean	SE	Mean	SE		Mean	SE		Mean	SE		Mean	SE		Mean	SE													
Frontal																			
Slow delta	3.234	0.058	3.250	0.056	3.058	0.063		3.112	0.060		3.108	0.058	#	3.159	0.056	###	3.321	0.059	§§,***	3.699	0.059	§§§	<0.001	0.026	0.001
Delta	2.852	0.066	2.823	0.064	2.704	0.071	††	2.748	0.068	†	3.015	0.066		2.984	0.064	###	3.179	0.067	§§§,*	3.460	0.067	§§§	<0.001	0.321	0.013
Theta	2.456	0.060	2.434	0.058	2.388	0.063	†	2.378	0.061	†	2.584	0.060		2.544	0.058	###	2.631	0.060	§§,**	2.942	0.060	§§§	<0.001	0.373	<0.001
Alpha	2.415	0.071	2.377	0.069	°°°	2.321	0.076	††,***	2.726	0.073	†††	2.639	0.071	***	3.202	0.069	##	2.642	0.072	§§,***	3.494	0.072	§§§	<0.001	<0.001	<0.001
Beta	2.393	0.052	2.346	0.051	°°°	2.236	0.057	***	2.946	0.054		2.178	0.052	##,***	3.018	0.051		1.975	0.053	§§,***	2.916	0.053		<0.001	<0.001	<0.001
Gamma	2.341	0.045	°°°	2.332	0.044	1.977	0.049	***	2.389	0.047		1.836	0.045	#,***	2.276	0.044		1.679	0.046	§§§,***	2.157	0.046	§§§	<0.001	<0.001	<0.001
Central																			
Slow delta	3.086	0.066	2.992	0.065	2.982	0.072		2.825	0.068		3.098	0.066	#	2.928	0.065	###	3.356	0.067	§§§	3.545	0.067	§§§	<0.001	0.359	0.007
Delta	2.796	0.061	2.672	0.060	2.658	0.066	†††	2.581	0.063	†††	2.898	0.061	###	2.763	0.060	###	3.050	0.062	§§§	3.076	0.062	§§§	<0.001	0.193	0.406
Theta	2.516	0.053	2.400	0.052	°°	2.410	0.057		2.214	0.055		2.526	0.053		2.359	0.052	##	2.529	0.054		2.552	0.054	§§§	<0.001	0.051	0.040
Alpha	2.677	0.061	°°	2.536	0.060	2.429	0.066		2.533	0.063	†††	2.516	0.061	***	2.854	0.060		2.428	0.062	***	2.989	0.062	§§§	<0.001	<0.001	<0.001
Beta	2.441	0.053	°	2.317	0.052	°°°	2.269	0.057	***	2.685	0.054		2.169	0.053	###,***	2.719	0.052		1.939	0.054	§§§,***	2.583	0.053		<0.001	<0.001	<0.001
Gamma	2.299	0.052	°°°	2.196	0.051	2.006	0.054	†,*	2.214	0.052		1.850	0.052	###,***	2.136	0.051	#	1.665	0.052	§§§,***	2.002	0.052	§§§	<0.001	0.004	<0.001
Temporal																			
Slow delta	3.354	0.058	°°	3.323	0.057	°°	3.104	0.063		3.054	0.060		3.152	0.058		3.036	0.057	###	3.348	0.059	§,***	3.722	0.059	§§§	<0.001	0.402	<0.001
Delta	2.963	0.056	°°°	2.922	0.055	°°°	2.683	0.060	††	2.699	0.058	††	2.868	0.056	###	2.817	0.055	###	2.957	0.057	§§§	3.115	0.057	§§§	<0.001	0.723	0.078
Theta	2.502	0.049	°°°	2.468	0.048	°°°	2.354	0.051		2.286	0.049		2.423	0.049		2.362	0.048		2.399	0.049	§§	2.492	0.049	§§	<0.001	0.757	0.062
Alpha	2.651	0.055	°°°	2.574	0.054		2.349	0.059	*	2.584	0.057	††	2.362	0.055	***	2.801	0.054		2.243	0.056	***	2.843	0.056	§§§	0.010	<0.001	<0.001
Beta	2.498	0.047	°°°	2.442	0.046	°°°	2.195	0.050	†,***	2.668	0.048		2.040	0.047	###,***	2.689	0.046	###	1.833	0.048	§§§,***	2.485	0.047	§§	<0.001	<0.001	<0.001
Gamma	2.502	0.048	°°°	2.439	0.047	°°°	2.079	0.051	†††	2.218	0.049	†	1.854	0.048	##,**	2.067	0.047	#	1.673	0.049	§§§,**	1.912	0.049	§§§	<0.001	0.012	<0.001
Posterior																			
Slow delta	3.055	0.062	3.060	0.060	3.014	0.067	††	2.916	0.064		3.289	0.062	*	3.070	0.060	###	3.487	0.063	§§§	3.700	0.063	§§§	<0.001	0.679	0.001
Delta	2.852	0.055	2.832	0.054	2.745	0.059	†††	2.724	0.056	†††	3.107	0.055	##	2.915	0.054	##	3.189	0.056	§§§	3.119	0.055	§§§	<0.001	0.189	0.148
Theta	2.680	0.058	°°	2.633	0.057	°°	2.600	0.061	†	2.436	0.059	†	2.736	0.058		2.524	0.057		2.696	0.059		2.470	0.058		0.007	0.014	0.106
Alpha	3.282	0.073	°°°	3.189	0.072	°°°	2.648	0.080		2.724	0.076		2.530	0.073	*	2.796	0.072		2.426	0.075		2.633	0.074		<0.001	0.114	0.021
Beta	2.631	0.057	°°°	2.577	0.056		2.239	0.060	***	2.634	0.058		2.104	0.057	#,***	2.630	0.056	###	1.929	0.058	§§§,***	2.381	0.057	§§§	<0.001	<0.001	<0.001
Gamma	2.320	0.049	°°°	2.298	0.048	°	1.994	0.051	††,*	2.179	0.049		1.863	0.049	###,**	2.111	0.048	###	1.699	0.049	§§§,**	1.925	0.049	§§§	<0.001	0.010	<0.001

In the 2-way RM ANOVA analyses (three columns to the right), a significant state effect indicates differences between the states, a significant treatment effect indicates an overall difference in the level of spectral powers between the drugs, and a significant state by treatment interaction indicates that the drug effects are different. Paired Bonferroni-corrected p-values for within-group post hoc comparisons of the different states (° Baseline vs. SED, † SED vs. LOR, # LOR vs. LOC and § SED vs. LOC; Baseline vs. LOR and Baseline vs. LOC contrasts not shown for clarity) and between-group comparisons at baseline, and the SED, LOR and LOC states (*Dexmedetomidine vs. Propofol). If the state by treatment interaction was not significant, treatment-adjusted post hoc comparisons of the different states are given. Within-group comparisons indicate dependency on state of consciousness and/or drug concentration and between-group comparisons differences between the drugs. The number of symbols refer to level of significance (e.g., *p<0.05, **p<0.01 and ***p<0.001 between the drugs). At baseline, there were no significant differences between the drugs in any of the spectral powers. RM = repeated measures, ANOVA = analysis of variance.

Table 10. Estimated means and standard errors (SE) of absolute (10log) spectral powers of slow delta (0.1−1 Hz), delta (1−4 Hz), theta (4−8 Hz), alpha (8−14 Hz), beta (14−25 Hz) and gamma (25−45 Hz) bands in four cortical areas (see Fig. 2 in I) in three pre-defined states, LOR, LORlate and ROR, during propofol (n=10) and dexmedetomidine (n=18) infusions (only arousable subjects were analyzed). Drug dosing was not changed during LOR and LORlate.

	LOR						LOR_{late}						ROR						2-way RM ANOVA (p-value)		
	Dexmedetomidine			Propofol			Dexmedetomidine			Propofol			Dexmedetomidine			Propofol			State	Treatment	State × Treatment
	Mean	SE		Mean	SE		Mean	SE		Mean	SE		Mean	SE		Mean	SE				
Frontal																					
Slow delta	3.090	0.066	†††	3.133	0.088	†††	3.357	0.066	###	3.262	0.088	###	3.004	0.066		3.116	0.088		<0.001	0.830	0.133
Delta	2.953	0.075	†††	2.910	0.100	†††	3.230	0.075	###	3.105	0.100	###	2.745	0.075	§§	2.725	0.100	§§	<0.001	0.565	0.595
Theta	2.550	0.081	††	2.441	0.109	††	2.659	0.081	###	2.601	0.109	###	2.357	0.081	§§§	2.340	0.109	§§§	<0.001	0.639	0.436
Alpha	2.579	0.087		3.007	0.116		2.611	0.087	###	3.205	0.116	###	2.272	0.087	§§§	2.738	0.116	§§§	<0.001	<0.001	0.337
Beta	2.193	0.057	†††,***	2.855	0.076		2.041	0.057	***	2.750	0.076	###	2.121	0.057	***	2.962	0.076		<0.001	<0.001	0.019
Gamma	1.856	0.044	†,***	2.254	0.059		1.754	0.044	***	2.150	0.059	###	1.829	0.044	***	2.382	0.059		<0.001	<0.001	0.030
Central																					
Slow delta	3.078	0.069	†††	2.911	0.093		3.414	0.069	###,*	3.120	0.093		2.931	0.069		2.912	0.093		<0.001	0.108	0.045
Delta	2.831	0.068	†††	2.725	0.091	†††	3.138	0.068	###	2.891	0.091	###	2.618	0.068	§§	2.564	0.091	§§	<0.001	0.176	0.132
Theta	2.510	0.067	†	2.304	0.090	†	2.564	0.067	###	2.396	0.090	###	2.321	0.067	§§§	2.215	0.090	§§§	<0.001	0.145	0.186
Alpha	2.508	0.065		2.706	0.087		2.431	0.065	##,**	2.834	0.087	###	2.293	0.065	§§§,*	2.572	0.087		<0.001	0.005	0.028
Beta	2.202	0.059	†††,***	2.610	0.079	††	2.027	0.059	#,***	2.473	0.079	###	2.106	0.059	§,***	2.706	0.079		<0.001	<0.001	0.001
Gamma	1.870	0.060	†††,*	2.131	0.081	††	1.768	0.060	*	2.020	0.081	###	1.782	0.060	§§,***	2.171	0.081		<0.001	0.003	0.003
Temporal																					
Slow delta	3.136	0.066	†††	3.016	0.088	†††	3.466	0.066	###	3.276	0.088	###	2.996	0.066		3.055	0.088		<0.001	0.349	0.084
Delta	2.815	0.062	†††	2.799	0.083	†††	3.113	0.062	###	2.979	0.083	###	2.616	0.062	§§	2.682	0.083	§§	<0.001	0.750	0.124
Theta	2.408	0.059	†	2.319	0.080	†	2.460	0.059	###	2.419	0.080	###	2.248	0.059	§§§	2.237	0.080	§§§	<0.001	0.619	0.369
Alpha	2.353	0.060		2.716	0.080		2.261	0.060	#	2.752	0.080	#	2.193	0.060	§§	2.644	0.080	§§	0.002	<0.001	0.135
Beta	2.069	0.050	†††,***	2.628	0.068	†††	1.927	0.050	#,***	2.451	0.068	###	2.024	0.050	***	2.781	0.068	§§	<0.001	<0.001	<0.001
Gamma	1.878	0.053	†	2.119	0.071	†	1.785	0.053	###	1.999	0.071	###	1.904	0.053	§	2.290	0.071	§	<0.001	<0.001	0.056
Posterior																					
Slow delta	3.258	0.066	†††	3.023	0.088	††	3.619	0.066	###	3.362	0.088	##	3.044	0.066	§	3.061	0.088		<0.001	0.074	0.041
Delta	3.055	0.062	†††	2.912	0.083	†††	3.318	0.062	###	3.101	0.083	###	2.830	0.062	§§§	2.774	0.083	§§§	<0.001	0.131	0.176
Theta	2.728	0.064		2.545	0.086		2.760	0.064	###	2.588	0.086	###	2.551	0.064	§§§	2.456	0.086	§§§	<0.001	0.144	0.285
Alpha	2.551	0.062		2.785	0.083		2.426	0.062		2.732	0.083		2.464	0.062		2.794	0.083		0.181	0.002	0.576
Beta	2.143	0.056	†††,***	2.638	0.075	†††	1.983	0.056	##,***	2.411	0.075	###	2.099	0.056	***	2.737	0.075		<0.001	<0.001	0.005
Gamma	1.880	0.056	†	2.192	0.075	†	1.782	0.056	###	2.058	0.075	###	1.852	0.056	§	2.183	0.075	§	<0.001	<0.001	0.056

In the 2-way RM ANOVA analyses (three columns to the right), a significant state effect indicates differences between the states, a significant treatment effect indicates an overall difference in the level of spectral powers between the drugs, and a significant state by treatment interaction indicates that the drug effects are different. Paired Bonferroni-corrected p-values for within-group post hoc comparisons of the different states († LOR vs. LORlate, # LORlate vs. ROR and § LOR vs. ROR) and between-group comparisons at these states (* Dexmedetomidine vs. Propofol). If the state by treatment interaction was not significant, treatment-adjusted post hoc comparisons of the different states are given. Within-group comparisons indicate dependency on state of consciousness irrespective of drug concentration and between-group comparisons differences between the drugs. The number of symbols refer to level of significance (e.g., *p<0.05, **p<0.01 and ***p<0.001 between the drugs). At baseline, there were no significant differences between the drugs in any of the spectral powers. RM = Repeated measures, ANOVA = analysis of variance.

5.3.3 Prediction of Arousability (Study I)

At BL, SED, and LOR_{late}, there were no statistically significant differences in spectral powers between arousable and non-arousable subjects, but at LOR, frontal alpha power was stronger in non-arousable subjects (P = 0.016, two-way ANOVA). The arousability–by–treatment interaction was not significant, and the differences did not reach statistical significance for either drug in post hoc comparisons. There were no differences in the targeted concentrations between arousable and nonarousable subjects for either drug.

5.3.4 Phase-Amplitude Coupling (Study I)

In the overall PAC analyses (with drug groups combined), there were significant differences both in the frontal (state P < 0.001, treatment P = 0.102, state-by-treatment interaction P < 0.001) and posterior (state P < 0.001, treatment P = 0.018, state–by–treatment interaction P = 0.013) regions. In the post hoc comparisons, two distinct PAC patterns were seen in the propofol group. In the dexmedetomidine group, state–by–treatment interaction did not reach statistical significance. Two illustrative modulograms from subjects 039 (propofol) and 050 (dexmedetomidine) are illustrated in Figure 10.

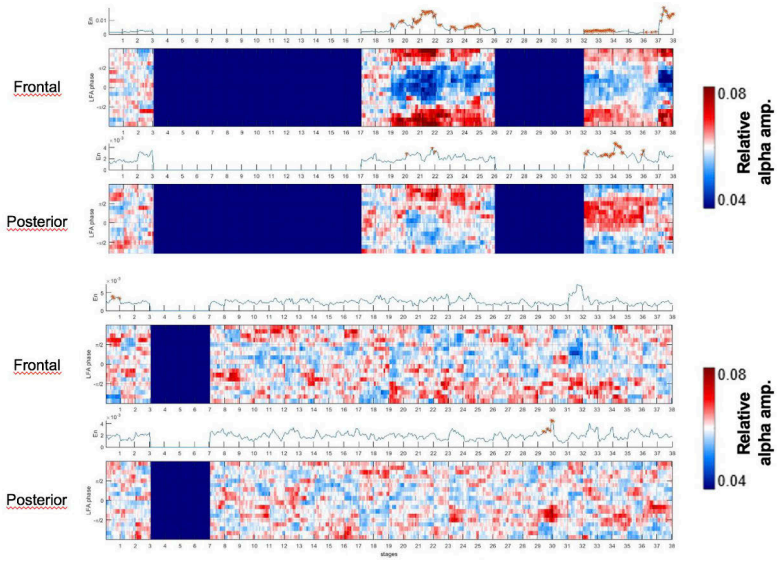

Figure 10. Two illustrative modulograms of alpha and slow-wave coupling. In a propofol subject (subject 039, upper two panels), a clear modulation of alpha power by LFA phase is observed. Relative alpha power is maximal frontally during SED and LOR in the pi-phase (low-frequency troughs), whereas it is maximal posteriorly during LOC in the 0-phase (low-frequency peaks). In a dexmedetomidine subject (subject 050, lower two panels), no such modulation of alpha power can be seen. For clarification of the concepts, see also Figure 4.

Group-level spatial distribution of propofol participants showed trough-max coupling (i.e., maximum alpha power at the pi phase of the slow-delta activity), concentrated in the frontal area before and during LOR (blue in Figure 11), while peak-max coupling (i.e., maximum alpha power at 0 phase) occurred in posterior and other regions at LOC (red in Figure 11). The interindividual variability in the posterior region at LOC was large in the propofol group, but LOC differed significantly from all other states and from the dexmedetomidine group, where no differences in phase-amplitude coupling was found between the states.

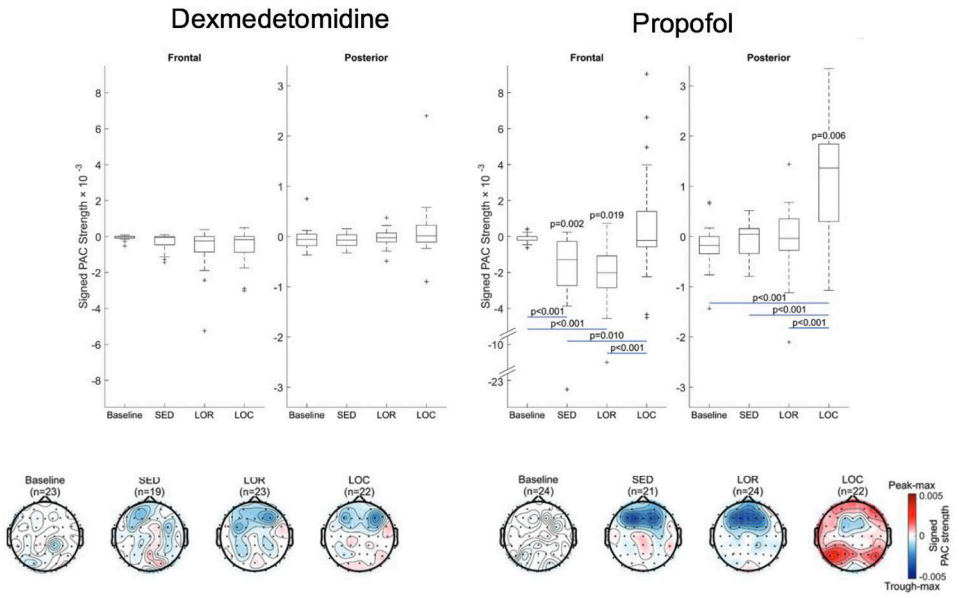

Figure 11. Box-plots of the signed PAC strengths (upper) and spatial distribution of average PAC strength (lower) at BL, SED, LOR and LOC states in the dexmedetomidine and propofol groups. On each box, the central mark is the median, the edges of the box are the 25th and 75th percentiles, the whiskers extend to the most extreme values, and the outliers are plotted individually. During propofol exposure, there was trough-max coupling (negative) at SED and LOR frontally, and peak-max coupling (positive) at LOC in the posteriorly. P-values for statistically significant differences within the groups are given below the boxplots and between the groups above. No significant differences in the dexmedetomidine group. Modified from Original Publication I.

5.4 Effects of propofol and dexmedetomidine on N400 Event-Related Potentials (Study II)

In the baseline state (both active and passive), the first words and incongruous last words of the sentences elicited an N400 component that was significantly more negative than the corresponding pre-stimulus control time window (Table 11 and

Figure 12.) Incongruous last words, the N400 effect was observed (i.e., the incongruous words evoked a more negative N400 component than congruous last words, P<0.001). The latencies of the components elicited by the first and incongruous last words were 441 ms [95% confidence interval (CI): 371–511] and 382 ms (95% CI: 331–433) in the active baseline, respectively. The corresponding latencies were 416 ms (95% CI: 400–432) and 414 ms (95% CI: 321–506) in the passive baseline.

Table 11. Effect estimates and two-sided significance tests for the presence of the N400 component and N400 effect in awake baseline and different levels of drug-induced unresponsiveness.

State	Stimulus	Time window	Dexmedetomidine						Propofol					
			n	Estimate	95% CI		*P* for N400 component	*P* for N400 effect	*n*	Estimate	95% CI		*P* for N400 component	*P* for N400 effect
Baseline, active	First word	Control	23	−0.04	−0.16	0.08	0.003		24	0.03	−0.05	0.11	<0.001	
		N400		−0.53	−0.81	−0.25				−0.81	−1.10	−0.52		
	Last word, congruous	Control	23	0.22	0.03	0.42	0.060	<0.001	24	0.01	−0.16	0.18	0.005	<0.001
		N400		0.66	0.26	1.05				0.75	0.30	1.20		
	Last word, incongruous	Control	23	−0.03	−0.19	0.13	<0.001		24	−0.06	−0.26	0.14	<0.001	
		N400		−2.03	−2.54	−1.52				−1.82	−2.31	−1.33		
Baseline, passive	First word	Control	23	0.02	−0.07	0.10	0.003		24	0.02	−0.07	0.11	<0.001	
		N400		−0.54	−0.84	−0.24				−0.71	−0.94	−0.49		
	Last word, congruous	Control	23	0.04	−0.16	0.23	0.020	<0.001	24	0.01	−0.10	0.12	0.102	<0.001
		N400		−0.40	−0.69	−0.11				−0.29	−0.64	0.06		
	Last word, incongruous	Control	23	0.03	−0.17	0.24	<0.001		24	−0.10	−0.22	0.01	<0.001	
		N400		−2.31	−2.78	−1.85				−1.96	−2.27	−1.65		
LOR1	First word	Control	22	−0.45	−0.91	0.01	0.016		22	−0.25	−0.44	−0.06	0.262	
		N400		−1.87	−2.89	−0.84				−0.63	−1.27	0.01		
	Last word, congruous	Control	22	0.36	−0.45	1.18	<0.001	0.149	21	−0.26	−0.74	0.21	0.366	0.706
		N400		−3.89	−5.38	−2.39				−0.86	−1.88	0.17		
	Last word, incongruous	Control	22	−0.39	−1.10	0.31	0.010		21	0.07	−0.32	0.46	0.017	
		N400		−2.49	−3.68	−1.29				−1.03	−1.72	−0.33		
LOR2	First word	Control	17	−0.20	−0.81	0.41	0.043		3	−0.20	−0.98	0.59	0.506	
		N400		−1.48	−2.25	−0.72				0.69	−2.22	3.61		
	Last word, congruous	Control	17	0.27	−0.25	0.79	0.010	0.575	3	0.96	−0.83	2.74	0.220	<0.001
		N400		−1.80	−3.39	−0.21				−1.26	−2.51	−0.01		
	Last word, incongruous	Control	17	0.18	−0.46	0.82	0.015		3	−0.41	−1.87	1.04	0.120	
		N400		−1.39	−2.28	−0.49				−2.72	−3.95	−1.48		
LOC	First word	Control	22	−0.15	−0.94	0.65	0.045		16	0.66	0.12	1.20	0.538	
		N400		−1.31	−2.24	−0.37				1.05	−0.05	2.15		
	Last word, congruous	Control	21	0.45	−0.27	1.17	0.022	0.116	17	−0.66	−1.57	0.25	0.032	0.355
		N400		−1.04	−2.04	−0.03				1.27	−0.25	2.79		
	Last word, incongruous	Control	21	0.74	−0.29	1.77	0.007		17	0.32	−0.34	0.97	0.957	
		N400		−1.50	−2.42	−0.58				0.27	−1.38	1.92		

CI = confidence interval; LOC = presumed loss of consciousness; LOR1 = first loss of responsiveness; LOR2 = second loss of responsiveness; n = number of study subjects. Modified from Original Publication II.

A significant N400 component, but no N400 effect, persisted during dexmedetomidine-induced unresponsiveness (Table 11 and Figure 12. See also figures 3–4 in Study II). The N400 component elicited by the first words was different in active baseline, LOR1, LOR2, and LOC (condition main effect $F_{3,19.4}$=4.1; P=0.021). It was more negative in LOR1 and LOR2 than in the active

awake baseline ($t_{21.8}$=2.7; P=0.043 and $t_{16.9}$=2.6; P=0.052, respectively). This was also the case for the N400 component evoked by congruous last words (condition main effect: $F_{3,18.5}$=11.2; P<0.001) in LOR1, LOR2, and LOC ($t_{23.2}$=5.8, P<0.001; $t_{16.8}$=3.3, P=0.014; and $t_{28.3}$=2.9, P=0.019, respectively). Regardless of the stimulus type (congruous or incongruous), the N400 component observed during dexmedetomidine-induced unresponsiveness resembled the large N400 component associated with incongruous last words in the awake state (Figure 12, see also figure 3 in Study II). The N400 component elicited by incongruous words did not differ between awake baseline and dexmedetomidine administration ($F_{3,17.6}$=1.3; P=0.316). The latency of the N400 component varied from 360 ms (95% CI: 134–586) observed for congruous last words in LOC to 462 ms (95% CI: 200–724) seen with incongruous last words in LOR2.

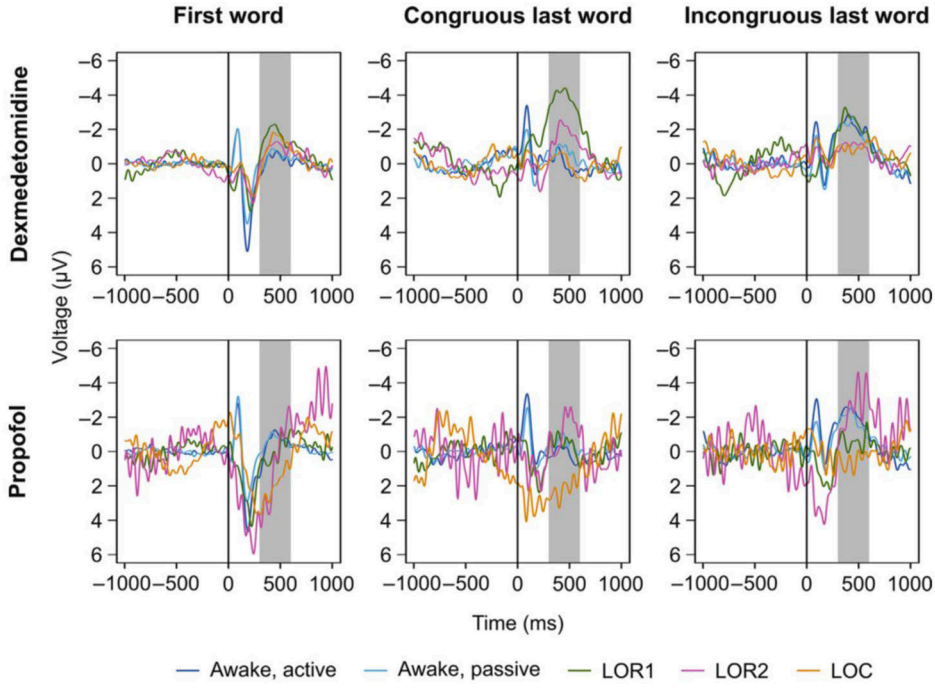

Figure 12. N400 components elicited by the first and last words of sentences in active and passive awake baseline, loss of responsiveness (LOR1 and LOR2), and presumed loss of consciousness (LOC). Data from C4 electrode are shown. The number of subjects in each condition is shown in Table 11. Reproduced from Original Publication II with the permission of the copyright holders.

During propofol-induced unresponsiveness, an indistinct N400 component was observed during LOR1 and LOR2 (Figure 12). The N400 component was mostly not statistically significant and completely disappeared in LOC (Table 11).

5.5 Subjective Experiences during Unresponsive states Induced by Propofol, Dexmedetomidine and Sleep (Study III)

Based on the reports attained from the study subjects, most anesthetic-induced unresponsive states and verified sleep stages denoted disconnected conscious states. In those subjects who could be interviewed, subjective experiences (including white reports and reports including specific content) were reported in 80 % and 71 % of the interviews in Experiments 1 and 2, respectively. Most often, internally generated dreaming or memory incorporation were described. In Experiment 1, the recall rates of subjective experiences were equal (80 % of interviews) in both drug groups. In Experiment 2, subjective experiences were reported in 58 %, 66 %, and 83 % of the N1, N2 and N3 interviews, respectively.

Signs of awareness (connected consciousness) were reported by one subject receiving propofol and one subject receiving dexmedetomidine, both after the second unresponsive period in Experiment 1, and by one subject after N2 sleep in Experiment 2. Apart from these cases, unresponsiveness denoted thus disconnected, albeit mostly not unconscious, states.

5.6 Regional Cerebral Blood Flow during Anesthesia and Sleep (Study III)

Overall, 39 subjects were scanned during different pre-defined states of consciousness, increasing and constant anesthetic levels using two distinct anesthetic drugs (Experiment 1). Subsequently, 37 subjects were scanned during different stages of physiologic sleep (Experiment 2). As described, both experiments were followed by two sets of analyses in order to separate the effects related specifically to consciousness from the overall effects of the different interventions. All concentration levels and behavioral states (Experiment 1), and sleep stages (Experiment 2) were first compared to a normal wakeful state (no drug, no sleep deprivation) to reveal overall effects of the interventions on brain activity in the different conditions. Thereafter, to discover the effects related specifically to consciousness, within-subject constant-dose connected and disconnected (Experiment 1), and sleep deprived wakeful (connected) and N2 sleep stage (disconnected, Experiment 2) were compared. For details on successful states and scans chosen for comparisons, see Realization of Experimental Designs and Table 7.

5.6.1 Overall Effects of Anesthesia and Sleep on rCBF (Study III)

In the first analysis, both drugs seemed to cause a fairly similar relative suppression of cerebral blood flow, which intensified along the administration period. The effects of physiologic sleep mimicked the effects of the anesthetics when different sleep stages were compared to the wakeful baseline state. Importantly, significant relative suppression of blood flow was seen already during sedative states and during SDW, and they were most profound frontally and parietally on the higher-order associative areas. As the level of anesthesia and sleep deepened, suppressions extended also to subcortical structures. Throughout the administration phase, the primary sensory and motor cortices seemed to be less affected, suggesting a functional dissociation of the higher-order associative and lower-order primary networks. This phenomenon was evident also during natural sleep. Noteworthy, the recovery responsiveness (connected) during a constant anesthetic infusion (UR dose) did not fully revert the effects of the anesthetics to baseline values. The distribution of suppression in the different conditions are illustrated in Figure 13. The findings demonstrate, that CBF changes during exposure to anesthetics are multifaceted – they do not merely reflect changes in the state of consciousness. Similarly, physiologic sleep induces widespread alterations in brain activity, which may not exclusively reflect state transitions.

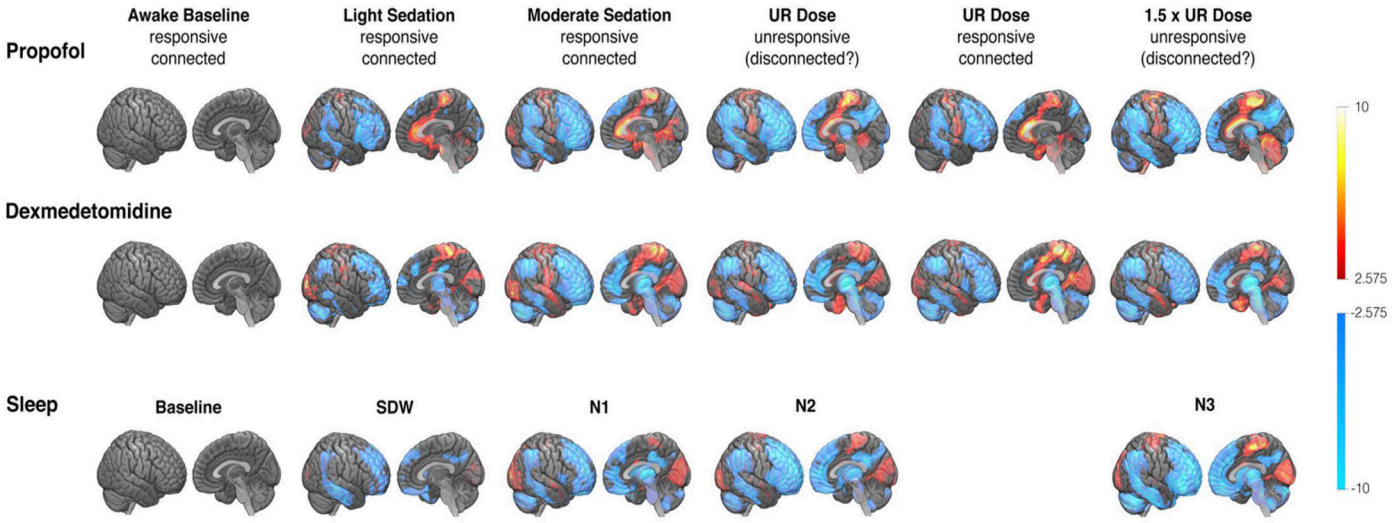

Figure 13. Distribution of relative rCBF changes in association with different concentration levels of propofol or dexmedetomidine (upper two panels) and different sleep stages (lower panel). All states are compared to a wakeful state (no drug, no sleep deprivation). Cool colors show the largest and warm colors the smallest relative suppression ($p<0.01$; color bars depict bootstrap ratios in PLS). Light and moderate sedation indicate responsive levels during escalating drug exposure. Unresponsive (UR) dose refers to drug concentration titrated individually to induce unresponsiveness, and 1.5 x UR dose refers to 50 % higher dose relative to UR. The actual states of consciousness (connected or disconnected) during unresponsive UR and 1.5 x UR levels could not always be verified because of lack of immediate interviews in unarousable subjects and/or after terminating the infusion, and are therefore marked as "(disconnected?)". Maximal suppression is seen in frontal and parietal cortical areas, as well as in subcortical structures, and the pattern is evident already during light sedation, resembling the awake sleep-deprived state. The intensity of suppression increases with drug dose level and depth of sleep, regardless of the behavioral state. The number of compared states is specified in Table 7. Reproduced with the right of the copyright holders.

5.6.2 State-Related Changes in rCBF during Anesthesia and Sleep (Study III)

The second analysis aimed to find those changes in brain activity, which would associate specifically to the state of consciousness. Thus, changes in relative CBF between connected and disconnected states were specifically studied. To specify, we used the forced awakening paradigm, where the state of consciousness –but not the drug level– changed (Experiment 1). In Experiment 2, only within-subject connected and disconnected states (SDW and N2 sleep) were compared. As described, the state of consciousness was verified by immediate interviews (see 5.5 Subjective Experiences during Unresponsive States). We hypothesized, that these comparisons would eliminate changes in brain activity, which were unrelated to the state transition (between connected and disconnected state).

We found, that during constant-dose anesthesia, the activity of the thalamus, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) and the angular gyri in the inferior parietal lobules consistently associated with the state of consciousness, thus revealing a core network of midline structures to be affected in this state transition (Figure 14). Additionally, this network was activated and deactivated in an opposite (reversed) manner, which was independent from the used anesthetic. Different from the first analysis, widespread suppression of the frontal-parietal areas was not manifested. Some cortical effects were observed on the cortical surface, but they were heterogeneous in terms of direction of change, drug, and areas affected (see Figure 15). Consistent state-specific differences in brain activity were thus distinct and separable from the overall effects of anesthesia.

The same analysis was then applied to Experiment 2. We accounted for the effects of sleep pressure (drowsiness) by choosing to compare states with minimal confounding effects. Thus, we compared the sleep-deprived (connected) state to N2 sleep (disconnected state). As reported in 5.5 States of Consciousness, the overall incidence of (reports of) internal experiences after N2 sleep was 66 % in the immediate interviews. Only one subject reported signs of awareness of the surrounding world and was not included in the analysis. Thus, most subjects were in a disconnected, rather than a fully unconscious state. Similar to the analyses in the anesthesia study, the comparisons between connected (SDW) and disconnected (N2) states were made within-subject, thus requiring successful scans from both states. The results were, again, clearly distinct from those of the first analysis. Paralleling the results from the anesthesia study, relative blood flow in a restricted network of core midline structures including the thalamus, anterior and posterior cingulate cortices, bilateral angular gyri, dorsolateral prefrontal cortex and right caudate nucleus was consistently associated with the state of consciousness (Figure 14). Cortical renderings from the same analysis revealed that state transitions between

connected and disconnected states are only minimally and inconsistently manifested on the cortical surface (Figure 15).

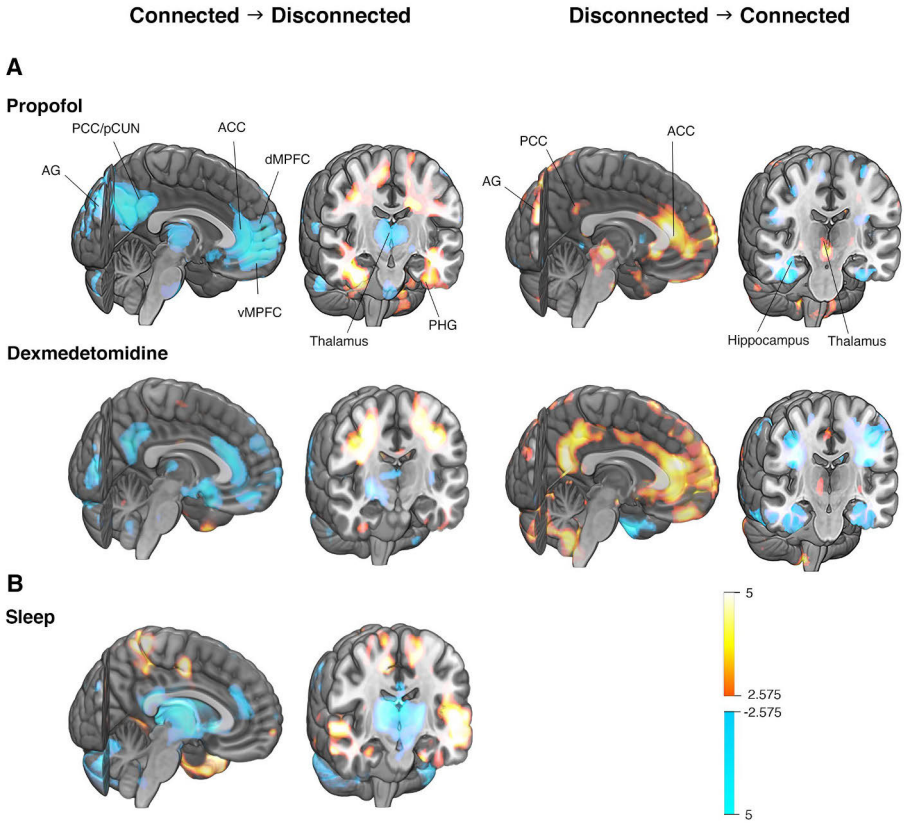

Figure 14. A central core network of consciousness was revealed by imaging anesthetic- and sleep-induced state transitions. Cool colors show the largest and warm colors the smallest relative suppression upon becoming disconnected (left panel) and warm colors show the largest and cool colors the smallest relative activation upon becoming connected (right panel) ($p<0.01$, corrected; color bars depict bootstrap ratios in PLS). During administration of both propofol (upper panel) and dexmedetomidine (middle panel), the activity changes of a core network were most associated to the transition between connected and disconnected states. Activity changes within the thalamus, anterior and posterior cingulate cortices, precuneal area and bilateral angular gyri were state-specific. During physiological sleep (lower panel), transition from sleep-deprived wakefulness to N2 sleep revealed the deactivation of the same core structures. In both experiments, changes on the cortical surface were heterogeneous and inconsistent (see Figure 15). The number of compared states is specified in Table 7. ACC = anterior cingulate cortex, AG = angular gyrus, dMPFC = dorsomedial prefrontal cortex, PCC = posterior cingulate cortex, pCUN = precuneus, PHG = parahippocampal gyrus, vMPFC = ventromedial prefrontal cortex. Reproduced with the right of the copyright holders.

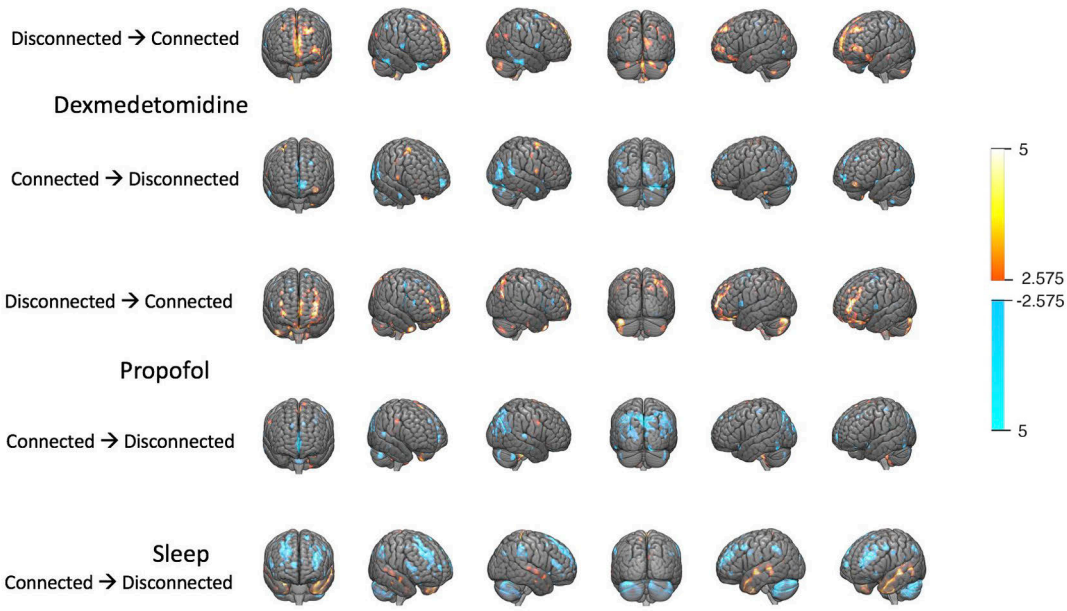

Figure 15. Cortical renderings from the second analysis (state-related changes, see also Figure 14). Warm colors show the largest and cool colors the smallest relative activation upon becoming connected (1st and 3rd rows), and cool colors show the largest and warm colors the smallest relative suppression upon becoming disconnected (2nd,, 4th and 5th rows, $p<0.01$, corrected; color bars depict bootstrap ratios in PLS). As illustrated, changes in rCBF between connected and disconnected states are minimal, heterogeneous and inconsistent between interventions. For subcortical renderings, see Figure 10. Reproduced with the right of the copyright holders.

6 Discussion

6.1 Our Findings

Three distinct experiments illustrated, that the effects of anesthesia and sleep on brain functions (reflected in EEG and functional imaging measures) are multifaceted. On a group level, state-related spectral EEG patterns are distinct and separable from the overall effects of the interventions; responsiveness was most associated to frontal alpha and slow-wave activity. PET imaging showed that activity changes in a core network –the thalamus, anterior and posterior cingulate cortices and bilateral angular gyri– are most associated to state transitions. Finally, threshold doses of anesthetics and natural sleep rarely induce unconsciousness, and this fact pleads for accuracy in the characterization of the explored states.

6.1.1 Separating State-Related and Overall Effects of Anesthesia Using EEG (Study I)

In Dose-Finding, our study demonstrates the interaction between the administered drug and the state of consciousness *per se* on the calculated spectral measures of the EEG. As to the overall spectral results, our findings largely corroborated previous descriptions of spectral effects induced by propofol and dexmedetomidine. However, our study is the first to have performed rigorous statistical analyses between these drugs and the pre-defined states, to find the patterns most associated to the behavioural state. Our study reveals the multifaceted nature of anesthesia-EEG.

On group-level, the most association to (un)responsiveness was found in SWA and frontal alpha activity. Frontal alpha was the only estimate to separate LOR from SED and ROR with both treatments. Also, low alpha power at LOR was associated with arousability during the infusions, which perhaps indicates individual susceptibility for general anesthetics. The alpha band power at baseline did not, however, predict the concentration needed for loss of responsiveness. Interestingly,

weak alpha band networks have previously been seen to relate to strong susceptibility for propofol (Chennu et al., 2016).

We also illustrated, that a steady-state anesthetic level does not signify stability in the achieved state. Indeed, despite a stable plasma concentration during LOR, statistically significant deepening of the anesthetic state (manifested as strengthening of the spectral changes) was evident, when LOR was compared to LOR_{late} with both drugs.

Throughout the study, a clear difference in the behavior of the beta band was detected between the treatment groups. Propofol is known to elicit paradoxical excitation, i.e., initial increase in beta power before starting to decrease in conjunction with deepening anesthetic levels (McCarthy et al., 2008). As demonstrated, paradoxical excitation is not evident during dexmedetomidine exposure. At ROR, the magnitude and distribution of beta power remained identical to LOR in both groups, which, however, contradicts a few previous studies with restored beta-activity at recovery from dexmedetomidine (Sleigh et al., 2018a; Akeju et al., 2016). Methodological differences may explain this discrepancy.

6.1.2 Phenomenology (Study III)

Traditionally, the phenomenology of the explored unresponsive states remain unaddressed in experimental studies on consciousness. In the current study, reports of subjective experiences were collected and analyzed in detail in Experiments 2 and 3. Subjective experiences from Dose-Finding have been reported previously (Radek et al., 2018), and explicit results of experiences during unresponsive and sleep states in Experiments 1 and 2 are to be reported later (manuscript under preparation). Based on previous (Noreika et al., 2011; Radek et al., 2018) and current findings, unconsciousness is relatively rare with moderate doses of anesthetics. Also physiologic non-REM sleep devoid of any dream content seems rare. This fact could be considered as trivial, but contrarily, is highly relevant in the study of human consciousness. Many inferences on human consciousness have been made based on heterogeneous samples of phenomenal and pharmacological conditions and ambiguous definitions on consciousness.

Ideally, the unresponsive/disconnected subjects in the current studies would have been further subcategorized to disconnected conscious and unconscious states. Also, comparison of brain activity between these states would have been of great interest and scientific novelty. As thoroughly discussed, these states represent distinct phenomenal states with fundamental (and insofar unknown) differences. Such as the work by Siclari and colleagues using EEG (Siclari et al., 2017) and Nieminen and colleagues using TMS-EEG (Nieminen et al., 2016), functional imaging could similarly reveal some of the anatomical and network-level prerequisites that

enable/induce internal consciousness. However, there were three reasons for not addressing this issue in the current study. 1) While we demonstrably placed value on the individual reports, we considered the 'no report' conditions especially unreliable due to possible amnesia caused by anesthetic agents (Sanders et al., 2017). This, together with 2) the low number of subjects who reported no recall (and who could thus be considered as unconscious) would have resulted in an unreliable sample of unconscious subjects. Despite that we felt tempted to set these facts aside and further sub-categorize and separately analyze the disconnected states, immersing ourselves in this issue would have 3) sidestepped the scope of the study, i.e., aiming to illustrate persistent methodological confounders in consciousness research and distinguish connectedness from disconnectedness. Ultimately, we feel that the approach we chose ensures the most reliable inferences on human consciousness without disregarding the limitations of the data.

6.1.3 Separating State-Related and Overall Effects of Anesthesia and Sleep on rCBF Using PET Imaging (Study III)

Using a similar paradigm in the PET study and comparing the most relevant scans between state transitions, we discovered that state-related activity changes were manifested in a restricted network including the thalamus, the ACC, PCC and precuneal area, as well as bilateral angular gyri. Importantly, intense cortical and subcortical suppressions in rCBF was also observed, but they reflected other, overall and possibly concentration–dependent effects of the anesthetics and the effects of drowsiness caused by sleep deprivation. In many previous brain imaging studies, the states selected for comparisons are suboptimal, as they differ in multiple aspects, such as pharmacologic profile and cognitive characteristics. Our experimental paradigm clearly highlights the fundamental importance of relevant contrasts in the study of human consciousness.

The emerged areas have been implicated in consciousness and its dimensions previously. Significant overlap between our state-related findings and the anatomical areas contributing to the DMN and SN (salience network) is evident. The default mode network is considered as foundational for self-referential mentation whereas the executive control network (ECN) for externally guided awareness. The SN is thought to play a coordinating role between the DMN and ECN (Menon and Uddin, 2010; Demertzi et al., 2013). Unresponsive states of different etiologies have been shown to associate with the suppression or disruption of functional connectivity within these networks (Boveroux et al., 2010; Qin et al., 2015; Guldenmund et al., 2017; Huang et al., 2020). Our findings corroborate these prior studies. Interestingly, decreased rCBF or BOLD fMRI signal in DMN areas and thalamus can also be seen

in a psychedelic state induced by psilocybin (CarhartHarris et al., 2012) and in DMN areas during meditation (Brewer et al., 2011). Both psychedelic and meditative states have been associated with decreased sense of self. Indeed, general anesthesia has been characterized as "fragmentation of selfhood" (Sleigh et al., 2018b).

The emerged areas have also individual implications. As reviewed by Paus (Paus, 2001), the ACC is considered to be involved in motor control, in cognition and in the arousal/drive state of the organism, together translating intentions into actions, a view that fits well with our current findings. The ACC in highly interconnected to other regions, especially the thalamus and limbic areas, as well as brainstem monoamine nuclei (Berger, 1992; Crino et al., 1993). It has also been suggested, that the ACC plays a key role in "self-regulation" (Posner et al., 2007) and even "free will" (Paus, 2001; Crick, 1995). Thus, the ACC finding in our study is not all surprising considering the aforementioned implications.

The PCC/precuneal area was also manifested as a crucial state-related functional cluster. It is an ongoing debate whether the anterior or posterior areas are more crucial to consciousness *per se*, but nevertheless, the PCC has also been implicated in self-referencial mentation, especially when coupled to other aspects of the DMN. Interestingly, there is evidence for a dissociation between explicit self-reference and default mode activity, which suggests that PCC is implicated in both but precuneal area in default mode functions only (Whitfield-Gabrieli et al., 2011).

The angular gyri (AG) in the inferior parietal lobules (IPL) also manifested in the state-transitions. The IPL is a heterogeneous region with 3 functional subdivisions, the supramarginal gyrus, the intraparietal sulcus (IPS) and the angular gyrus (AG). The AG is situated at the junction of the temporal, parietal, and occipital lobes, and has been shown to contribute to multiple cognitive functions, such as semantic processing (Binder 2009), as well as spatial attention (Chambers 2004) and mathematical fact retrieval (Dehaene 2004). It is also a key node in the DMN (Shulman et al., 1997; Raichle et al., 2001; Greicius et al., 2003; Uddin 2009). An interesting case report (seven patients) by Desmurget and colleagues (Desmurget 2009) showed that electrical stimulation of the IPL during awake craniotomy induced a strong intention and desire to move the contralateral hand, arm, or foot. Left inferiorparietal stimulation provoked the intention to move the lips and to talk. Recently, repetitive TMS delivered to the AG was shown to improve the coma recovery scale revised (CRS-R) total score in MCS patients (Legostaeva et al., 2019).

Remarkably, the changes observed during the state transitions were almost identical during anesthesia and natural sleep. These findings suggest network-level similarities between pharmacological and physiological disconnectedness/ unresponsiveness. Despite serving as hubs for specific cognitive functions, the emerged areas clearly form a functional network. Additional studies are needed to

unravel the inter-dependencies of these regions and the causality of events during transitions between different states of consciousness.

6.1.4 Effects of Anesthesia on N400 ERP's (Study II)

Our ERP results from Dose-Finding show a persistent N400 component during dexmedetomidine-induced unresponsiveness. Nevertheless, discrimination of congruous and incongruous words (N400 effect) was lost at LOR. Such findings were not observable with propofol subjects. The N400 is a late cognitive ERP, which is thought to reflect higher-order cognitive processing and to index the effort of retrieving the representation of a semantic stimulus (Lau et al., 2008). In addition, attention has been considered a prerequisite for the N400 effects, while not being necessary for the N400 component (Bentin et al., 1995).

The N400 effect is not evident in all awake individuals (Rohaut et al., 2015), indicating only partial sensitivity at single-subject level. In the current study, we screened healthy subjects awake (n=79, Kallionpää et al., 2019) in order to include subjects with the most apparent N400 effects. However, the increased delta activity during the administration overlapped the wavelength of the N400 and increased the variation in signal amplitudes even in the absence of stimuli. This prevented us from performing single-subject analyses, which would be necessary for the diagnostic use of N400. Furthermore, the N400 is not an indicator of consciousness or awareness (Beukema et al., 2016), but it correlates with positive prognosis in disorders of consciousness, suggesting association to processes relevant to consciousness (Steppacher et al., 2013; Daltrozzo et al., 2007). The ERP's recorded during anesthetic-induced unresponsiveness might not be fully analogous with the N400 observed awake, but nevertheless, our results suggest that semantic processing may at least partly be preserved. In the current study, loss of the N400 effect during dexmedetomidine administration was attributable to the increased negativity of the N400 component elicited by congruous words, whilst the component resulting from incongruous stimuli remained unchanged. We speculate that all words (congruous or incongruous) triggered maximal effort to retrieve the representation of the word, possibly because of loss of context or expectations. This might be caused by loss of integration capacity or amnestic effects by the drug.

The N400 has been previously reported during N2 sleep (Brualla et al., 1998; Perrin et al., 2002), and in some patients with disorders of consciousness (Steppacher et al., 2013; Beukema et al., 2016; Rohaut et al., 2015). These conditions also associate to an increase in delta power, yet the increase in the negativity of the N400 component seems to be a unique effect of dexmedetomidine-induced unresponsiveness. This is apparently the first report on the N400 ERP component during anesthetic-induced unresponsiveness. The evoked potential P3b has been

studied before during propofol and ketamine sedation, which show that it attenuates or reduces already at sedative levels (Sneyd et al., 1994; Watson et al., 2009). Our study adds to the sparse data on semantic processing during LOR.

6.2 Study Design Issues

There are several issues related to study designs in consciousness science. As summarized in the Review of the Literature (2.4.6 Study Design Challenges), many evident limitations have been largely disregarded in the past. As to finding the neural correlates of consciousness, previous studies have disregrded a fundamental limitation. The reference state, to which any unconscious/unresponsive state has been compared, has often been a normal wakeful state without any drug exposure. This state represents an alert state, devoid of sedation, sleep pressure or any other decline in cognitive capacities. When consciousness then fades, the state does not abruptly shift to an unconscious state, but passes through several dynamic states with characteristic decline in both external alertness and self-referencial thoughts. This continuum of different states can also be compared to those induced by alcohol (drunkenness) or sleep deprivation (extreme sleep pressure). We argue, that comparing (presumed) unconsciousness to normal wakefulness disregards these effects and is over-inclusive, i.e., interprets all changes to be state-related. Indeed, we used the most appropriate state as the wakeful reference and overcame these confounding cognitive and pharmacological effects. Abrupt awakenings during a constant-dose TCI has not been a standard method in studies using anesthesia, but rather, the drug has been allowed to dissipate and subjects have been further investigated after spontaneous recovery of consciousness. Thus, the drug level between the compared unconscious and recovery states have not been standardized and the results may be confounded by effects not related to the state transition. The aforementioned limitations have been largely resolved using our study design. The experimental sessions were conducted as planned, with only a few drop outs and prematurely terminated study sessions (See Results).

6.3 Limitations

Despite our rigorous study protocol, some fundamental and persistent challenges have to be addressed. When consciousness is manipulated either pharmacologically or physiologically, there is a strong assumption that the induced states – and the related measures of brain activity– would be relatively stable. As we noted during this study, this is not the case. We observed, that the apparent unconscious (unresponsive/disconnected) state tended to “deepen” along the examination period

and administration phase of the drug, despite that the target concentration was kept constant (Dose-Finding and Experiment 1). This was especially apparent in Dose-Finding, where the pseudo steady-state was relatively long and EEG measures indicated a clear deepening of the anesthetized state along the administration period. Also unintended awakenings mid-experiment were observed, further highlighting some of the challenges related to the experimental paradigm. In Experiment 1 (anesthesia/PET), challenges were experienced especially in the SED, UR and R states: Due to the duration of the scanning, unintended changes in the state of consciousness were somewhat inevitable. Based on our experience, metastability is common, but this is rarely addressed in any imaging or electroencephalogram studies, except for two recent EEG studies on functional connectivity (Li et al., 2019; Vlisides et al., 2019). To minimize erroneous EEG and scanning data with regard to the targeted state, every behavioral state was confirmed both before and after each collected EEG epoch and PET scan, and unreliable epochs and scans were removed from the analyses. In future experimental studies, the duration of different conditions should be carefully contemplated to acknowledge the non-stationarity of the behavioral states.

As clarified in 5.1 Realization of Experimental Designs, the UR2 state was achieved only by two subjects in the propofol group. Due to lack of statistical power, the UR2 state could not be used in the R/UR2 -comparison in the "becoming disconnected" -analysis. As explained, we thus used the SED_{mod} -state, which was achieved by all subjects. The targeted concentration in UR was approximately 25% higher compared to concentrations in SED_{mod}.

6.4 Ethical Considerations

This study was conducted in accordance with the current revision of Declaration of Helsinki guiding physicians in medical research involving human subjects (Edinburgh, Scotland, 2000 as amended in Washington, USA, 2002 and Tokyo, Japan, 2004). Prior to commencement of this investigation, the study protocol, subject information and informed consent form was submitted for approval to the Ethics Committee (EC) of the Health Care District of Southwest Finland. The total amount of radiation the volunteers participating in Experiments 1 and 2 (approx.14 scans) was exposed to equals 3.9 mSv. The annual background radiation in Finland equals approximately 3.7 mSv.

The aim of this study – obtaining important information on human consciousness and the CNS effects of anesthetic drugs as well as their putative mechanism of anesthetic action – is scientifically sound and ethically justified as no other means exist on doing such in humans. The investigators are aware of the ethical issues and

risks associated with anesthetizing healthy volunteers for research purposes. Anesthesia itself has been estimated to be the actual cause of death in only 1:200 000 –300 000 cases of ASA I and II patients (Eichhorn, 1989; Lagasse, 2002). However, since this estimate is based on patient material treated in 1976–1988 and included also ASA II physical status patients, the risk for carefully selected ASA I patients dying for a reason solely due to anesthesia can be presently considered much lower. Furthermore, our subjects were breathing spontaneously throughout the sessions and thus, no intubation or securing of airway was needed, lowering the risk even more. In a clinical setting, the risk caused from an anesthesia is low, when it is compared to an everyday risk of dying in, e.g., accident at home or work (1:40 000 – 1:20 000) or in the road traffic accident (1:8000) during a period of one year (Adams and Smith, 2001). As understanding the nature of anesthesia, its inconveniences and risks is a crucial matter in this investigation, only subjects that were able to identify with these risks were recruited.

Two anesthesiologists were present during the study sessions (one specialist and one resident), as well as two research assistants. After the session, a nurse anesthetist monitored the subjects until the subject was allowed to leave with an escort. The facility was fully equipped with ICU/recovery room monitoring and resuscitation equipment.

6.5 Recent Findings and Future Directions

It's justified to say that the "Rosetta Stone" of consciousness has not yet been found. However, the search is ongoing and there is increasing knowledge about the different dimensions of consciousness. In the most recent years, the debate regarding the frontal versus the posterior regions as most fundamental for consciousness has been visible (Raccah et al 2021; Odegaard et al., 2017; Boly et al., 2017; Reardon, 2019; Ihalainen et al., 2021; Siclari et al., 2017), and both views continue to be supported by empirical data. Different analytical approaches to a single dataset and more refined conceptual approaches could clarify some persisting questions (Noel et al., 2019; Del Pin et al., 2021).

Relevant to the aforementioned rivalry, there are interesting recent observations on the effects brain stimulation. For instance, cholinergic stimulation of the prefrontal cortex has been shown to reanimate rats from general anesthesia, despite ongoing anesthetic exposure (Pal et al., 2018). Also recently, the dopaminergic nucleus VTA has been shown to disconnect from the DMN (Spindler et al., 2021) during propofol-induced unresponsiveness and in DOC patients. The VTA projects widely to the prefrontal cortex and as described earlier, also electrical and optogenic stimulation of the VTA induce reanimation from general anesthesia in rats (Solt et

al., 2014, Taylor et al., 2016). In macaques, electrical stimulation of central lateral thalamus (CLT) has been shown to restore arousal and wake-like neural processes (Redinbaugh et al., 2021).

On the other hand, some suggest that any specific anatomical structure is nonessential, but rather, (un)consciousness is highly dependent on different anticorrelated systems and on the stability of brain dynamics (Huang et al., 2020, Lopez-Gonzalez et al., 2020). Some controversies may also be explained by the fact that different studies investigate opposite phenomena (i.e., the loss and/or recovery of consciousness). If recovery of consciousness can be induced/accelerated by stimulating specific thalamic nuclei (Schiff et al., 2007, Baker et al., 2016, Donoghue et al., 2019, Redinbaugh et al., 2020), the VTA (Solt et al., 2014, Taylor et al., 2016) or the angular gyri (Legostaeva et al., 2019), does a suppression of the same structures induce unconsciousness? There is a relatively strong agreement that anesthetic-induced loss and recovery of consciousness are not functionally mirror phenomena in terms of neural dynamics (Warnaby et al., 2017, Kim et al., 2018, Huang et al., 2021). In our current study, almost opposite effects were observed at loss and recovery of a connected state. We speculate, that the differences may partly be explained by methodological choices and pharmacological differences. Importantly, a transition between two states entails also the prerequisites and aftereffects of the transition. As seen in our current study, the cerebral cortex was largely affected before a change in the state of consciousness was observed. Thus, we suggest that these effects are not sufficient –albeit perhaps necessary– for the transition from a connected to a disconnected state. Taken together, several phenomena influence the interpretations/theories regarding the asymmetry of loss and recovery of consciousness.

Key objectives in future studies are the therapeutical developments in the fields of anesthesiology, neurology and intensive care. In anesthesiology, reliable individual assessment methods of consciousness are still needed. Due to the methodological benefits, easy accessibility and non-invasiveness, EEG still offers the best technique to monitor the brain in real-time. Recent proposals for EEG-based monitoring of the brain during surgery include resting-state spectral exponent (Colombo et al., 2018), Directed Transfer Function of the alpha band (Juel et al., 2018), and PCI (Sarasso et al., 2015), none of which are devoid of their own limitations. Different machine learning algorithms have also recently been proposed (Ramaswamy et al., 2019, Abel et al., 2021). Any methodology used to assess consciousness during surgery should include 1) simple installment of the electrodes, 2) no extensive preprocessing of the data and 3) good temporal resolution. Any time-consuming step in acquiring the data is unsuitable for clinical use.

DoC patients also rely on clinical advancements. As these patients are a heterogeneous group from various etiologies, have different degrees of pathology-

related manifestations and individual neurological deficits, they encounter diagnostic, therapeutic and ethical challenges (Rissman and Paquette, 2020, Peterson et al., 2021). Neuroimaging and neurophysiological tests have recently been introduced for diagnostic purposes (Carrière et al., 2020), prognostic indicators of recovery (Bareham et al., 2020; Velly 2018, Estraneo et al., 2020), and surrogate markers of therapeutic efficacy (Mensen et al., 2020; Thibaut et al., 2019, Alkhachroum et al., 2020, Edlow et al., 2020). Importantly, a recent advancement is the novel guideline that help this patient group, often neglected by the healthcare system (Kondziella et al., 2020).

In the study of human consciousness, major breakthroughs have been accomplished in recent years. In order to offer the best therapy for our patients, we need reliable methods to measure and detect consciousness, which would optimize anesthetic care, as well as resolve some persisting ethical and therapeutic issues related to different pathologic brain states. As we didn't study surgical anesthesia nor pathologic brain states, our EEG and PET results do not have direct clinical implications to these patient groups. However, we illustrate the multi-faceted nature of anesthesia-EEG and highlight the metastability of EEG measures. We conclude that EEG is a valuable component in anesthesia monitoring and our findings add to our understanding of the physiology of the brain during sedation and anesthesia. Importantly, our study has major implications to consciousness science. We have illustrated, that the correlates of (un)consciousness cannot be found based on traditional and suboptimal experimental designs. Neurophysiologic and functional imaging methods should include relevant reference states, accompanied by rigorous statistical analyses between different pre-defined conditions. By acknowledging these issues, we are on the path to resolving the most fundamental mystery of humankind. Time will tell, if the famous words of physicist Richard Feynman are accurate; *What you cannot create, you cannot understand*.

7 Summary and Conclusions

1. Using propofol and dexmedetomidine to induce unresponsiveness, EEG characteristic were similar but not identical. Along an incremental anesthetic level, slow-wave activity and frontal alpha activity increased, although the magnitude and regional distribution differed between the drugs. Interindividual variation was large. Despite a pseudo steady-state TCI, an intensification of the spectral patterns related to the drug administration was observed, suggesting non-stationarity of the induced states.
2. Using propofol and dexmedetomidine, both drug- and state-related effects were seen on the EEG. By applying abrupt awakenings during pseudo steady-state TCI, spectral power of frontal alpha and slow-wave activity had most association to the behavioral state, i.e., (un)responsiveness.
3. The N400 ERP (N400 component) was preserved during dexmedetomidine (but not propofol) -induced unresponsiveness, suggesting partial preservation of semantic processing in this state.
4. Incremental anesthetic levels (regardless of the state of consciousness) and deepening levels of physiologic sleep was associated with a widespread suppression of CBF across cortical and subcortical areas, with notably similar distribution between interventions. These changes depicted overall effects of the interventions, i.e., anesthesia and sleep.
5. Unresponsiveness induced by propofol, dexmedetomidine and physiologic sleep was mostly characterized by a disconnected conscious state with pleasant, dream-like experiences with no awareness of the outside world. Anesthetic-induced unresponsiveness, thus, rarely depicted unconsciousness and phenomenally resembled natural sleep.
6. Abrupt awakening from an unresponsive state during TCI did not restore CBF values to wakeful level, suggesting cerebral hemodynamics to be both drug– and state–dependent. Using both anesthesia and natural sleep to induce a disconnected state, activity changes in a core network of midline brain structures associated most to the state of consciousness, i.e., connectedness.

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References

Abel, J. H. et al., 2021, Machine learning of EEG spectra classifies unconsciousness during GABAergic anesthesia: PLOS ONE, v. 16, no. 5, p. e0246165, doi:10.1371/journal.pone.0246165.

Adams, A. M., A. F. Smith, 2001, Risk perception and communication: recent developments and implications for anaesthesia. Anaesthesia, 56:745–755.

Akeju, O. et al., 2014, A comparison of propofol- and dexmedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis.: Anesthesiology, v. 121, no. 5, p. 978 989, doi:10.1097/aln.0000000000000419.

Akeju, O. et al., 2014, Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness.: eLife, v. 3, p. e04499, doi:10.7554/elife.04499.

Akeju, O. et al., 2018, Dexmedetomidine promotes biomimetic non-rapid eye movement stage 3 sleep in humans: A pilot study: Clinical Neurophysiology, v. 129, no. 1, p. 69–78, doi:10.1016/j.clinph.2017.10.005.

Akeju, O, S. E. Kim, R. Vazquez, J. Rhee, and K. J. Pavone, 2016, Spatiotemporal dynamics of dexmedetomidine-induced electroencephalogram oscillations: PLOS ONE, doi:10.1371/journal.pone.0163431.s005.

Akeju, Oluwaseun, A. H. Song, A. E. Hamilos, K. J. Pavone, F. J. Flores, E. N. Brown, and P. L. Purdon, 2016, Electroencephalogram signatures of ketamine anesthesia-induced unconsciousness: Clinical Neurophysiology, v. 127, no. 6, p. 2414–2422, doi:10.1016/j.clinph.2016.03.005.

Alkhachroum, A. et al., 2020, EEG to detect early recovery of consciousness in amantadine-treated acute brain injury patients: Journal of Neurology, Neurosurgery & Psychiatry, v. 91, no. 6, p. 675–676, doi:10.1136/jnnp-2019-322645

Alkire, M. T., R. J. Haier, S. J. Barker, N. K. Shah, J. C. Wu, and J. Y. Kao, 1995, Cerebral Metabolism during Propofol Anesthesia in Humans Studied with Positron Emission Tomography: Anesthesiology, v. 82, no. 2, p. 393–403, doi:10.1097/00000542-199502000-00010.

Alkire, M. T., R. J. Haier, and J. H. Fallon, 2000, Toward a Unified Theory of Narcosis: Brain Imaging Evidence for a Thalamocortical Switch as the Neurophysiologic Basis of Anesthetic-Induced Unconsciousness: Consciousness and Cognition, v. 9, no. 3, p. 370–386, doi:10.1006/ccog.1999.0423.

Alkire, M. T. M., R. J. P. Haier, N. K. M. Shah, and C. T. M. Anderson, 1997, Positron Emission Tomography Study of Regional Cerebral Metabolism in Humans during Isoflurane Anesthesia: Anesthesiology, v. 86, no. 3, p. 549–557, doi:10.1097/00000542-199703000-00006.

Andres-Enguix, I., A. Caley, R. Yustos, M. A. Schumacher, P. D. Spanu, R. Dickinson, M. Maze, and N. P. Franks, 2007, Determinants of the Anesthetic Sensitivity of Two-pore Domain Acid-sensitive Potassium Channels MOLECULAR CLONING OF AN ANESTHETIC-ACTIVATED POTASSIUM CHANNEL FROM LYMNAEA STAGNALIS*: Journal of Biological Chemistry, v. 282, no. 29, p. 20977–20990, doi:10.1074/jbc.m610692200.

Anis N. A., S. C Berry, N. R Burton, D. Lodge, 1983, The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br J Pharmacol, Jun;79(2):565-75. doi: 10.1111/j.1476-5381.1983.tb11031.x. PMID: 6317114; PMCID: PMC2044888.

Aranake, A. et al., 2013, Increased risk of intraoperative awareness in patients with a history of awareness.: Anesthesiology, v. 119, no. 6, p. 1275 1283, doi:10.1097/aln.0000000000000023.

Aru J., T. Bachmann, 2017, In and Out of Consciousness: How Does Conscious Processing (D)evolve Over Time? Front Psychol. Feb 2;8:128. doi: 10.3389/fpsyg.2017.00128. PMID: 28210236; PMCID: PMC5288355.

Avidan, M. S. et al., 2008, Anesthesia awareness and the bispectral index.: The New England journal of medicine, v. 358, no. 11, p. 1097 1108, doi:10.1056/nejmoa0707361.

Avidan, M. S. et al., 2011, Prevention of intraoperative awareness in a high-risk surgical population.: The New England journal of medicine, v. 365, no. 7, p. 591 600, doi:10.1056/nejmoa1100403.

Baars BJ, 1988, A cognitive theory of consciousness, Cambridge University Press, New York

Bachmann, T., and A. G. Hudetz, 2014, It is time to combine the two main traditions in the research on the neural correlates of consciousness: C = L × D.: Front. Psychol., v. 5, no. 82, p. 940, doi:10.3389/fpsyg.2014.00940.

Baker, J. L., J.-W. Ryou, X. F. Wei, C. R. Butson, N. D. Schiff, and K. P. Purpura, 2016, Robust modulation of arousal regulation, performance, and frontostriatal activity through central thalamic deep brain stimulation in healthy nonhuman primates: Journal of Neurophysiology, v. 116, no. 5, p. 2383–2404, doi:10.1152/jn.01129.2015.

Balconi, M., R. Arangio, and C. Guarnerio, 2013, Disorders of consciousness and N400 ERP measures in response to a semantic task.: The Journal of neuropsychiatry and clinical neurosciences, v. 25, no. 3, p. 237 243, doi:10.1176/appi.neuropsych.12090227.

Bareham, C. A., N. Roberts, J. Allanson, P. J. A. Hutchinson, J. D. Pickard, D. K. Menon, and S. Chennu, 2020, Bedside EEG predicts longitudinal behavioural changes in disorders of consciousness: NeuroImage: Clinical, v. 28, p. 102372, doi:10.1016/j.nicl.2020.102372.

Bar-Joseph, G., Y. Guilburd, A. Tamir, and J. N. Guilburd, 2009, Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension: Clinical article: Journal of Neurosurgery: Pediatrics, v. 4, no. 1, p. 40–46, doi:10.3171/2009.1.peds08319.

Bayne, T., J. Hohwy, and A. M. Owen, 2016, Are There Levels of Consciousness? Trends in Cognitive Sciences, v. 20, no. 6, p. 405–413, doi:10.1016/j.tics.2016.03.009.

Belelli, D., M. Pistis, J. A. Peters, and J. J. Lambert, 1999, General anaesthetic action at transmitter-gated inhibitory amino acid receptors: Trends in Pharmacological Sciences, v. 20, no. 12, p. 496–502, doi:10.1016/s0165-6147(99)01405-4.

Bell, J. D., 2017, In Vogue: Ketamine for Neuroprotection in Acute Neurologic Injury: Anesthesia & Analgesia, v. 124, no. 4, p. 1237–1243, doi:10.1213/ane.0000000000001856.

Bentin, S., M. Kutas, and S. A. Hillyard, 1995, Semantic Processing and Memory for Attended and Unattended Words in Dichotic Listening: Behavioral and Electrophysiological Evidence: Journal of Experimental Psychology: Human Perception and Performance, v. 21, no. 1, p. 54–67, doi:10.1037/0096-1523.21.1.54.

Berger, B, 1992, Dopaminergic innervation of the frontal cerebral cortex: evolutionary trends and functional implications. Advances in neurology, 57, 525-544.

Beukema, S., L. E. Gonzalez-Lara, P. Finoia, E. Kamau, J. Allanson, S. Chennu, R. M. Gibson, J. D. Pickard, A. M. Owen, and D. Cruse, 2016, A hierarchy of event-related potential markers of auditory processing in disorders of consciousness: NeuroImage: Clinical, v. 12, p. 359–371, doi:10.1016/j.nicl.2016.08.003.

Binder, J. R., R. H. Desai, W. W. Graves, and L. L. Conant, 2009, Where Is the Semantic System? A Critical Review and Meta-Analysis of 120 Functional Neuroimaging Studies: Cerebral Cortex, v. 19, no. 12, p. 2767–2796, doi:10.1093/cercor/bhp055.

Blain-Moraes, S., U. Lee, S. Ku, G. Noh, and G. A. Mashour, 2014, Electroencephalographic effects of ketamine on power, cross-frequency coupling, and connectivity in the alpha bandwidth: Frontiers in Systems Neuroscience, v. 8, p. e29072, doi:10.3389/fnsys.2014.00114.

Boly, M. et al., 2012, Connectivity Changes Underlying Spectral EEG Changes during Propofol-Induced Loss of Consciousness: The Journal of Neuroscience, v. 32, no. 20, p. 7082–7090, doi:10.1523/jneurosci.3769-11.2012.

Boly, M. et al., 2008a, Consciousness and cerebral baseline activity fluctuations: Human Brain Mapping, v. 29, no. 7, p. 868–874, doi:10.1002/hbm.20602.

Boly, M. et al., 2008b, Perception of pain in the minimally conscious state with PET activation: an observational study: The Lancet Neurology, v. 7, no. 11, p. 1013–1020, doi:10.1016/s1474-4422(08)70219-9.

Boly, M., M. I. Garrido, O. Gosseries, M.-A. Bruno, P. Boveroux, C. Schnakers, M. Massimini, V. Litvak, S. Laureys, and K. Friston, 2011, Preserved Feedforward But Impaired Top-Down Processes in the Vegetative State: Science, v. 332, no. 6031, p. 858–862, doi:10.1126/science.1202043.

Boly, M., M. Massimini, N. T. J. of, and 2017, 2017, Are the neural correlates of consciousness in the front or in the back of the cerebral cortex? Clinical and neuroimaging evidence: Soc Neuroscience, v. 37, no. 40, p. 9593 9602, doi:10.1523/jneurosci.3217-16.2017.

Bonhomme, V. et al., 2019, General Anesthesia: A Probe to Explore Consciousness: Frontiers in Systems Neuroscience, v. 13, p. 36, doi:10.3389/fnsys.2019.00036.

Boveroux, P. et al., 2010, Breakdown of within- and between-network Resting State Functional Magnetic Resonance Imaging Connectivity during Propofol-induced Loss of Consciousness: Anesthesiology, v. 113, no. 5, p. 1038–1053, doi:10.1097/aln.0b013e3181f697f5.

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

Brewer, J. A., P. D. Worhunsky, J. R. Gray, Y.-Y. Tang, J. Weber, and H. Kober, 2011, Meditation experience is associated with differences in default mode network activity and connectivity: Proceedings of the National Academy of Sciences, v. 108, no. 50, p. 20254–20259, doi:10.1073/pnas.1112029108.

BRICE, D. D., R. R. HETHERINGTON, and J. E. UTTING, 1970, A SIMPLE STUDY OF AWARENESS AND DREAMING DURING ANAESTHESIA: BJA: British Journal of Anaesthesia, v. 42, no. 6, p. 535–542, doi:10.1093/bja/42.6.535.

Brohan, J., and B. G. Goudra, 2017, The Role of GABA Receptor Agonists in Anesthesia and Sedation: CNS Drugs, v. 31, no. 10, p. 845–856, doi:10.1007/s40263-017-0463-7.

Brown, E. N., R. Lydic, and N. D. Schiff, 2010, General Anesthesia, Sleep, and Coma: The New England Journal of Medicine, v. 363, no. 27, p. 2638–2650, doi:10.1056/nejmra0808281.

Brualla, J., M. F. Romero, M. Serrano, and J. R. Valdizán, 1998, Auditory event-related potentials to semantic priming during sleep.: Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, v. 108, no. 3, p. 283–290, doi:10.1016/s0168-5597(97)00102-0.

Bruhn, J., T. W. Bouillon, and S. L. Shafer, 2000, Bispectral Index (BIS) and Burst Suppression: Revealing a Part of the BIS Algorithm: Journal of Clinical Monitoring and Computing, v. 16, no. 8, p. 593–596, doi:10.1023/a:1012216600170.

Bullmore, E., and O. Sporns, 2009, Complex brain networks: graph theoretical analysis of structural and functional systems: Nature Reviews Neuroscience, v. 10, no. 3, p. 186–198, doi:10.1038/nrn2575.

Bullmore E, and O. Sporns, 2012, The economy of brain network organization. Nat Rev Neurosci. Apr 13;13(5):336-49. doi: 10.1038/nrn3214. PMID: 22498897.

CALDWELL, C. B., and J. B. GROSS, 1982, Physostigmine Reversal of Midazolam-induced Sedation: Anesthesiology, v. 57, no. 2, p. 125–126, doi:10.1097/00000542-198208000-00011.

Canolty, R. T., E. Edwards, S. S. Dalal, M. Soltani, S. S. Nagarajan, H. E. Kirsch, M. S. Berger, N. M. Barbaro, and R. T. Knight, 2006, High gamma power is phase-locked to theta oscillations in human neocortex.: Science (New York, N.Y.), v. 313, no. 5793, p. 1626 1628, doi:10.1126/science.1128115.

Carhart-Harris, R. L. et al., 2012, Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin: Proceedings of the National Academy of Sciences, v. 109, no. 6, p. 2138–2143, doi:10.1073/pnas.1119598109.

Carrière, M., H. Cassol, C. Aubinet, R. Panda, A. Thibaut, S. K. Larroque, S. K, J. Simon, C. Martial, M. A. Bahri, C. Chatelle, G. Martens, S. Chenny, S. Laureys, O. Gosseries, 2020, Auditory localization should be considered as a sign of minimally conscious state based on multimodal findings. Brain communications, 2(2), fcaa195.

Casali, A. G. et al., 2013, A Theoretically Based Index of Consciousness Independent of Sensory Processing and Behavior: Science Translational Medicine, v. 5, no. 198, p. 198ra105-198ra105, doi:10.1126/scitranslmed.3006294.

Cavanna, F., M. G. Vilas, M. Palmucci, and E. Tagliazucchi, 2018, Dynamic functional connectivity and brain metastability during altered states of consciousness: NeuroImage, v. 180, no. Pt B, p. 383–395, doi:10.1016/j.neuroimage.2017.09.065.

Cavazzuti, M., C. A. Porro, A. Barbieri, A. Galetti, BRAIN AND SPINAL CORD METABOLIC ACTIVITY DURING PROPOFOL ANAESTHESIA, 1991, British Journal of Anaesthesia, April, Volume 66, Issue 4, Pages 490–495, https://doi.org/10.1093/bja/66.4.490

Cavinato, M., U. Freo, C. Ori, M. Zorzi, P. Tonin, F. Piccione, and A. Merico, 2009, Post-acute P300 predicts recovery of consciousness from traumatic vegetative state: Brain Injury, v. 23, no. 12, p. 973–980, doi:10.3109/02699050903373493.

Chalmers, D. J, 1995, Facing up to the problem of consciousness: Journal of consciousness studies, v. 2, no 3, p. 200–219.

Chan, M. T. V., B. C. P. Cheng, T. M. C. Lee, T. Gin, and C. T. Group, 2013, BIS-guided Anesthesia Decreases Postoperative Delirium and Cognitive Decline: Journal of Neurosurgical Anesthesiology, v. 25, no. 1, p. 33–42, doi:10.1097/ana.0b013e3182712fba.

Chemali, J. J., C. J. V. Dort, E. N. Brown, and K. Solt, 2012, Active emergence from propofol general anesthesia is induced by methylphenidate.: Anesthesiology, v. 116, no. 5, p. 998 1005, doi:10.1097/aln.0b013e3182518bfc.

Chennu, S., S. O'Connor, R. Adapa, D. K. Menon, and T. A. Bekinschtein, 2016, Brain Connectivity Dissociates Responsiveness from Drug Exposure during Propofol-Induced Transitions of Consciousness: PLOS Computational Biology, v. 12, no. 1, p. e1004669, doi:10.1371/journal.pcbi.1004669.s002.

Ching, S., and E. N. Brown, 2014, Modeling the dynamical effects of anesthesia on brain circuits: Current Opinion in Neurobiology, v. 25, p. 116–122, doi:10.1016/j.conb.2013.12.011.

Ching, S., A. Cimenser, P. L. Purdon, E. N. Brown, and N. J. Kopell, 2010, Thalamocortical model for a propofol-induced -rhythm associated with loss of consciousness: Proceedings of the National Academy of Sciences, v. 107, no. 52, p. 22665 22670, doi:10.1073/pnas.1017069108.

Chui, J., R. Mariappan, J. Mehta, P. Manninen, and L. Venkatraghavan, 2014, Comparison of propofol and volatile agents for maintenance of anesthesia during elective craniotomy procedures: systematic review and meta-analysis: Canadian Journal of Anesthesia/Journal canadien d'anesthésie, v. 61, no. 4, p. 347–356, doi:10.1007/s12630-014-0118-9.

Clark, D. L., and B. S. Rosner, 1973, Neurophysiologic Effects of General Anesthetics: Anesthesiology, v. 38, no. 6, p. 564–582, doi:10.1097/00000542-197306000-00011.

Colombo, M. A. et al., 2019, The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine: NeuroImage, v. 189, p. 631–644, doi:10.1016/j.neuroimage.2019.01.024.

Comtat, C., F. C. Sureau, M. Sibomana, I. K. Hong, N. Sjöholm, and R. Trébossen, 2008, Image Based Resolution Modeling for the HRRT OSEM Reconstructions Software: 2008 IEEE Nuclear Science Symposium Conference Record, p. 4120–4123, doi:10.1109/nssmic.2008.4774188.

Correa-Sales, C., B. C. Rabin, and M. Maze, 1992, A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats.: Anesthesiology: The Journal of the American Society of Anesthesiologists, v. 76, no. 6, p. 948 952.

CORSSEN, G., E. F. DOMINO, and R. L. BREE, 1969, Electroencephalographic Effects of Ketamine Anesthesia in Children.: Anesthesia & Analgesia, v. 48, no. 1, p. 141, doi:10.1213/00000539-196901000-00029.

Crick, F., 1995, The Astonishing Hypothesis: The scientific search for the soul. A Touchstone Book, Published by Simon & Schuster, New York

Cruse, D., S. Chennu, C. Chatelle, T. A. Bekinschtein, D. Fernández-Espejo, J. D. Pickard, S. Laureys, and A. M. Owen, 2012, Bedside detection of awareness in the vegetative state: a cohort study: The Lancet, v. 378, no. 9809, p. 2088–2094, doi:10.1016/s0140-6736(11)61224-5.

Cul, A. D., S. Baillet, and S. Dehaene, 2007, Brain Dynamics Underlying the Nonlinear Threshold for Access to Consciousness: PLoS Biology, v. 5, no. 10, p. e260, doi:10.1371/journal.pbio.0050260.

Daltrozzo, J., N. Wioland, V. Mutschler, and B. Kotchoubey, 2007, Predicting coma and other low responsive patients outcome using event-related brain potentials: A meta-analysis: Clinical Neurophysiology, v. 118, no. 3, p. 606–614, doi:10.1016/j.clinph.2006.11.019.

Dam, M., C. Ori, G. Pizzolato, G. L. Ricchieri, A. Pellegrini, G. P. Giron, L. Battistin, 1990, The effects of propofol anesthesia on local cerebral glucose utilization in the rat. The Journal of the American Society of Anesthesiologists, 73(3), 499-505.

Dehaene, S., and J.-P. Changeux, 2011, Experimental and Theoretical Approaches to Conscious Processing: Neuron, v. 70, no. 2, p. 200–227, doi:10.1016/j.neuron.2011.03.018.

Dehaene, S., N. Molko, L. Cohen, and A. J. Wilson, 2004, Arithmetic and the brain: Current Opinion in Neurobiology, v. 14, no. 2, p. 218–224, doi:10.1016/j.conb.2004.03.008.

Delorme, A., and S. Makeig, 2004, EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis: Journal of Neuroscience Methods, v. 134, no. 1, p. 9 21, doi:10.1016/j.jneumeth.2003.10.009.

Del Pin, S. H., Z. Skóra, K. Sandberg, M. Overgaard, and M. Wierzchoń, 2021, Comparing theories of consciousness: why it matters and how to do it: Neuroscience of Consciousness, v. 2021, no. 2, p. niab019, doi:10.1093/nc/niab019.

Dement, W., and N. Kleitman, 1957, The relation of eye movements during sleep to dream activity: An objective method for the study of dreaming: Journal of Experimental Psychology, v. 53, no. 5, p. 339–346, doi:10.1037/h0048189.

Demertzi, A., A. Soddu, and S. Laureys, 2013, Consciousness supporting networks: Current Opinion in Neurobiology, v. 23, no. 2, p. 239–244, doi:10.1016/j.conb.2012.12.003.

Deshpande, G., C. Kerssens, P. S. Sebel, and X. Hu, 2010, Altered local coherence in the default mode network due to sevoflurane anesthesia: Brain Research, v. 1318, p. 110–121, doi:10.1016/j.brainres.2009.12.075.

Desmurget, M., K. T. Reilly, N. Richard, A. Szathmari, C. Mottolese, and A. Sirigu, 2009, Movement Intention After Parietal Cortex Stimulation in Humans: Science, v. 324, no. 5928, p. 811–813, doi:10.1126/science.1169896.

Chambers, C. D., J. M. Payne, M. G. Stokes, and J. B. Mattingley, 2004, Fast and slow parietal pathways mediate spatial attention: Nature Neuroscience, v. 7, no. 3, p. 217–218, doi:10.1038/nn1203.

Dickinson, R., B. K. Peterson, P. Banks, C. Simillis, J. C. S. Martin, C. A. Valenzuela, M. Maze, and N. P. Franks, 2007, Competitive Inhibition at the Glycine Site of the N-Methyl-d-aspartate Receptor by the Anesthetics Xenon and Isoflurane: Anesthesiology, v. 107, no. 5, p. 756–767, doi:10.1097/01.anes.0000287061.77674.71.

Courtin R. F., R. G. Bickford, A. Faulconer Jr, 1950, The classification and significance of electro-encephalographic patterns produced by nitrous oxide-ether anesthesia during surgical operations. Proc Staff Meet Mayo Clin, Apr 12;25(8):197-206. PMID: 15412959.

Crino, P. B., J. H. Morrison, P. R. Hof, 1993, Neurobiology of Cingulate Cortex and Limbic Thalamus: a Comprehensive Handbook (eds Vogt, B. A. & Gabriel, M.) 285–299 (Birkhäuser, Boston).

Doerig, A., A. Schurger, K. Hess, and M. H. Herzog, 2019, The unfolding argument: Why IIT and other causal structure theories cannot explain consciousness: Consciousness and Cognition, v. 72, p. 49–59, doi:10.1016/j.concog.2019.04.002.

Donoghue, J. A., A. M. Bastos, J. Yanar, S. Kornblith, M. Mahnke, E. N. Brown, and E. K. Miller, 2019, Neural signatures of loss of consciousness and its recovery by thalamic stimulation: bioRxiv, p. 806687, doi:10.1101/806687.

Dowd, N. P., D. C. H. Cheng, J. M. Karski, D. T. Wong, J. A. C. Munro, and A. N. Sandler, 1998, Intraoperative Awareness in Fast-track Cardiac Anesthesia: Anesthesiology, v. 89, no. 5, p. 1068–1073, doi:10.1097/00000542-199811000-00006.

Dutta, S., R. Lal, M. D. Karol, T. Cohen, and T. Ebert, 2000, Influence of cardiac output on dexmedetomidine pharmacokinetics.: Journal of pharmaceutical sciences, v. 89, no. 4, p. 519 527, doi:10.1002/(sici)1520-6017(200004)89:4<519::aid-jps9>3.0.co;2-u.

Edlow, B. L. et al., 2020, Personalized Connectome Mapping to Guide Targeted Therapy and Promote Recovery of Consciousness in the Intensive Care Unit: Neurocritical Care, v. 33, no. 2, p. 364–375, doi:10.1007/s12028-020-01062-7.

Edmonds HL Jr, M. Paloheimo, 1985, Computerized monitoring of EMG and EEG during anesthesia: an evaluation of the anesthesia and brain activity monitor (ABM). Int J Clin Monit Comp; 1:201–210.

Eichenlaub, J.-B., E. van Rijn, M. G. Gaskell, P. A. Lewis, E. Maby, J. Malinowski, M. P. Walker, F. Boy, and M. Blagrove, 2018, Incorporation of recent waking-life experiences in dreams correlates with frontal theta activity in REM sleep: Social Cognitive and Affective Neuroscience, v. 13, no. 6, doi:10.1093/scan/nsy041.

Eichhorn, J. H., 1989, Prevention of intraoperative anesthesia accidents and related severe injury through safety monitoring. Anesthesiology, 70:572–577

Estraneo, A., S. Fiorenza, A. Magliacano, R. Formisano, D. Mattia, A. Grippo, A. M. Romoli, E. Angelakis, H. Cassol, A. Thibaut, O. Gosseries, G. Lamberti, E. Noé, S. Bagnato, B. L., Edlow, C. Chatelle, N. Lejeune, V. Veeramuthu, M. Bartolo, J. Toppi, N. Zasler, C. Schnakers, L. Trojano, H, 2020, Multicenter prospective study on predictors of short-term outcome in disorders of consciousness. Neurology, 95(11), e1488–e1499. https://doi.org/10.1212/wnl.0000000000010254

Faugeras, F. et al., 2011, Probing consciousness with event-related potentials in the vegetative state: Neurology, v. 77, no. 3, p. 264–268, doi:10.1212/wnl.0b013e3182217ee8.

Faulconer A. Jr, 1952, Correlation of concentrations of ether in arterial blood with electro-encephalographic patterns occurring during ether-oxygen and during nitrous oxide, oxygen and ether anesthesia of human surgical patients, Anesthesiology, Jul;13(4):361-9. doi: 10.1097/00000542-195207000-00004. PMID: 14943989.

Ferrarelli, F., M. Massimini, S. Sarasso, A. Casali, B. A. Riedner, G. Angelini, G. Tononi, and R. A. Pearce, 2010, Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness: Proceedings of the National Academy of Sciences, v. 107, no. 6, p. 2681–2686, doi:10.1073/pnas.0913008107.

Findeiss, J. C., G. A. Kien, K. O. W. Huse, H. W. Linde, 1969, Power Spectral Density of the Electroencephalogram During Halothane and Cyclopropane Anesthesia in Man, Anesthesia & Analgesia, Nov, Volume 48 - Issue 6 - p 1018-1023

Fiset, P., T. Paus, T. Daloze, G. Plourde, P. Meuret, V. Bonhomme, N. Hajj-Ali, S. B. Backman, and A. C. Evans, 1999, Brain Mechanisms of Propofol-Induced Loss of Consciousness in Humans: a Positron Emission Tomographic Study: The Journal of Neuroscience, v. 19, no. 13, p. 5506–5513, doi:10.1523/jneurosci.19-13-05506.1999.

Flohr, H., U. Glade, and D. Motzko, 1998, The role of the NMDA synapse in general anesthesia: Toxicology Letters, v. 100, p. 23–29, doi:10.1016/s0378-4274(98)00161-1.

Foulkes, W. D, 1962, Dream reports from different stages of sleep, The Journal of Abnormal and Social Psychology, 65(1), 14

Fox, M. D., A. Z. Snyder, J. L. Vincent, M. Corbetta, D. C. V. Essen, and M. E. Raichle, 2005, The human brain is intrinsically organized into dynamic, anticorrelated functional networks: Proceedings of the National Academy of Sciences of the United States of America, v. 102, no. 27, p. 9673–9678, doi:10.1073/pnas.0504136102.

Franks, N. P., 2008, General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal: Nature Reviews Neuroscience, v. 9, no. 5, p. 370–386, doi:10.1038/nrn2372.

Franks, N. P., and W. R. Lieb, 1988, Volatile general anaesthetics activate a novel neuronal K+ current: Nature, v. 333, no. 6174, p. 662–664, doi:10.1038/333662a0.

Fritz, B. A., P. L. Kalarickal, H. R. Maybrier, M. R. Muench, D. Dearth, Y. Chen, K. E. Escallier, A. B. Abdallah, N. Lin, and M. S. Avidan, 2016, Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium: Anesthesia & Analgesia, v. 122, no. 1, p. 234–242, doi:10.1213/ane.0000000000000989.

Gan, T. J., P. S. Glass, A. Windsor, F. Payne, C. Rosow, P. Sebel, and P. Manberg, 1997, Bispectral Index Monitoring Allows Faster Emergence and Improved Recovery from Propofol, Alfentanil, and Nitrous Oxide Anesthesia: Anesthesiology, v. 87, no. 4, p. 808–815, doi:10.1097/00000542-199710000-00014.

Geukes, S., R. J. Huster, A. Wollbrink, M. Junghöfer, P. Zwitserlood, and C. Dobel, 2013, A Large N400 but No BOLD Effect – Comparing Source Activations of Semantic Priming in Simultaneous EEG-fMRI: PLoS ONE, v. 8, no. 12, p. e84029, doi:10.1371/journal.pone.0084029.

Ghoneim, M. M., 2007, Incidence of and risk factors for awareness during anaesthesia: Best Practice & Research Clinical Anaesthesiology, v. 21, no. 3, p. 327–343, doi:10.1016/j.bpa.2007.05.002.
Ghoneim, M. M., R. I. Block, M. Haffarnan, and M. J. Mathews, 2009, Awareness During Anesthesia; Risk Factors, Causes and Sequelae; A Review of Reported Cases in the Literature: Anesthesia & Analgesia, v. 108, no. 2, p. 527–535, doi:10.1213/ane.0b013e318193c634.
Giacino, J. T. et al., 2002, The minimally conscious state: Neurology, v. 58, no. 3, p. 349–353, doi:10.1212/wnl.58.3.349.
Gibbs FA, LE Gibbs, WG Lennox, 1937, Effect on the electroencephalogram of certain drugs which influence nervous activity, Arch Intern Med 60:154-166
Goldfine, A. M., J. C. Bardin, Q. Noirhomme, J. J. Fins, N. D. Schiff, and J. D. Victor, 2013, Reanalysis of “Bedside detection of awareness in the vegetative state: a cohort study”: The Lancet, v. 381, no. 9863, p. 289–291, doi:10.1016/s0140-6736(13)60125-7.
Greenberg DL, 2007, Comment on "Detecting awareness in the vegetative state", Science, Mar 2;315(5816):1221; author reply 1221. doi: 10.1126/science.1135284. PMID: 17332395.
Greicius M. D., B. Krasnow, A. L. Reiss, V. Menon, 2003, Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A. Jan 7; 100(1): 253-8. doi: 10.1073/pnas.0135058100.
Gugino, L. D., R. J. Chabot, L. S. Prichep, E. R. John, V. Formanek, and L. S. Aglio, 2001, Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane: BJA: British Journal of Anaesthesia, v. 87, no. 3, p. 421–428, doi:10.1093/bja/87.3.421.
Guldenmund, P. et al., 2017, Brain functional connectivity differentiates dexmedetomidine from propofol and natural sleep: British Journal of Anaesthesia, v. 119, no. 4, p. 674–684, doi:10.1093/bja/aex257.
Guldenmund, P. et al., 2016, Propofol-Induced Frontal Cortex Disconnection: A Study of Resting-State Networks, Total Brain Connectivity, and Mean BOLD Signal Oscillation Frequencies: Brain Connectivity, v. 6, no. 3, p. 225–237, doi:10.1089/brain.2015.0369.
Hambrecht-Wiedbusch, V. S., D. Li, and G. A. Mashour, 2017, Paradoxical Emergence: Anesthesiology, v. 126, no. 3, p. 482–494, doi:10.1097/aln.0000000000001512.
Hans, P., and V. Bonhomme, 2006, Why we still use intravenous drugs as the basic regimen for neurosurgical anaesthesia: Current Opinion in Anaesthesiology, v. 19, no. 5, p. 498–503, doi:10.1097/01.aco.0000245274.69292.ad.
Hashmi, J. A., M. L. Loggia, S. Khan, L. Gao, J. Kim, V. Napadow, E. N. Brown, and O. Akeju, 2017, Dexmedetomidine Disrupts the Local and Global Efficiencies of Large-scale Brain Networks.: Anesthesiology, v. 126, no. 3, p. 419–430, doi:10.1097/aln.0000000000001509.
Hautus M. J., 1995, Corrections for extreme proportions and their biasing effects on estimated values of d0 . Behav Res Methods 1995; 27: 46–51
HERING, W., G. GEISSLINGER, H. D. KAMP, M. DINKEL, K. TSCHAIKOWSKY, E. RUGHEIMER, and K. BRUNE, 1994, Changes in the EEG power spectrum after midazolam anaesthesia combined with racemic or S – (+) ketamine: Acta Anaesthesiologica Scandinavica, v. 38, no. 7, p. 719–723, doi:10.1111/j.1399-6576.1994.tb03984.x.
Horovitz, S. G., A. R. Braun, W. S. Carr, D. Picchioni, T. J. Balkin, M. Fukunaga, and J. H. Duyn, 2009, Decoupling of the brain’s default mode network during deep sleep: Proceedings of the National Academy of Sciences, v. 106, no. 27, p. 11376–11381, doi:10.1073/pnas.0901435106.
Hohwy, J., 2009, The neural correlates of consciousness: New experimental approaches needed? Consciousness and Cognition, v. 18, no. 2, p. 428–438, doi:10.1016/j.concog.2009.02.006.
Huang, Z. et al., 2018, Brain imaging reveals covert consciousness during behavioral unresponsiveness induced by propofol.: Scientific reports, v. 8, no. 1, p. 13195, doi:10.1038/s41598-018-31436-z.
Huang, Z., V. Tarnal, P. E. Vlisides, E. L. Janke, A. M. McKinney, P. Picton, G. A. Mashour, and A. G. Hudetz, 2021, Asymmetric neural dynamics characterize loss and recovery of consciousness: NeuroImage, v. 236, p. 118042, doi:10.1016/j.neuroimage.2021.118042.
Huang, Z., J. Zhang, J. Wu, G. A. Mashour, and A. G. Hudetz, 2020, Temporal circuit of macroscale dynamic brain activity supports human consciousness: Science Advances, v. 6, no. 11, p. eaaz0087, doi:10.1126/sciadv.aaz0087.

Hudetz, A. G., 2006, Suppressing consciousness: Mechanisms of general anesthesia, Seminars in Anesthesia, Perioperative Medicine and Pain (Vol. 25, No. 4, pp. 196-204), WB Saunders.

Hudetz A. G., 2009, Cortical Disintegration Mechanism of Anesthetic-Induced Unconsciousness. Suppressing the Mind, Contemporary Clinical Neuroscience, Humana Press. https://doi.org/10.1007/978-1-60761-462-3_5

Hudson, A. E., 2017, Metastability of Neuronal Dynamics during General Anesthesia: Time for a Change in Our Assumptions? Frontiers in Neural Circuits, v. 11, p. 58, doi:10.3389/fncir.2017.00058.

Huupponen, E. et al., 2008, Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep.: Acta Anaesthesiologica Scandinavica, v. 52, no. 2, p. 289–294, doi:10.1111/j.1399-6576.2007.01537.x.

Ihalainen, R., O. Gosseries, F. V. de Steen, F. Raimondo, R. Panda, V. Bonhomme, D. Marinazzo, H. Bowman, S. Laureys, and S. Chennu, 2021, How hot is the hot zone? Computational modelling clarifies the role of parietal and frontoparietal connectivity during anaesthetic-induced loss of consciousness: NeuroImage, v. 231, p. 117841, doi:10.1016/j.neuroimage.2021.117841.

Irifune, M., T. Shimizu, M. Nomoto, and T. Fukuda, 1992, Ketamine-induced anesthesia involves the N-methyl-d-aspartate receptor-channel complex in mice: Brain Research, v. 596, no. 1–2, p. 1–9, doi:10.1016/0006-8993(92)91525-j.

Jankel W. R. and E. Niedermeyer, 1985, Sleep spindles. J Clin Neurophysiol, Jan;2(1):1-35. doi: 10.1097/00004691-198501000-00001. PMID: 3932462.

Jennett B, F Plum, 1972, Persistent vegetative state after brain damage. A syndrome in search of a name. Lancet. Apr 1;1(7753):734-7. doi: 10.1016/s0140-6736(72)90242-5. PMID: 4111204.

Johansson, J., S. Keller, J. Tuisku, and M. Teras, 2016, Performance of an image-based motion compensation algorithm for the hrrt: A striatum-phantom study with true motion: 2016 IEEE Nuclear Science Symposium, Medical Imaging Conference and Room-Temperature Semiconductor Detector Workshop (NSS/MIC/RTSD), p. 1–3, doi:10.1109/nssmic.2016.8069586.

Jordan, D., R. Ilg, V. Riedl, A. Schorer, S. Grimberg, S Neufang, A. Omerovic, S. Berger, G. Untergehrer, C. Preibisch, E. Schulz, T. Schuster, M. Schröter, V. Spoormaker, C. Zimmer, B. Hemmer, A. Wohlschläger, E.F. Kochs, G Schneider, 2013, Simultaneous Electroencephalographic and Functional Magnetic Resonance Imaging Indicate Impaired Cortical Top–Down Processing in Association with Anesthetic-induced Unconsciousness: Anesthesiology, v. 119, no. 5, p. 1031–1042, doi:10.1097/aln.0b013e3182a7ca92.

JORM, C. M., and J. A. STAMFORD, 1993, ACTIONS OF THE HYPNOTIC ANAESTHETIC, DEXMEDETOMIDINE, ON NORADRENALINE RELEASE AND CELL FIRING IN RAT LOCUS COERULEUS SLICES: BJA: British Journal of Anaesthesia, v. 71, no. 3, p. 447–449, doi:10.1093/bja/71.3.447.

Juel, B. E., L. Romundstad, F. Kolstad, J. F. Storm, and P. G. Larsson, 2018, Distinguishing Anesthetized from Awake State in Patients: A New Approach Using One Second Segments of Raw EEG: Frontiers in Human Neuroscience, v. 12, p. 40, doi:10.3389/fnhum.2018.00040.

Jurd, R. et al., 2003, General anesthetic actions in vivo strongly attenuated by a point mutation in the GABAA receptor β3 subunit: The FASEB Journal, v. 17, no. 2, p. 250–252, doi:10.1096/fj.02-0611fje.

Kaisti, K. K., J. W. Långsjö, S. Aalto, V. Oikonen, H. Sipilä, M. Teräs, S. Hinkka, L. Metsähonkala, and H. Scheinin, 2003, Effects of Sevoflurane, Propofol, and Adjunct Nitrous Oxide on Regional Cerebral Blood Flow, Oxygen Consumption, and Blood Volume in Humans: Anesthesiology, v. 99, no. 3, p. 603–613, doi:10.1097/00000542-200309000-00015.

Kaisti, K. K., L. Metsähonkala, M. Teräs, V. Oikonen, S. Aalto, S. Jääskeläinen, S. Hinkka, and H. Scheinin, 2002, Effects of Surgical Levels of Propofol and Sevoflurane Anesthesia on Cerebral Blood Flow in Healthy Subjects Studied with Positron Emission Tomography: Anesthesiology, v. 96, no. 6, p. 1358–1370, doi:10.1097/00000542-200206000-00015.

Kajimura, N. et al., 1999, Activity of Midbrain Reticular Formation and Neocortex during the Progression of Human Non-Rapid Eye Movement Sleep: Journal of Neuroscience, v. 19, no. 22, p. 10065–10073, doi:10.1523/jneurosci.19-22-10065.1999.

Kallioinen, M. et al., 2019, The influence of dexmedetomidine and propofol on circulating cytokine levels in healthy subjects: BMC Anesthesiology, v. 19, no. 1, p. 222, doi:10.1186/s12871-019-0895-3.

Kallionpää, R. E., K. Valli, A. Scheinin, J. Långsjö, A. Maksimow, T. Vahlberg, A. Revonsuo, H. Scheinin, G. A. Mashour, and D. Li, 2020, Alpha band frontal connectivity is a state-specific electroencephalographic correlate of unresponsiveness during exposure to dexmedetomidine and propofol: British Journal of Anaesthesia, v. 125, no. 4, p. 518–528, doi:10.1016/j.bja.2020.05.068.

Kallionpää, R. E., H. Pesonen, A. Scheinin, N. Sandman, R. Laitio, H. Scheinin, A. Revonsuo, and K. Valli, 2019, Single-subject analysis of N400 event-related potential component with five different methods: International Journal of Psychophysiology, v. 144, p. 14–24, doi:10.1016/j.ijpsycho.2019.06.012.

Kaskinoro, K., A. Maksimow, J. Långsjö, R. Aantaa, S. Jääskeläinen, K. Kaisti, M. Särkelä, and H. Scheinin, 2011, Wide inter-individual variability of bispectral index and spectral entropy at loss of consciousness during increasing concentrations of dexmedetomidine, propofol, and sevoflurane: BJA: British Journal of Anaesthesia, v. 107, no. 4, p. 573–580, doi:10.1093/bja/aer196.

Kenny, J. D., N. E. Taylor, E. N. Brown, and K. Solt, 2015, Dextroamphetamine (but Not Atomoxetine) Induces Reanimation from General Anesthesia: Implications for the Roles of Dopamine and Norepinephrine in Active Emergence.: PLOS ONE, v. 10, no. 7, p. e0131914, doi:10.1371/journal.pone.0131914.

KIERSEY, D. K., R. G. BICKFORD, and A. FAULCONER, 1951, ELECTRO-ENCEPHALOGRAPHIC PATTERNS PRODUCED BY THIOPENTAL SODIUM DURING SURGICAL OPERATIONS: DESCRIPTION AND CLASSIFICATION: BJA: British Journal of Anaesthesia, v. 23, no. 3, p. 141–152, doi:10.1093/bja/23.3.141.

Kim, H., J. Y Moon, G. A. Mashour, U. Lee, 2018, Mechanisms of hysteresis in human brain networks during transitions of consciousness and unconsciousness: Theoretical principles and empirical evidence. PLoS computational biology, 14(8), e1006424

Koch, C, 2004, The Quest for Consciousness a Neurobiological Approach, Roberts & Co.

Koch, C., M. Massimini, M. Boly, and G. Tononi, 2016, Neural correlates of consciousness: progress and problems: Nature Reviews Neuroscience, v. 17, no. 5, p. 307–321, doi:10.1038/nrn.2016.22.

Kondziella, D. et al., 2020, European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness: European Journal of Neurology, v. 27, no. 5, p. 741–756, doi:10.1111/ene.14151.

Kreuer, S., A. Biedler, R. Larsen, S. Schoth, S. Altmann, and W. Wilhelm, 2001, The NarcotrendTM–a new EEG monitor designed to measure the depth of anaesthesia A comparison with bispectral index monitoring during propofol-remifentanil-anaesthesia: Der Anaesthesist, v. 50, no. 12, p. 921–925, doi:10.1007/s00101-001-0242-0.

Kreuer, S., and W. Wilhelm, 2006, The Narcotrend monitor: Best Practice & Research Clinical Anaesthesiology, v. 20, no. 1, p. 111–119, doi:10.1016/j.bpa.2005.08.010.

Kuizenga, K., J. M. K. H. Wierda, and C. J. Kalkman, 2001, Biphasic EEG changes in relation to loss of consciousness during induction with thiopental, propofol, etomidate, midazolam or sevoflurane: BJA: British Journal of Anaesthesia, v. 86, no. 3, p. 354–360, doi:10.1093/bja/86.3.354.

Kutas, M., and K. D. Federmeier, 2011, Thirty years and counting: finding meaning in the N400 component of the event-related brain potential (ERP).: Annual review of psychology, v. 62, no. 1, p. 621 647, doi:10.1146/annurev.psych.093008.131123.

Kutas M, S. A. Hillyard, 1980, Reading senseless sentences: brain potentials reflect semantic incongruity, Science; 207: 203–5 11.

Kutas M., S. A. Hillyard, 1989, An electrophysiological probe of incidental semantic association. J Cogn Neurosci; 1: 38–49.

Kwong, K. K., J. W. Belliveau, D. A. Chesler, I. E. Goldberg, R. M. Weisskoff, B. P. Poncelet, D. N. Kennedy, B. E. Hoppel, M. S. Cohen, and R. Turner, 1992, Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation.: Proceedings of the National Academy of Sciences, v. 89, no. 12, p. 5675–5679, doi:10.1073/pnas.89.12.5675.

Laaksonen, L. et al., 2018, Comparative effects of dexmedetomidine, propofol, sevoflurane, and S-ketamine on regional cerebral glucose metabolism in humans: a positron emission tomography study: British Journal of Anaesthesia, v. 121, no. 1, p. 281–290, doi:10.1016/j.bja.2018.04.008.

Lagasse, R. S., 2002, Anesthesia safety: model or myth? A review of the published literature and analysis of current original data. Anesthesiology, 97:1609–1617.

Laine, M., P. Virtanen, 1999, WordMill lexical search program, Center for Cognitive Neuroscience, University of Turku, Finland.

Laitio, R. M. et al., 2007, Effects of Xenon Anesthesia on Cerebral Blood Flow in Humans: Anesthesiology, v. 106, no. 6, p. 1128–1133, doi:10.1097/01.anes.0000267596.57497.92.

Laitio, R. M. et al., 2009, The Effects of Xenon Anesthesia on the Relationship Between Cerebral Glucose Metabolism and Blood Flow in Healthy Subjects; A Positron Emission Tomography Study: Anesthesia & Analgesia, v. 108, no. 2, p. 593–600, doi:10.1213/ane.0b013e31818ffc9d.

Lamme, V. A. F., 2018, Challenges for theories of consciousness: seeing or knowing, the missing ingredient and how to deal with panpsychism: Philosophical Transactions of the Royal Society B: Biological Sciences, v. 373, no. 1755, p. 20170344, doi:10.1098/rstb.2017.0344.

Lamme, V. A. F., and P. R. Roelfsema, 2000, The distinct modes of vision offered by feedforward and recurrent processing: Trends in Neurosciences, v. 23, no. 11, p. 571–579, doi:10.1016/s0166-2236(00)01657-x.

Lassen NA, Ingvar DH, Skinhøj E, 1978, Brain function and blood flow, Sci Am. 1978 Oct;239(4):62-71. doi: 10.1038/scientificamerican1078-62. PMID: 705327.

Lau, E. F., C. Phillips, and D. Poeppel, 2008, A cortical network for semantics: (de)constructing the N400: Nature Reviews Neuroscience, v. 9, no. 12, p. 920–933, doi:10.1038/nrn2532.

Laureys, S., A. M. Owen, and N. D. Schiff, 2004, Brain function in coma, vegetative state, and related disorders: The Lancet Neurology, v. 3, no. 9, p. 537–546, doi:10.1016/s1474-4422(04)00852-x.

Laureys, S. et al., 2000, Auditory processing in the vegetative state: Brain, v. 123, no. 8, p. 1589–1601, doi:10.1093/brain/123.8.1589.

LAUREYS, S., C. LEMAIRE, P. MAQUET, C. PHILLIPS, and G. FRANCK, 1999a, Cerebral metabolism during vegetative state and after recovery to consciousness: Journal of Neurology, Neurosurgery & Psychiatry, v. 67, no. 1, p. 121, doi:10.1136/jnnp.67.1.121.

Laureys, S., S. Goldman, C. Phillips, P. V. Bogaert, J. Aerts, A. Luxen, G. Franck, and P. Maquet, 1999b, Impaired Effective Cortical Connectivity in Vegetative State: Preliminary Investigation Using PET: NeuroImage, v. 9, no. 4, p. 377–382, doi:10.1006/nimg.1998.0414.

Lee, U., S. Ku, G. Noh, S. Baek, B. Choi, and G. A. Mashour, 2013, Disruption of Frontal–Parietal Communication by Ketamine, Propofol, and Sevoflurane: Anesthesiology, v. 118, no. 6, p. 1264–1275, doi:10.1097/aln.0b013e31829103f5.

Lee, H., G. Noh, P. Joo, B. Choi, B. H. Silverstein, M. Kim, J. Wang, W. Jung, and S. Kim, 2017, Diversity of functional connectivity patterns is reduced in propofol-induced unconsciousness: Human Brain Mapping, v. 38, no. 10, p. 4980–4995, doi:10.1002/hbm.23708.

Lee, U., G. Oh, S. Kim, G. Noh, B. Choi, and G. A. Mashour, 2010, Brain Networks Maintain a Scale-free Organization across Consciousness, Anesthesia, and Recovery: Anesthesiology, v. 113, no. 5, p. 1081–1091, doi:10.1097/aln.0b013e3181f229b5.

Legostaeva, L. et al., 2019, Stimulation of the Angular Gyrus Improves the Level of Consciousness: Brain Sciences, v. 9, no. 5, p. 103, doi:10.3390/brainsci9050103.

Levy, D. E., J. J. Sidtis, D. A. Rottenberg, J. O. Jarden, S. C. Strother, V. Dhawan, J. Z. Ginos, M. J. Tramo, A. C. Evans, and F. Plum, 1987, Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients: Annals of Neurology, v. 22, no. 6, p. 673–682, doi:10.1002/ana.410220602.

Li, D. et al., 2019, Dynamic Cortical Connectivity during General Anesthesia in Healthy Volunteers: Anesthesiology, v. Publish Ahead of Print, no. NA;, p. NA;, doi:10.1097/aln.0000000000002656.

Linassi, F., D. P. Obert, E. Maran, P. Tellaroli, M. Kreuzer, R. D. Sanders, and M. Carron, 2021, Implicit Memory and Anesthesia: A Systematic Review and Meta-Analysis: Life, v. 11, no. 8, p. 850, doi:10.3390/life11080850.

Liu, X., K. K. Lauer, B. D. Ward, S. M. Rao, S. Li, and A. G. Hudetz, 2012, Propofol disrupts functional interactions between sensory and high-order processing of auditory verbal memory: Human Brain Mapping, v. 33, no. 10, p. 2487–2498, doi:10.1002/hbm.21385.

Liu, X., K. K. Lauer, B. D. Ward, S.-J. Li, and A. G. Hudetz, 2013, Differential Effects of Deep Sedation with Propofol on the Specific and Nonspecific Thalamocortical Systems: Anesthesiology, v. 118, no. 1, p. 59–69, doi:10.1097/aln.0b013e318277a801.

Llinás R., U. Ribary, D. Contreras, C. Pedroarena, 1998, The neuronal basis for consciousness, Phil. Trans. R. Soc. Lond. B., 353; 1841–1849, http://doi.org/10.1098/rstb.1998.0336

Logothetis, N. K., J. Pauls, M. Augath, T. Trinath, and A. Oeltermann, 2001, Neurophysiological investigation of the basis of the fMRI signal: Nature, v. 412, no. 6843, p. 150–157, doi:10.1038/35084005.

Loomis, A. L., E. N. Harvey, and G. A. Hobart, 1937, Cerebral states during sleep, as studied by human brain potentials: Journal of Experimental Psychology, v. 21, no. 2, p. 127–144, doi:10.1037/h0057431.

Loomis, A. L., E. N. Harvey, and G. Hobart, 1935, POTENTIAL RHYTHMS OF THE CEREBRAL CORTEX DURING SLEEP: Science, v. 81, no. 2111, p. 597–598, doi:10.1126/science.81.2111.597.

López-González, A., R. Panda, A. Ponce-Alvarez, G. Zamora-López, A. Escrichs, C. Martial, A. Thibaut, O. Gosseries, L. M. Kringelbach, J. Annen, S. Laureys,G. Deco, 2021, Loss of consciousness reduces the stability of brain hubs and the heterogeneity of brain dynamics. Communications biology, 4(1), 1-15.

Lull, N., E. Noé, J. J. Lull, J. García-Panach, J. Chirivella, J. Ferri, D. López-Aznar, P. Sopena, and M. Robles, 2010, Voxel-based statistical analysis of thalamic glucose metabolism in traumatic brain injury: Relationship with consciousness and cognition: Brain Injury, v. 24, no. 9, p. 1098–1107, doi:10.3109/02699052.2010.494592.

Luo, T., and L. S. Leung, 2011, Involvement of Tuberomamillary Histaminergic Neurons in Isoflurane Anesthesia: Anesthesiology, v. 115, no. 1, p. 36–43, doi:10.1097/aln.0b013e3182207655.

Långsjö, J. W., M. T. Alkire, K. Kaskinoro, H. Hayama, A. Maksimow, K. Kaisti, S. Aalto, R. Aantaa, S. K. Jääskeläinen, A. Revonsuo, and H. Scheinin, 2012, Returning from Oblivion: Imaging the Neural Core of Consciousness: The Journal of Neuroscience, v. 32, no. 14, p. 4935–4943, doi:10.1523/jneurosci.4962-11.2012.

Långsjö, J. W., K. K. Kaisti, S. Aalto, S. Hinkka, R. Aantaa, V. Oikonen, H. Sipilä, T. Kurki, M. Silvanto, and H. Scheinin, 2003, Effects of Subanesthetic Doses of Ketamine on Regional Cerebral Blood Flow, Oxygen Consumption, and Blood Volume in Humans: Anesthesiology, v. 99, no. 3, p. 614–623, doi:10.1097/00000542-200309000-00016.

Långsjö, J. W., E. Salmi, K. Kaisti, S. Aalto, S. Hinkka, R. Aantaa, V. Oikonen, T. Viljanen, T. Kurki, M. Silvanto, and H. Scheinin, 2004, Effects of Subanesthetic Ketamine on Regional Cerebral Glucose Metabolism in Humans: Anesthesiology, v. 100, no. 5, p. 1065–1071, doi:10.1097/00000542-200405000-00006.

Långsjö, J. W., A. Maksimow, E. Salmi, K. Kaisti, S. Aalto, V. Oikonen, S. Hinkka, R. Aantaa, H. Sipilä, T. Viljanen, R. Parkkola, and H. Scheinin, 2005, S-Ketamine Anesthesia Increases Cerebral Blood Flow in Excess of the Metabolic Needs in Humans: Anesthesiology, v. 103, no. 2, p. 258–268, doi:10.1097/00000542-200508000-00008.

MacKenzie, K. K., A. M. Britt-Spells, L. P. Sands, and J. M. Leung, 2018, Processed Electroencephalogram Monitoring and Postoperative Delirium - A Systematic Review and Meta-Analysis: Anesthesiology, v. 129, no. 3, p. 417–427, doi:10.1097/aln.0000000000002323.

McCarthy, M. M., E. N. Brown, and N. Kopell, 2008, Potential Network Mechanisms Mediating Electroencephalographic Beta Rhythm Changes during Propofol-Induced Paradoxical Excitation: Journal of Neuroscience, v. 28, no. 50, p. 13488 13504, doi:10.1523/jneurosci.3536-08.2008.

McIntosh, A. R., and N. J. Lobaugh, 2004, Partial least squares analysis of neuroimaging data: applications and advances: NeuroImage, v. 23, p. S250–S263, doi:10.1016/j.neuroimage.2004.07.020.

Maksimow, A., M. Sarkela, J. W. Långsjö, E. Salmi, K. K. Kaisti, A. Yli-Hankala, S. Hinkka-Yli-Salomäki, H. Scheinin, and S. K. Jääskeläinen, 2006, Increase in high frequency EEG activity

explains the poor performance of EEG spectral entropy monitor during S-ketamine anesthesia.: Clinical Neurophysiology, v. 117, no. 8, p. 1660 1668, doi:10.1016/j.clinph.2006.05.011.

Maksimow, A., M. Silfverhuth, J. Långsjö, K. Kaskinoro, S. Georgiadis, S. Jääskeläinen, and H. Scheinin, 2014, Directional Connectivity between Frontal and Posterior Brain Regions Is Altered with Increasing Concentrations of Propofol: PLoS ONE, v. 9, no. 11, p. e113616, doi:10.1371/journal.pone.0113616.

Maquet, P., 2000, Functional neuroimaging of normal human sleep by positron emission tomography: Journal of Sleep Research, v. 9, no. 3, p. 207–231, doi:10.1046/j.1365-2869.2000.00214.x.

Maquet, P., C. Degueldre, G. Delfiore, J. Aerts, J.-M. Péters, A. Luxen, and G. Franck, 1997, Functional Neuroanatomy of Human Slow Wave Sleep: Journal of Neuroscience, v. 17, no. 8, p. 2807–2812, doi:10.1523/jneurosci.17-08-02807.1997.

MARSH, B., M. WHITE, N. MORTON, and G. N. C. KENNY, 1991, PHARMACOKINETIC MODEL DRIVEN INFUSION OF PROPOFOL IN CHILDREN: BJA: British Journal of Anaesthesia, v. 67, no. 1, p. 41–48, doi:10.1093/bja/67.1.41.

Martuzzi, R., R. Ramani, M. Qiu, N. Rajeevan, and R. T. Constable, 2010, Functional connectivity and alterations in baseline brain state in humans: NeuroImage, v. 49, no. 1, p. 823 834, doi:10.1016/j.neuroimage.2009.07.028.

Mashour, G. A., 2013, Cognitive unbinding: A neuroscientific paradigm of general anesthesia and related states of unconsciousness: Neuroscience & Biobehavioral Reviews, v. 37, no. 10, p. 2751–2759, doi:10.1016/j.neubiorev.2013.09.009.

Mashour, G. A. et al., 2012, Prevention of intraoperative awareness with explicit recall in an unselected surgical population: a randomized comparative effectiveness trial.: Anesthesiology, v. 117, no. 4, p. 717 725, doi:10.1097/aln.0b013e31826904a6.

Mashour, G. A., 2014, Top-down mechanisms of anesthetic-induced unconsciousness: Frontiers in Systems Neuroscience, v. 8, p. 115, doi:10.3389/fnsys.2014.00115.

Mashour, G. A., and M. S. Avidan, 2015, Intraoperative awareness: controversies and non-controversies: BJA: British Journal of Anaesthesia, v. 115, no. suppl_1, p. i20–i26, doi:10.1093/bja/aev034.

Mashour, G. A., and A. G. Hudetz, 2018, Neural Correlates of Unconsciousness in Large-Scale Brain Networks: Trends in Neurosciences, v. 41, no. 3, p. 150 160, doi:10.1016/j.tins.2018.01.003.

Mason, M. F., M. I. Norton, J. D. V. Horn, D. M. Wegner, S. T. Grafton, and C. N. Macrae, 2007, Wandering Minds: The Default Network and Stimulus-Independent Thought: Science, v. 315, no. 5810, p. 393–395, doi:10.1126/science.1131295.

Massimini, M., F. Ferrarelli, R. Huber, S. K. Esser, H. Singh, and G. Tononi, 2005, Breakdown of Cortical Effective Connectivity During Sleep: Science, v. 309, no. 5744, p. 2228–2232, doi:10.1126/science.1117256.

Mazoyer B, Zago L, Mellet E, Bricogne S, Etard O, Houdé O, Crivello F, Joliot M, Petit L, Tzourio-Mazoyer N, 2001, Cortical networks for working memory and executive functions sustain the conscious resting state in man. Brain Res Bull;54(3):287-98. doi: 10.1016/s0361-9230(00)00437-8. PMID: 11287133.

McCarthy, M. M., E. N. Brown, and N. Kopell, 2008, Potential Network Mechanisms Mediating Electroencephalographic Beta Rhythm Changes during Propofol-Induced Paradoxical Excitation: Journal of Neuroscience, v. 28, no. 50, p. 13488 13504, doi:10.1523/jneurosci.3536-08.2008.

Menon, V., and L. Q. Uddin, 2010, Saliency, switching, attention and control: a network model of insula function: Brain Structure and Function, v. 214, no. 5–6, p. 655–667, doi:10.1007/s00429-010-0262-0.

Mensen, A., O. Bodart, A. Thibaut, S. Wannez, J. Annen, S. Laureys, and O. Gosseries, 2020, Decreased Evoked Slow-Activity After tDCS in Disorders of Consciousness: Frontiers in Systems Neuroscience, v. 14, p. 62, doi:10.3389/fnsys.2020.00062.

Meuret, P., S. B. Backman, V. Bonhomme, G. Plourde, and P. Fiset, 2000, Physostigmine Reverses Propofol-induced Unconsciousness and Attenuation of the Auditory Steady State Response and Bispectral Index in Human Volunteers: Anesthesiology, v. 93, no. 3, p. 708, doi:10.1097/00000542-200009000-00020.

Mhuircheartaigh, R. N., D. Rosenorn-Lanng, R. Wise, S. Jbabdi, R. Rogers, and I. Tracey, 2010, Cortical and Subcortical Connectivity Changes during Decreasing Levels of Consciousness in Humans: A Functional Magnetic Resonance Imaging Study using Propofol: The Journal of Neuroscience, v. 30, no. 27, p. 9095–9102, doi:10.1523/jneurosci.5516-09.2010.

Mhuircheartaigh, R. N., C. Warnaby, R. Rogers, S. Jbabdi, and I. Tracey, 2013, Slow-wave activity saturation and thalamocortical isolation during propofol anesthesia in humans.: Science translational medicine, v. 5, no. 208, p. 208ra148 208ra148, doi:10.1126/scitranslmed.3006007.

Mišić, B., R. F. Betzel, M. A. de Reus, M. P. van den Heuvel, M. G. Berman, A. R. McIntosh, and O. Sporns, 2016, Network-Level Structure-Function Relationships in Human Neocortex.: Cerebral cortex (New York, N.Y. : 1991), v. 26, no. 7, p. 3285–96, doi:10.1093/cercor/bhw089.

Mitra, P., 2007, Observed Brain Dynamics: Oxford University Press, Oxford University Press.

Monti, M. M., E. S. Lutkenhoff, M. Rubinov, P. Boveroux, A. Vanhaudenhuyse, O. Gosseries, M.-A. Bruno, Q. Noirhomme, M. Boly, and S. Laureys, 2013, Dynamic Change of Global and Local Information Processing in Propofol-Induced Loss and Recovery of Consciousness: PLoS Computational Biology, v. 9, no. 10, p. e1003271, doi:10.1371/journal.pcbi.1003271.

Monti, M. M., A. Vanhaudenhuyse, M. R. Coleman, M. Boly, J. D. Pickard, L. Tshibanda, A. M. Owen, and S. Laureys, 2010, Willful Modulation of Brain Activity in Disorders of Consciousness: The New England Journal of Medicine, v. 362, no. 7, p. 579–589, doi:10.1056/nejmoa0905370.

Moore, J. T., J. Chen, B. Han, Q. C. Meng, S. C. Veasey, S. G. Beck, and M. B. Kelz, 2012, Direct Activation of Sleep-Promoting VLPO Neurons by Volatile Anesthetics Contributes to Anesthetic Hypnosis: Current Biology, v. 22, no. 21, p. 2008–2016, doi:10.1016/j.cub.2012.08.042.

Mukamel, E. A. et al., 2014, A Transition in Brain State during Propofol-Induced Unconsciousness: Journal of Neuroscience, v. 34, no. 3, p. 839 845, doi:10.1523/jneurosci.5813-12.2014.

Münte, S., T. F. Münte, J. Grotkamp, G. Haeseler, K. Raymondos, S. Piepenbrock, and G. Kraus, 2003, Implicit Memory Varies as a Function of Hypnotic Electroencephalogram Stage in Surgical Patients: Anesthesia&Analgesia, v. 97, no. 1, p. 132–138, doi:10.1213/01.ane.0000068828.76045.c3.

Myles, P. S., K. Leslie, J. McNeil, A. Forbes, and M. Chan, 2004, Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial: The Lancet, v. 363, no. 9423, p. 1757 1763, doi:10.1016/s0140-6736(04)16300-9.

Nachev P, M. Husain M, 2007, Comment on "Detecting awareness in the vegetative state", Science, Mar 2;315(5816):1221. doi: 10.1126/science.1135096. PMID: 17332394; PMCID: PMC2658464.

Nacif-Coelho, C., C. Correa-Sales, L. L. Chang, and M. Maze, 1994, Perturbation of Ion Channel Conductance Alters the Hypnotic Response to the α2-Adrenergic Agonist Dexmedetomidine in the Locus Coeruleus of the Rat: Anesthesiology, v. 81, no. 6, p. 1527–1534, doi:10.1097/00000542-199412000-00029.

Nagel, T., 1974, What Is It Like to Be a Bat? The Philosophical Review, v. 83, no. 4, p. 435–450, doi:10.2307/2183914.

Naitoh P, V. Antony-Baas, A. Muzet, J. Ehrhart, 1982, Dynamic relation of sleep spindles and K-complexes to spontaneous phasic arousal in sleeping human subjects. Sleep; 5(1):58-72. doi: 10.1093/sleep/5.1.58. PMID: 7071452.

Nelson, L. E., T. Z. Guo, J. Lu, C. B. Saper, N. P. Franks, and M. Maze, 2002, The sedative component of anesthesia is mediated by GABAA receptors in an endogenous sleep pathway: Nature Neuroscience, v. 5, no. 10, p. 979–984, doi:10.1038/nn913.

Nelson, L. E., J. Lu, T. Guo, C. B. Saper, N. P. Franks, and M. Maze, 2003, The α2-Adrenoceptor Agonist Dexmedetomidine Converges on an Endogenous Sleep-promoting Pathway to Exert Its Sedative Effects: Anesthesiology, v. 98, no. 2, p. 428–436, doi:10.1097/00000542-200302000-00024.

Nielsen, T. A., 2000, A review of mentation in REM and NREM sleep: “Covert” REM sleep as a possible reconciliation of two opposing models: Behavioral and Brain Sciences, v. 23, no. 6, p. 851–866, doi:10.1017/s0140525x0000399x.

Nieminen, J. O., O. Gosseries, M. Massimini, E. Saad, A. D. Sheldon, M. Boly, F. Siclari, B. R. Postle, and G. Tononi, 2016, Consciousness and cortical responsiveness: a within-state study during non-rapid eye movement sleep: Scientific Reports, v. 6, no. 1, p. 30932, doi:10.1038/srep30932.

Noel, J.-P., Y. Ishizawa, S. R. Patel, E. N. Eskandar, and M. T. Wallace, 2019, Leveraging Nonhuman Primate Multisensory Neurons and Circuits in Assessing Consciousness Theory: The Journal of Neuroscience, v. 39, no. 38, p. 7485–7500, doi:10.1523/jneurosci.0934-19.2019.

Nofzinger, E. A. et al., 2002, Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking: Brain, v. 125, no. 5, p. 1105–1115, doi:10.1093/brain/awf103.

Nofzinger, E. A., M. A. Mintun, M. Wiseman, D. J. Kupfer, and R. Y. Moore, 1997, Forebrain activation in REM sleep: an FDG PET study1Presented in abstract form at the Society for Neuroscience Meeting, 1996.1: Brain Research, v. 770, no. 1–2, p. 192–201, doi:10.1016/s0006-8993(97)00807-x.

Noreika, V., L. Jylhänkangas, L. Móró, K. Valli, K. Kaskinoro, R. Aantaa, H. Scheinin, and A. Revonsuo, 2011, Consciousness lost and found: Subjective experiences in an unresponsive state: Brain and Cognition, v. 77, no. 3, p. 327–334, doi:10.1016/j.bandc.2011.09.002.

Nutt, D., 2006, GABAA Receptors: Subtypes, Regional Distribution, and Function: Journal of Clinical Sleep Medicine, v. 02, no. 02, doi:10.5664/jcsm.26525.

Odegaard, B., R. T. Knight, and H. Lau, 2017, Should a Few Null Findings Falsify Prefrontal Theories of Conscious Perception? The Journal of Neuroscience, v. 37, no. 40, p. 9593–9602, doi:10.1523/jneurosci.3217-16.2017.

Ogawa, S., D. W. Tank, R. Menon, J. M. Ellermann, S. G. Kim, H. Merkle, and K. Ugurbil, 1992, Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging: Proceedings of the National Academy of Sciences, v. 89, no. 13, p. 5951–5955, doi:10.1073/pnas.89.13.5951.

Onslow, A. C. E., R. Bogacz, and M. W. Jones, 2011, Quantifying phase–amplitude coupling in neuronal network oscillations: Progress in Biophysics and Molecular Biology, v. 105, no. 1–2, p. 49–57, doi:10.1016/j.pbiomolbio.2010.09.007.

Owen, A. M., M. R. Coleman, M. Boly, M. H. Davis, S. Laureys, and J. D. Pickard, 2006, Detecting Awareness in the Vegetative State: Science, v. 313, no. 5792, p. 1402–1402, doi:10.1126/science.1130197.

Palanca, B. J. A., A. Mitra, L. Larson-Prior, A. Z. Snyder, M. S. Avidan, and M. E. Raichle, 2015, Resting-state Functional Magnetic Resonance Imaging Correlates of Sevoflurane-induced Unconsciousness: Anesthesiology, v. 123, no. 2, p. 346–356, doi:10.1097/aln.0000000000000731.

Pal, D., J. G. Dean, T. Liu, D. Li, C. J. Watson, A. G. Hudetz, and G. A. Mashour, 2018, Differential Role of Prefrontal and Parietal Cortices in Controlling Level of Consciousness: Current Biology, v. 28, no. 13, p. 2145-2152.e5, doi:10.1016/j.cub.2018.05.025.

Patel, A. J., E. Honoré, F. Lesage, M. Fink, G. Romey, and M. Lazdunski, 1999, Inhalational anesthetics activate two-pore-domain background K+ channels: Nature Neuroscience, v. 2, no. 5, p. 422–426, doi:10.1038/8084.

Paus, T., 2001, Primate anterior cingulate cortex: Where motor control, drive and cognition interface: Nature Reviews Neuroscience, v. 2, no. 6, p. 417–424, doi:10.1038/35077500.

Peltier, S. J., C. Kerssens, S. B. Hamann, P. S. Sebel, M. Byas-Smith, and X. Hu, 2005, Functional connectivity changes with concentration of sevoflurane anesthesia: NeuroReport, v. 16, no. 3, p. 285–288, doi:10.1097/00001756-200502280-00017.

Petersen, K. D., U. Landsfeldt, G. E. Cold, C. B. Petersen, S. Mau, J. Hauerberg, P. Holst, and K. S. Olsen, 2003, Intracranial Pressure and Cerebral Hemodynamic in Patients with Cerebral Tumors: Anesthesiology, v. 98, no. 2, p. 329–336, doi:10.1097/00000542-200302000-00010.

Peterson, A., S. Aas, and D. Wasserman, 2021, What Justifies the Allocation of Health Care Resources to Patients with Disorders of Consciousness? AJOB Neuroscience, v. 12, no. 2–3, p. 1–13, doi:10.1080/21507740.2021.1896594.

Petrenko, A. B., T. Yamakura, N. Fujiwara, A. R. Askalany, H. Baba, and K. Sakimura, 2004, Reduced Sensitivity to Ketamine and Pentobarbital in Mice Lacking the N-Methyl-d-Aspartate Receptor GluR&egr;1 Subunit: Anesthesia & Analgesia, v. 99, no. 4, p. 1136–1140, doi:10.1213/01.ane.0000131729.54986.30.

Petrenko, A. B., T. Yamakura, K. Sakimura, and H. Baba, 2014, Defining the role of NMDA receptors in anesthesia: Are we there yet? European Journal of Pharmacology, v. 723, p. 29–37, doi:10.1016/j.ejphar.2013.11.039.

Perrin, F., H. Bastuji, and L. Garcia-Larrea, 2002, Detection of verbal discordances during sleep: Neuroreport, v. 13, no. 10, p. 1345–1349, doi:10.1097/00001756-200207190-00026.

Pilge, S., J. Blum, E. F. Kochs, S.-A. Schöniger, M. Kreuzer, and G. Schneider, 2011, Does the Cerebral State Index Separate Consciousness from Unconsciousness? Anesthesia & Analgesia, v. 113, no. 6, p. 1403–1410, doi:10.1213/ane.0b013e31823007cd

Plourde, G., P. Belin, D. Chartrand, P. Fiset, S. B. Backman, G. Xie, and R. J. Zatorre, 2006, Cortical Processing of Complex Auditory Stimuli during Alterations of Consciousness with the General Anesthetic Propofol: Anesthesiology, v. 104, no. 3, p. 448–457, doi:10.1097/00000542-200603000-00011.

Posner, M. I., M. K. Rothbart, B. E. Sheese, and Y. Tang, 2007, The anterior cingulate gyrus and the mechanism of self-regulation: Cognitive, Affective, & Behavioral Neuroscience, v. 7, no. 4, p. 391–395, doi:10.3758/cabn.7.4.391.

Possati, S., A. Faulconer Jr, R. G. Bickford, R. C. Hunter, 1953, Electroencephalographic patterns during anesthesia with cyclopropane; correlation with concentration of cyclopropane in arterial blood, Curr Res Anesth Analg, Mar-Apr; 32(2):130-5. PMID: 13043241.

Pribish, A., N. Wood, and A. Kalava, 2020, A Review of Nonanesthetic Uses of Ketamine: Anesthesiology Research and Practice, v. 2020, p. 5798285, doi:10.1155/2020/5798285.

Prielipp, R. C. et al., 2002, Dexmedetomidine-Induced Sedation in Volunteers Decreases Regional and Global Cerebral Blood Flow: Anesthesia & Analgesia, v. 95, no. 4, p. 1052–1059, doi:10.1213/00000539-200210000-00048.

Purdon, P. L. et al., 2013, Electroencephalogram signatures of loss and recovery of consciousness from propofol: Proceedings of the National Academy of Sciences, v. 110, no. 12, p. E1142–E1151, doi:10.1073/pnas.1221180110.

Purdon, P. L., A. Sampson, K. J. Pavone, and E. N. Brown, 2015, Clinical Electroencephalography for Anesthesiologists: Part I: Background and Basic Signatures.: Anesthesiology, v. 123, no. 4, p. 937 960, doi:10.1097/aln.0000000000000841.

Qin, P., H. Di, X. Yan, S. Yu, D. Yu, S. Laureys, and X. Weng, 2008, Mismatch negativity to the patient's own name in chronic disorders of consciousness: Neuroscience Letters, v. 448, no. 1, p. 24–28, doi:10.1016/j.neulet.2008.10.029.

Qin, P. et al., 2015, How are different neural networks related to consciousness? Annals of Neurology, v. 78, no. 4, p. 594–605, doi:10.1002/ana.24479.

Raccah, O., N. Block, and K. C. R. Fox, 2021, Does the Prefrontal Cortex Play an Essential Role in Consciousness? Insights from Intracranial Electrical Stimulation of the Human Brain: The Journal of Neuroscience, v. 41, no. 10, p. 2076–2087, doi:10.1523/jneurosci.1141-20.2020.

Radek, L. et al., 2018, Dreaming and awareness during dexmedetomidine- and propofol-induced unresponsiveness: British Journal of Anaesthesia, v. 121, no. 1, p. 260–269, doi:10.1016/j.bja.2018.03.014.

Raichle, M. E., 2001, Bold insights: Nature, v. 412, no. 6843, p. 128–130, doi:10.1038/35084300.

Raichle, M. E., 2010, Two views of brain function: Trends in Cognitive Sciences, v. 14, no. 4, p. 180–190, doi:10.1016/j.tics.2010.01.008.

Raichle, M. E., A. M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard, and G. L. Shulman, 2001, A default mode of brain function: Proceedings of the National Academy of Sciences, v. 98, no. 2, p. 676–682, doi:10.1073/pnas.98.2.676.

Ramaswamy, S. M., M. H. Kuizenga, M. A. S. Weerink, H. E. M. Vereecke, M. M. R. F. Struys, and S. B. Nagaraj, 2019, Novel drug-independent sedation level estimation based on machine learning of quantitative frontal electroencephalogram features in healthy volunteers: British Journal of Anaesthesia, v. 123, no. 4, p. 479–487, doi:10.1016/j.bja.2019.06.004.

Rampil, I. J., 1998, A Primer for EEG Signal Processing in Anesthesia: Anesthesiology, v. 89, no. 4, p. 980–1002, doi:10.1097/00000542-199810000-00023.

Ranft, A. et al., 2016, Neural Correlates of Sevoflurane-induced Unconsciousness Identified by Simultaneous Functional Magnetic Resonance Imaging and Electroencephalography: Anesthesiology, v. 125, no. 5, p. 861–872, doi:10.1097/aln.0000000000001322.

Reardon, S., 2019, Rival theories face off over brain's source of consciousness: Science, v. 366, no. 6463, p. 293–293, doi:10.1126/science.366.6463.293.

Redinbaugh, M. J., J. M. Phillips, N. A. Kambi, S. Mohanta, S. Andryk, G. L. Dooley, M. Afrasiabi, A. Raz, and Y. B. Saalmann, 2020, Thalamus Modulates Consciousness via Layer-Specific Control of Cortex: Neuron, v. 106, no. 1, p. 66-75.e12, doi:10.1016/j.neuron.2020.01.005.

Reynolds, D. S. et al., 2003, Sedation and Anesthesia Mediated by Distinct GABAA Receptor Isoforms: Journal of Neuroscience, v. 23, no. 24, p. 8608–8617, doi:10.1523/jneurosci.23-24-08608.2003.

Rissman, L., and E. T. Paquette, 2020, Ethical and legal considerations related to disorders of consciousness: Current Opinion in Pediatrics, v. 32, no. 6, p. 765–771, doi:10.1097/mop.0000000000000961.

Rohaut, B., F. Faugeras, N. Chausson, J.-R. King, I. E. Karoui, L. Cohen, and L. Naccache, 2015, Probing ERP correlates of verbal semantic processing in patients with impaired consciousness: Neuropsychologia, v. 66, p. 279–292, doi:10.1016/j.neuropsychologia.2014.10.014.

Robinson, L. R., P. J. Micklesen, D. L. Tirschwell, and H. L. Lew, 2003, Predictive value of somatosensory evoked potentials for awakening from coma: Critical Care Medicine, v. 31, no. 3, p. 960–967, doi:10.1097/01.ccm.0000053643.21751.3b.

Rudolf, J., Mehran Ghaemi, Morad Ghaemi, W. F. Haupt, B. Szelies, and W.-D. Heiss, 1999, Cerebral Glucose Metabolism in Acute and Persistent Vegetative State: Journal of Neurosurgical Anesthesiology, v. 11, no. 1, p. 17–24, doi:10.1097/00008506-199901000-00004.

Sanders, R. D. et al., 2017, Incidence of Connected Consciousness after Tracheal Intubation: A Prospective, International, Multicenter Cohort Study of the Isolated Forearm Technique.: Anesthesiology, v. 126, no. 2, p. 214–222, doi:10.1097/aln.0000000000001479.

Sanders, R. D., G. Tononi, S. Laureys, and J. W. Sleigh, 2012, Unresponsiveness ≠ Unconsciousness: Anesthesiology, v. 116, no. 4, p. 946–959, doi:10.1097/aln.0b013e318249d0a7.

Sandin, R. H., G. Enlund, P. Samuelsson, and C. Lennmarken, 2000, Awareness during anaesthesia: a prospective case study: The Lancet, v. 355, no. 9205, p. 707 711, doi:10.1016/s0140-6736(99)11010-9.

Sarasso, S. et al., 2015, Consciousness and Complexity during Unresponsiveness Induced by Propofol, Xenon, and Ketamine.: Current biology : CB, v. 25, no. 23, p. 3099 3105, doi:10.1016/j.cub.2015.10.014.

Sato, Y., E. Kobayashi, T. Murayama, M. Mishina, and N. Seo, 2005, Effect of N-methyl-d-aspartate Receptor ε1 Subunit Gene Disruption of the Action of General Anesthetic Drugs in Mice: Anesthesiology, v. 102, no. 3, p. 557–561, doi:10.1097/00000542-200503000-00013.

SAVOLA, J. -M., H. RUSKOAHO, J. PUURUNEN, J. S. SALONEN, and N. T. KÄRKI, 1986, EVIDENCE FOR MEDETOMIDINE AS A SELECTIVE AND POTENT AGONIST α2-ADRENORECEPTORS: Journal of Autonomic Pharmacology, v. 6, no. 4, p. 275–284, doi:10.1111/j.1474-8673.1986.tb00654.x.

Scheinin H, R. Virtanen, E. MacDonald, R. Lammintausta, M. Scheinin, 1989, Medetomidine – a novel alpha 2-adrenoceptor agonist: a review of its pharmacodynamic effects, Prog Neuropsychopharmacol Biol Psychiatry; 13(5):635-51. doi: 10.1016/0278-5846(89)90051-1. PMID: 2571177.

Schiff, N. D. et al., 2002, Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain: Brain, v. 125, no. 6, p. 1210–1234, doi:10.1093/brain/awf131.

Schiff, N. D. et al., 2007, Behavioural improvements with thalamic stimulation after severe traumatic brain injury: Nature, v. 448, no. 7153, p. 600–603, doi:10.1038/nature06041.

Schlünzen, L., G. E. Cold, M. Rasmussen, and M. S. Vafaee, 2006, Effects of dose-dependent levels of isoflurane on cerebral blood flow in healthy subjects studied using positron emission tomography: Acta Anaesthesiologica Scandinavica, v. 50, no. 3, p. 306–312, doi:10.1111/j.1399-6576.2006.00954.x.

SCHLÜNZEN, L., N. JUUL, K. V. HANSEN, and G. E. COLD, 2012, Regional cerebral blood flow and glucose metabolism during propofol anaesthesia in healthy subjects studied with positron

emission tomography: Acta Anaesthesiologica Scandinavica, v. 56, no. 2, p. 248–255, doi:10.1111/j.1399-6576.2011.02561.x.

SCHLÜNZEN, L., N. JUUL, K. V. HANSEN, A. GJEDDE, and G. E. COLD, 2010, Regional cerebral glucose metabolism during sevoflurane anaesthesia in healthy subjects studied with positron emission tomography: Acta Anaesthesiologica Scandinavica, v. 54, no. 5, p. 603–609, doi:10.1111/j.1399-6576.2010.02208.x.

Schlünzen, L., M. S. Vafaee, G. E. Cold, M. Rasmussen, J. F. Nielsen, and A. Gjedde, 2004, Effects of subanaesthetic and anaesthetic doses of sevoflurane on regional cerebral blood flow in healthy volunteers. A positron emission tomographic study: Acta Anaesthesiologica Scandinavica, v. 48, no. 10, p. 1268–1276, doi:10.1111/j.1399-6576.2004.00505.x.

Schneider, G., E. F. Kochs, B. Horn, M. Kreuzer, and M. Ningler, 2004, Narcotrend® Does Not Adequately Detect the Transition between Awareness and Unconsciousness in Surgical Patients: Anesthesiology, v. 101, no. 5, p. 1105–1111, doi:10.1097/00000542-200411000-00009.

Schoenle, P. W., and W. Witzke, 2004, How vegetative is the vegetative state? Preserved semantic processing in VS patients--evidence from N 400 event-related potentials.: NeuroRehabilitation, v. 19, no. 4, p. 329–34.

Schoenle, P. W., and W. Witzke, 2004, How vegetative is the vegetative state? Preserved semantic processing in VS patients--evidence from N 400 event-related potentials.: NeuroRehabilitation, v. 19, no. 4, p. 329–34.

Schreckenberger, M., C. Lange-Asschenfeldt, C. Lange-Asschenfeld, M. Lochmann, K. Mann, T. Siessmeier, H.-G. Buchholz, P. Bartenstein, and G. Gründer, 2004, The thalamus as the generator and modulator of EEG alpha rhythm: a combined PET/EEG study with lorazepam challenge in humans: NeuroImage, v. 22, no. 2, p. 637 644.

Schröter, M. S., V. I. Spoormaker, A. Schorer, A. Wohlschläger, M. Czisch, E. F. Kochs, C. Zimmer, B. Hemmer, G. Schneider, D. Jordan, R. Ilg, 2012, Spatiotemporal reconfiguration of large-scale brain functional networks during propofol-induced loss of consciousness, Journal of Neuroscience, 32(37), 12832-12840.

Schwartz, S., and P. Maquet, 2002, Sleep imaging and the neuro-psychological assessment of dreams: Trends in Cognitive Sciences, v. 6, no. 1, p. 23–30, doi:10.1016/s1364-6613(00)01818-0.

SCHWARTZ, M. S., S. VIRDEN, and D. F. SCOTT, 1974, Effects of ketamine on the electroencephalograph: Anaesthesia, v. 29, no. 2, p. 135–140, doi:10.1111/j.1365-2044.1974.tb00611.x.

Searle, J. R., 2005, Consciousness: What we still don't know. The New York Review of Books, 52(1), 36-39.

Sebel, P. S., T. A. Bowdle, M. M. Ghoneim, I. J. Rampil, R. E. Padilla, T. J. Gan, and K. B. Domino, 2004, The Incidence of Awareness During Anesthesia: A Multicenter United States Study: Anesthesia & Analgesia, v. 99, no. 3, p. 833 839, doi:10.1213/01.ane.0000130261.90896.6c.

Segal, I. S., R. G. Vickery, J. K. Walton, V. A. Doze, M. Maze, 1988, Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha 2 adrenergic receptor. Anesthesiology, 69(6), 818-823.

Shafiq, F., H. I. Naqvi, and A. Ahmed, 2012, Effects of bispectral index monitoring on isoflurane consumption and recovery profiles for anesthesia in an elderly asian population: Journal of Anaesthesiology, Clinical Pharmacology, v. 28, no. 3, p. 348–352, doi:10.4103/0970-9185.98335.

Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, Petersen SE, 1997, Common Blood Flow Changes across Visual Tasks: II. Decreases in Cerebral Cortex, J Cogn Neurosci;9(5):648-63. doi: 10.1162/jocn.1997.9.5.648. PMID: 23965122.

Siclari, F., B. Baird, L. Perogamvros, G. Bernardi, J. J. LaRocque, B. Riedner, M. Boly, B. R. Postle, and G. Tononi, 2017, The neural correlates of dreaming: Nat. Neurosci., v. 20, no. 6, p. 872–878, doi:10.1038/nn.4545.

Sleigh, J. W., S. Vacas, A. M. Flexman, and P. O. Talke, 2018a, Electroencephalographic Arousal Patterns Under Dexmedetomidine Sedation: Anesthesia & Analgesia, v. 127, no. 4, p. 951–959, doi:10.1213/ane.0000000000003590.

Sleigh, J., C. Warnaby, I. Tracey, 2018b, General anaesthesia as fragmentation of selfhood: insights from electroencephalography and neuroimaging, British journal of anaesthesia, 121(1), 233-240.

Sneyd, J. R., S. K. Samra, B. Davidson, T. Kishimoto, C. Kadoya, and E. F. Domino, 1994, Electrophysiologic Effects of Propofol Sedation: Anesthesia & Analgesia, v. 79, no. 6, p. 1151???1158, doi:10.1213/00000539-199412000-00022.

Sokoloff, L., M. Reivich, C. Kennedy, M. D. Rosiers, C. S. Patlak, K. E. A. Pettigrew, M. Shinohara, 1977, The [14C] deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat, Journal of neurochemistry, 28(5), 897-916.

Sokoloff, L, 1996, The History of Neuroscience in Autobiography, Vol. 1, Washington, DC Soc.

Solt, K., J. F. Cotten, A. Cimenser, K. F. K. Wong, J. J. Chemali, and E. N. Brown, 2011, Methylphenidate Actively Induces Emergence from General Anesthesia: Anesthesiology, v. 115, no. 4, p. 791–803, doi:10.1097/aln.0b013e31822e92e5.

Solt, K., C. J. V. Dort, J. J. Chemali, N. E. Taylor, J. D. Kenny, and E. N. Brown, 2014, Electrical Stimulation of the Ventral Tegmental Area Induces Reanimation from General Anesthesia: Anesthesiology, v. 121, no. 2, p. 311–319, doi:10.1097/aln.0000000000000117.

Sonner, J. M., D. F. Werner, F. P. Elsen, Y. Xing, M. Liao, R. A. Harris, N. L. Harrison, M. S. Fanselow, E. I. Eger, and G. E. Homanics, 2007, Effect of Isoflurane and Other Potent Inhaled Anesthetics on Minimum Alveolar Concentration, Learning, and the Righting Reflex in Mice Engineered to Express α1 γ-Aminobutyric Acid Type A Receptors Unresponsive to Isoflurane: Anesthesiology, v. 106, no. 1, p. 107–113, doi:10.1097/00000542-200701000-00019.

Spindler, L. R. B. et al., 2021, Dopaminergic brainstem disconnection is common to pharmacological and pathological consciousness perturbation: Proceedings of the National Academy of Sciences, v. 118, no. 30, p. e2026289118, doi:10.1073/pnas.2026289118.

Steppacher, I., S. Eickhoff, T. Jordanov, M. Kaps, W. Witzke, and J. Kissler, 2013, N400 predicts recovery from disorders of consciousness: Annals of Neurology, v. 73, no. 5, p. 594–602, doi:10.1002/ana.23835.

Stickgold, R., A. Malia, R. Fosse, R. Propper, and J. A. Hobson, 2001, Brain-Mind States: I. Longitudinal Field Study of Sleep/Wake Factors Influencing Mentation Report Length: Sleep, v. 24, no. 2, p. 171–179, doi:10.1093/sleep/24.2.171.

Tagliazucchi, E., F. von Wegner, A. Morzelewski, V. Brodbeck, S. Borisov, K. Jahnke, and H. Laufs, 2013, Large-scale brain functional modularity is reflected in slow electroencephalographic rhythms across the human non-rapid eye movement sleep cycle: NeuroImage, v. 70, p. 327–339, doi:10.1016/j.neuroimage.2012.12.073.

Talke, P., E. Lobo, and R. Brown, 2003, Systemically Administered α2-Agonist-induced Peripheral Vasoconstriction in Humans: Anesthesiology, v. 99, no. 1, p. 65–70, doi:10.1097/00000542-200307000-00014.

Tammisto T., K. Wirtavuori K, B Rantala, 1983, Estimation of Anaesthetic Depth by monitoring Spontaneous Scalp EMG and Evoked Hypothenar EMG. In: Vickers M.D., Lunn J.N. (eds) Mortality in Anaesthesia. European Academy of Anaesthesiology, vol 3. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-69355-7_22

Taylor, N. E., C. J. V. Dort, J. D. Kenny, J. Pei, J. A. Guidera, K. Y. Vlasov, J. T. Lee, E. S. Boyden, E. N. Brown, and K. Solt, 2016, Optogenetic activation of dopamine neurons in the ventral tegmental area induces reanimation from general anesthesia: Proceedings of the National Academy of Sciences, v. 113, no. 45, p. 12826–12831, doi:10.1073/pnas.1614340113.

Thibaut, A., N. Schiff, J. Giacino, S. Laureys, and O. Gosseries, 2019, Therapeutic interventions in patients with prolonged disorders of consciousness: The Lancet Neurology, v. 18, no. 6, p. 600–614, doi:10.1016/s1474-4422(19)30031-6.

Threlkeld, Z. D., Y. G. Bodien, E. S. Rosenthal, J. T. Giacino, A. Nieto-Castanon, O. Wu, S. Whitfield-Gabrieli, and B. L. Edlow, 2018, Functional networks reemerge during recovery of consciousness after acute severe traumatic brain injury: Cortex, v. 106, p. 299–308, doi:10.1016/j.cortex.2018.05.004.

Tinker, J. H., F. W. Sharbrough, and J. D. Michenfelder, 1977, Anterior shift of the dominant EEG rhytham during anesthesia in the Java monkey: correlation with anesthetic potency.: Anesthesiology: The Journal of the American Society of Anesthesiologists, v. 46, no. 4, p. 252 259.

Todd, M. M., D. S. Warner, M. D. Sokoll, M. A. Maktabi, B. J. Hindman, F. L. Scamman, and J. Kirschner, 1993, A Prospective, Comparative Trial of Three Anesthetics for Elective Supratentorial Craniotomy: Anesthesiology, v. 78, no. 6, p. 1005–1020, doi:10.1097/00000542-199306000-00002.

Tommasino, C., C. Grana, G. Lucignani, G. Torri, and F. Fazio, 1995, Regional Cerebral Metabolism of Glucose in Comatose and Vegetative State Patients: Journal of Neurosurgical Anesthesiology, v. 7, no. 2, p. 109–116, doi:10.1097/00008506-199504000-00006.

Tononi, G., and G. M. Edelman, 1998, Consciousness and Complexity: Science, v. 282, no. 5395, p. 1846–1851, doi:10.1126/science.282.5395.1846.

Tononi, G., 2004, An information integration theory of consciousness: BMC Neuroscience, v. 5, no. 1, p. 42–42, doi:10.1186/1471-2202-5-42.

Tononi, G., M. Boly, M. Massimini, and C. Koch, 2016, Integrated information theory: from consciousness to its physical substrate: Nature Reviews Neuroscience, v. 17, no. 7, p. 450–461, doi:10.1038/nrn.2016.44.

Toro-Matos A, A. M. Rendon-Platas, E. Avila-Valdez, R. A. Villarreal-Guzman, 1980, Physostigmine antagonizes ketamine. Anesth Analg. Oct; 59(10): 764-7. PMID: 6999946.

Tort, A. B. L., M. A. Kramer, C. Thorn, D. J. Gibson, Y. Kubota, A. M. Graybiel, and N. J. Kopell, 2008, Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task: Proceedings of the National Academy of Sciences, v. 105, no. 51, p. 20517 20522, doi:10.1073/pnas.0810524105.

Uddin, L. Q., K. Supekar, H. Amin, E. Rykhlevskaia, D. A. Nguyen, M. D. Greicius, and V. Menon, 2010, Dissociable Connectivity within Human Angular Gyrus and Intraparietal Sulcus: Evidence from Functional and Structural Connectivity: Cerebral Cortex, v. 20, no. 11, p. 2636–2646, doi:10.1093/cercor/bhq011.

Untergehrer, G., D. Jordan, E. F. Kochs, R. Ilg, and G. Schneider, 2014, Fronto-Parietal Connectivity Is a Non-Static Phenomenon with Characteristic Changes during Unconsciousness: PLoS ONE, v. 9, no. 1, p. e87498, doi:10.1371/journal.pone.0087498.

Vakkuri, A., A. Yli-Hankala, P. Talja, S. Mustola, H. Tolvanen-Laakso, T. Sampson, and H. Viertiö-Oja, 2004, Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia: Acta Anaesthesiologica Scandinavica, v. 48, no. 2, p. 145–153, doi:10.1111/j.0001-5172.2004.00323.x.

Vanhaudenhuyse, A. et al., 2010, Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients: Brain, v. 133, no. 1, p. 161–171, doi:10.1093/brain/awp313.

Vanhaudenhuyse, A. et al., 2011, Two Distinct Neuronal Networks Mediate the Awareness of Environment and of Self: Journal of Cognitive Neuroscience, v. 23, no. 3, p. 570–578, doi:10.1162/jocn.2010.21488.

Velly, L., V. Perlbarg, T. Boulier, N. Adam, S. Delphine, C.–E. Luyt, V. Battisti, G. Torkomian, C. Arbelot, R. Chabanne, B. Jean, C. D. Perri, S. Laureys, G. Citerio, A. Vargiolu, B. Rohaut, N. Bruder, N. Girard, S. Silva, S., V. Cottenceau, T. Tourdias, O. Coulon, B. Riou, L. Naccache, R. Gupta, H. Benali, D. Galanaud, L. Puybasset, 2018, Use of brain diffusion tensor imaging for the prediction of long-term neurological outcomes in patients after cardiac arrest: a multicentre, international, prospective, observational, cohort study. The Lancet Neurology, 17(4), 317–326. https://doi.org/10.1016/s1474-4422(18)30027-9

Veselis, R. A., R. A. Reinsel, B. J. Beattie, O. R. Mawlawi, V. A. Feshchenko, G. R. DiResta, S. M. Larson, and R. G. Blasberg, 1997, Midazolam changes cerebral blood flow in discrete brain regions: an H2(15)O positron emission tomography study.: Anesthesiology: The Journal of the American Society of Anesthesiologists, v. 87, no. 5, p. 1106 1117.

Viertiö-Oja, H., V. Maja, M. Särkelä, P. Talja, N. Tenkanen, H. Tolvanen-Laakso, M. Paloheimo, A. Vakkuri, A. Yli-Hankala, and P. Meriläinen, 2004, Description of the Entropy™ algorithm as applied in the Datex-Ohmeda S/5™ Entropy Module: Acta Anaesthesiologica Scandinavica, v. 48, no. 2, p. 154–161, doi:10.1111/j.0001-5172.2004.00322.x.

Vlisides, P. E. et al., 2017, Neurophysiologic Correlates of Ketamine Sedation and Anesthesia: Anesthesiology, v. 127, no. 1, p. 58–69, doi:10.1097/aln.0000000000001671.

Vlisides, P. E., D. Li, M. Zierau, A. P. Lapointe, K. I. Ip, A. M. McKinney, and G. A. Mashour, 2019, Dynamic Cortical Connectivity during General Anesthesia in Surgical Patients: Anesthesiology, v. Publish Ahead of Print, no. NA;, p. NA;, doi:10.1097/aln.0000000000002677.

Warnaby, C. E., M. Seretny, R. N. Mhuircheartaigh, R. Rogers, S. Jbabdi, J. Sleigh, and I. Tracey, 2016, Anesthesia-induced Suppression of Human Dorsal Anterior Insula Responsivity at Loss of Volitional Behavioral Response: Anesthesiology, v. 124, no. 4, p. 766–778, doi:10.1097/aln.0000000000001027.

Warnaby, C. E., J. W. Sleigh, D. Hight, S. Jbabdi, and I. Tracey, 2017, Investigation of Slow-wave Activity Saturation during Surgical Anesthesia Reveals a Signature of Neural Inertia in Humans: Anesthesiology, v. 127, no. 4, p. 645–657, doi:10.1097/aln.0000000000001759.

Watson, T. D., I. L. Petrakis, J. Edgecombe, A. Perrino, J. H. Krystal, D. H. Mathalon, 2009, Modulation of the cortical processing of novel and target stimuli by drugs affecting glutamate and GABA neurotransmission. The The International Journal of Neuropsychopharmacology, 12(3), 357-370.

Whitfield-Gabrieli, S., J. M. Moran, A. Nieto-Castañón, C. Triantafyllou, R. Saxe, and J. D. E. Gabrieli, 2011, Associations and dissociations between default and self-reference networks in the human brain: NeuroImage, v. 55, no. 1, p. 225–232, doi:10.1016/j.neuroimage.2010.11.048.

WHITING, P. J. et al., 1999, Molecular and Functional Diversity of the Expanding GABA-A Receptor Gene Family: Annals of the New York Academy of Sciences, v. 868, no. 1, p. 645–653, doi:10.1111/j.1749-6632.1999.tb11341.x.

Wickens T. D., 2002, Elementary signal detection theory. 1st ed. New York, NY, USA: Oxford University Press

Wildes, T. S. et al., 2019, Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery: JAMA, v. 321, no. 5, p. 473–483, doi:10.1001/jama.2018.22005.

Windt, J. M., T. Nielsen, and E. Thompson, 2016, Does Consciousness Disappear in Dreamless Sleep? Trends in Cognitive Sciences, v. 20, no. 12, p. 871–882, doi:10.1016/j.tics.2016.09.006.

Xie, G., A. Deschamps, S. B. Backman, P. Fiset, D. Chartrand, A. Dagher, and G. Plourde, 2011, Critical involvement of the thalamus and precuneus during restoration of consciousness with physostigmine in humans during propofol anaesthesia: a positron emission tomography study: BJA: British Journal of Anaesthesia, v. 106, no. 4, p. 548–557, doi:10.1093/bja/aeq415.

Yeganeh, M. H., and I. Ramzan, 1997, Determination of propofol in rat whole blood and plasma by high-performance liquid chromatography: Journal of Chromatography B: Biomedical Sciences and Applications, v. 691, no. 2, p. 478–482, doi:10.1016/s0378-4347(96)00469-0.

Zhang, Z. et al., 2015, Neuronal ensembles sufficient for recovery sleep and the sedative actions of α2 adrenergic agonists: Nature Neuroscience, v. 18, no. 4, p. 553–561, doi:10.1038/nn.3957.

Zecharia, A. Y., L. E. Nelson, T. C. Gent, M. Schumacher, R. Jurd, U. Rudolph, S. G. Brickley, M. Maze, and N. P. Franks, 2009, The Involvement of Hypothalamic Sleep Pathways in General Anesthesia: Testing the Hypothesis Using the GABAA Receptor β3N265M Knock-In Mouse: The Journal of Neuroscience, v. 29, no. 7, p. 2177–2187, doi:10.1523/jneurosci.4997-08.2009.

Zeiler, F. A., J. Teitelbaum, M. West, and L. M. Gillman, 2014, The ketamine effect on intracranial pressure in nontraumatic neurological illness: Journal of Critical Care, v. 29, no. 6, p. 1096–1106, doi:10.1016/j.jcrc.2014.05.024.

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