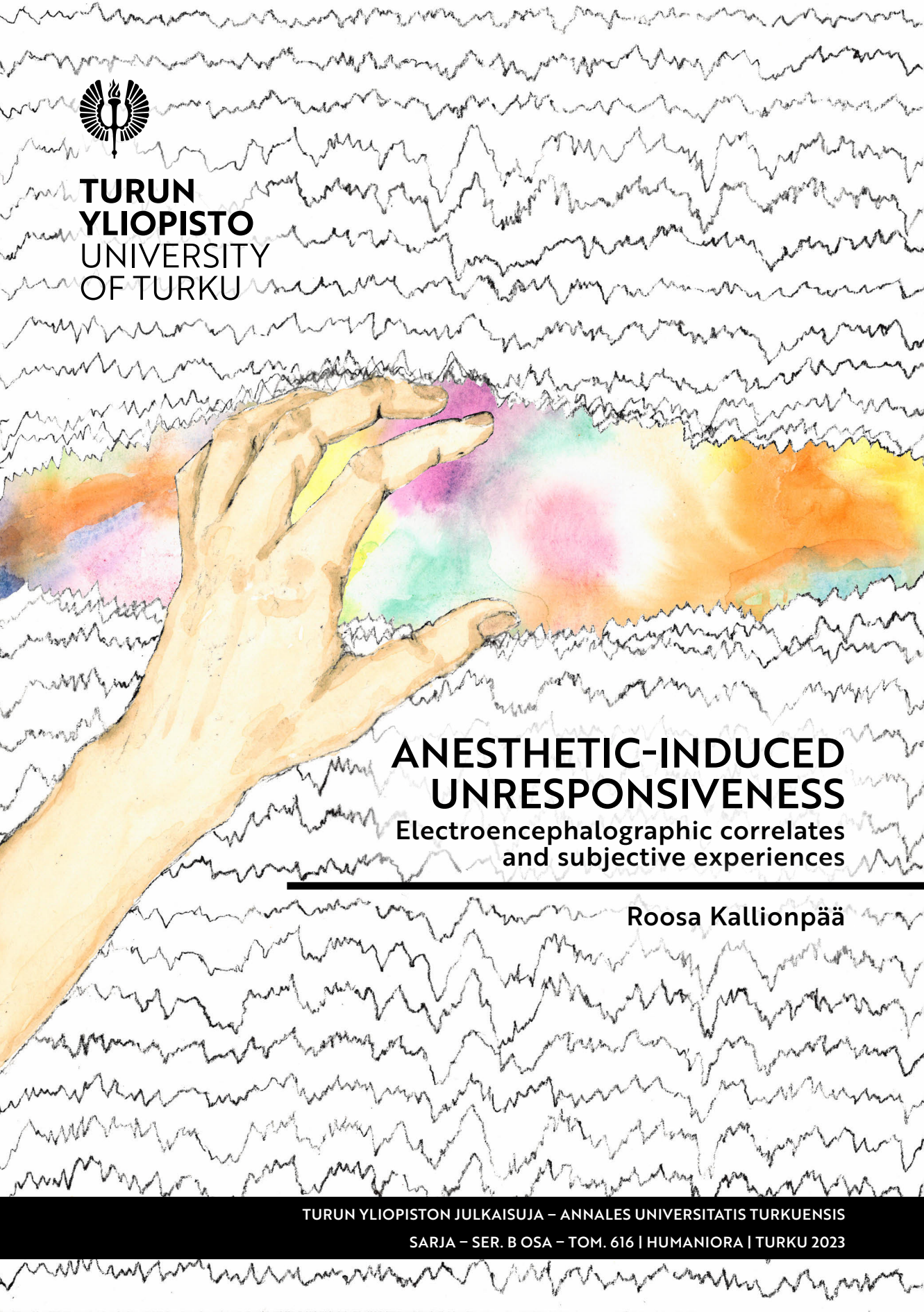

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UNIVERSITY OF TURKU

ANESTHETIC-INDUCED UNRESPONSIVENESS

Electroencephalographic correlates and subjective experiences

Roosa Kallionpää

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University of Turku

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

Cover Image: Roosa Kallionpää, “Behind” (2023)

ISBN 978-951-29-9215-7 (PRINT)
ISBN 978-951-29-9216-4 (PDF)
ISSN 0082-6987 (Print)
ISSN 2343-3191 (Online)
Painosalama, Turku, Finland 2023

UNIVERSITY OF TURKU
Faculty of Social Sciences
Department of Psychology and Speech-Language Pathology
Faculty of Medicine
Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine
ROOSA KALLIONPÄÄ: Anesthetic-induced unresponsiveness:
Electroencephalographic correlates and subjective experiences
Doctoral Dissertation, 241 pp.
Doctoral Programme of Social and Behavioural Sciences
April 2023

ABSTRACT

Anesthetic drugs can induce reversible alterations in responsiveness, connectedness and consciousness. The measures based on electroencephalogram (EEG) have marked potential for monitoring the anesthetized state because of their relatively easy use in the operating room.

In this study, 79 healthy young men participated in an awake experiment, and 47 participants continued to an anesthesia experiment where they received either dexmedetomidine or propofol as target-controlled infusion with stepwise increments until the loss of responsiveness. The participants were roused during the constant drug infusion and interviewed. The drug dose was increased to 1.5-fold to achieve a deeper unresponsive state. After regaining responsiveness, the participants were interviewed. EEG was measured throughout the experiment and the N400 event-related potential component and functional and directed connectivity were studied.

Prefrontal-frontal connectivity in the alpha frequency band discriminated the states that differed with respect to responsiveness or drug concentration. The net direction of connectivity was frontal-to-prefrontal during unresponsiveness and reversed back to prefrontal-to-frontal upon return of responsiveness. The understanding of the meaning of spoken language, as measured with the N400 effect, was lost along with responsiveness but, in the dexmedetomidine group, the N400 component was preserved suggesting partial preservation of the processing of words during anesthetic-induced unresponsiveness. However, the N400 effect could not be detected in all the awake participants and the choice of analysis method had marked impact on its detection rate at the individual-level. Subjective experiences were common during unresponsiveness induced by dexmedetomidine and propofol but the experiences most often suggested disconnectedness from the environment.

In conclusion, the doses of dexmedetomidine or propofol minimally sufficient to induce unresponsiveness do not render the participants unconscious and dexmedetomidine does not completely abolish the processing of semantic stimuli. The local anterior EEG connectivity in the alpha frequency band may have potential in monitoring the depth of dexmedetomidine- and propofol-induced anesthesia.

KEYWORDS: anesthesia, connectivity, consciousness, dexmedetomidine, EEG, event-related potentials, interview, N400, propofol, responsiveness

TURUN YLIOPISTO
Yhteiskuntatieteellinen tiedekunta
Psykologian ja logopedian laitos
Lääketieteellinen tiedekunta
Anestesiologia, tehohoito, ensihoito ja kivunhoito
ROOSA KALLIONPÄÄ: Anesteettien aiheuttama vastauskyvyttömyys: aivosähkökäyräpohjaiset korrelaatit ja subjektiiviset kokemukset
Väitöskirja, 241 s.
Yhteiskunta- ja käyttäytymistieteiden tohtoriohjelma
Huhtikuu 2023

TIIVISTELMÄ

Anestesialääkkeillä voidaan saada aikaan palautuvia muutoksia vastauskykyisyydessä, kytkeytyneisyydessä ja tajunnassa. Aivosähkökäyrään (EEG) pohjautuvat menetelmät tarjoavat lupaavia mahdollisuuksia mitata anestesian vaikutusta aivoissa, sillä niitä on suhteellisen helppo käyttää leikkaussalissa.

Tässä tutkimuksessa 79 tervettä nuorta miestä osallistui valvekokeeseen ja 47 heistä jatkoi anestesiakokeeseen. Anestesiakokeessa koehenkilöille annettiin joko deksmedetomidiinia tai propofolia tavoiteohjattuna infuusiona nousevia annosportaita käyttäen, kunnes he menettivät vastauskykynsä. Koehenkilöt herätettiin tasaisen lääkeinfuusion aikana ja haastateltiin. Koko kokeen ajan mitattiin EEG:tä, josta tutkittiin N400-herätevastetta sekä toiminnallista ja suunnattua konnektiivisuutta.

Prefrontaali-frontaalivälillä mitattu konnektiivisuus alfa-taajuuskaistassa erotteli toisistaan tilat, jotka erosivat vastauskykyisyyden tai lääkepitoisuuden suhteen. Konnektiivisuuden vallitseva suunta oli frontaalialueilta prefrontaalialueille vastauskyvyttömyyden aikana, mutta se kääntyi takaisin prefrontaalisesta frontaaliseen kulkevaksi koehenkilöiden vastauskyvyn palatessa. N400-efektillä mitattu puhutun kielen ymmärtäminen katosi vastauskyvyn menettämisen myötä. Deksmedetomidiiniryhmässä N400-komponentti säilyi, mikä viittaa siihen, että anesteettien aiheuttaman vastauskyvyttömyyden aikana sanojen prosessointi voi säilyä osittain. Yksilötasolla N400-efektiä ei kuitenkaan havaittu edes kaikilla hereillä olevilla henkilöillä, ja analyysimenetelmän valinnalla oli suuri vaikutus herätevasteen havaitsemiseen. Subjektiiviset kokemukset olivat yleisiä deksmedetomidiinin ja propofolin aiheuttaman vastauskyvyttömyyden aikana, mutta kokemukset olivat usein ympäristöstä irtikytkeytyneitä.

Yhteenvetona voidaan todeta, että deksmedetomidiini- ja propofoliannokset, jotka juuri ja juuri riittävät aikaansaamaan vastauskyvyttömyyden, eivät aiheuta tajuttomuutta. Deksmedetomidiini ei myöskään täysin estä merkityssisällöllisten ärsykkeiden käsittelyä. Frontaalialueen sisällä EEG:llä mitattu konnektiivisuus alfa-taajuuskaistassa saattaa olla tulevaisuudessa hyödyllinen menetelmä deksmedetomidiini- ja propofolianestesian syvyyden mittaamiseksi.

ASIASANAT: anestesia, konnektiivisuus, tajunta, deksmedetomidiini, EEG, herätevasteet, haastattelu, N400, propofoli, vastauskykyisyys

Acknowledgements

During the preparation of this thesis, I have had the privilege to work with many people who have helped me in the process. First, I would like to thank my three supervisors who have guided me through the PhD studies. I wish to thank Professor Katja Valli who is an expert on every aspect of studying subjective experiences and sleep-related phenomena. She masters the widest perspectives and is interested in the smallest details, and I have learned very much from her. Katja, it has been a pleasure to work with you since preparing the stimuli until today! I would like to thank Professor Antti Revonsuo who introduced the N400 to me. Antti comes up with constructive views on every scientific problem and has also encouraged me to interpret the data which is necessary for formulating new theories to be tested in the future. I am grateful to Adjunct Professor Harry Scheinin, the principal investigator of the LOC-2013/2016 project, for his guidance. He has led the massive project involving six experiments, hundreds of study sessions and tremendous amount of data. The international and national collaborations of this thesis would not have been possible without Harry's connections and expertise.

I would like to thank the reviewers of this thesis, Professor Emeritus Arvi Yli-Hankala and Professor Emeritus Michael Wang. Their constructive comments helped to considerably improve the manuscript and also encouraged me when the results of many years of work were compiled into one book. I especially wish to thank Professor Yli-Hankala who agreed to serve as an opponent in the public examination of this thesis.

I am grateful to the Department of Psychology and Speech-Language Pathology and Heikki Hämäläinen, Jukka Hyönä, Ari Kaukiainen, Elina Mainela-Arnold, Paula Salo, and Jukka Leppänen for the research infrastructure provided in Publicum. I want to thank Tuula Manner, Minna Tallgren, and Teijo Saari and Timo Laitio for the infrastructure in the Department of Perioperative Services, Intensive Care and Pain Medicine of Turku University Hospital, in the Intensive Care Unit of Turku University Hospital, and in the Department of Anesthesiology in the University of Turku, respectively.

I would like to thank the members of the Anesthesia Mechanisms Group – Kaike Kaisti, Minna Kallioinen, Oskari Kantonen, Kimmo Kaskinoro, Lauri Laaksonen,

Ruut Laitio, Timo Laitio, Jaakko Långsjö, Anu Maksimow, Aleksi Nummela, Linda Radek, and Annalotta Scheinin – for efficient and inspiring collaboration. I wish to especially thank Annalotta: you experienced the whole project with me and I am always thankful for your great company! Obviously, your role has been essential in the data collection of this study. We have experienced and learned a lot together! I would also like to thank Oskari and Linda for many good conversations, and the pleasant and fun travelling together.

I am thankful to the world-renowned experts, George Mashour and Duan Li, for the fruitful and productive collaboration. I wish to thank my co-authors Henri Pesonen, Tero Vahlberg and Tom Kuusela who have provided essential methodological contributions to this study. Mika Särkelä, Warren D. Smith, and Vladimir Bostanov have shared important methodological insights regarding P_K and t-CWT. I would also like to thank the people who have helped when piloting and preparing the experiments of this project: Maria Ek, Teemu Laine, Seppo Vainio and Janika Paavola. Especially Maria and Teemu's work was essential when constructing the experimental setup and they had a major role in creating the atmosphere of the Centre for Cognitive Neuroscience (KNT). I am thankful to Milla Karvonen, Irmeli Dahlblom, Ville Rajala, Hanna Määttänen, Viivi Moberg, Otso Saariluoma, Leena Vierikko, Jarno Korhonen, Marke Kaitala, Nora Österman, Sanna Ojala, Lauri Koskinen, Mimmi Hannula, Elina Kukkonen, and Ville Huuskonen for their contributions during and after the study sessions of these experiments and the whole project. The collaboration with the radiographers, medical laboratory technologists and all other staff of Turku PET Centre has been pleasant in the PET experiments outside the scope of this thesis.

Nils Sandman and Jarno Tuominen have been important persons in the process of this thesis. Nils has had a major role in brightening up my every-day life at KNT, for example during the long lunches and conversations that happened around the dog. Nils has actively organized numerous events, like the PhD shadow seminars, and has openly shared his experiences in various fields of scientific and non-scientific life. Jarno has read every book and article in the world and is always ready to listen and discover great new ideas and points of view. Nils and Jarno, I have been very lucky to enter the academia with you!

I would like to thank the people who have shared the office with me for the pleasant company: Pilleriin Sikka, Ville Rajala, Henri Olkoniemi, and Teddy Landron. I would especially like to thank Pilleriin for the joy she brings to the world and for all the bubbling and great ideas! I have had many inspiring discussions with the chess club philosophers Heidi Haanila, Sanna Suni, and Anne Salminen who also reviewed my very first poster presentation.

I would also like to thank all the others who have been part of the Consciousness Research Group and/or KNT. I have had the pleasure of working there at the same

time as Niina Salminen-Vaparanta (thank you for the most delightful lunches in Macciavelli!), Milla Karvonen, Carina Saarela, Henry Railo, Mika Koivisto, Mikko Hurme, Valtteri Arstila, Sakari Kallio, Valdas Noreika, Simone Grassini, Jussi Jylkkä, Dmitri Filimonov, Gabriel Sjödin, Teddy Landron, Marius Klug, Angeliki Kokoura and Amor the Dog. We have had a good time together in KNT and upstairs! Also, I would like to thank all the other people in the Department of Psychology and Speech-Language Pathology, especially Suvi Holm, Faramosh Rashid Izullah, Kati Renvall, Anna Kautto, Ida Luotonen, Sonja Kumlander, Oskari Lahtinen, and Ramona Pulli.

I would like to thank my colleagues in Auria Biobank for support and helping me to quickly adapt to another field of biomedical science. During our shared years, I have lived in two (or more) different worlds but it has always been obvious that the keys for successful research are universal.

This research and the thesis have been made possible by the project funding from the Academy of Finland (Human Mind programme) and Jane and Aatos Erkko Foundation. I am thankful to Emil Aaltonen Foundation and the Faculty of Social Sciences for the grants for finalizing this doctoral dissertation. Important international connections were made and the newest news of the field were learned in Towards the Science of Consciousness conference 2015, ASA Anesthesiology Annual Meeting 2016, and Memory and Awareness in Anaesthesia conferences 2017 and 2022. I was happy to receive grants for the travelling from the Turku University Foundation and the Doctoral Programme of Social and Behavioural Sciences.

Friends and family highlight the importance of things other than work. I would like to thank my friends, many of whom have been in my life since childhood: Emma, Henrik, Valentina, Aida, Henri, Aino, Teemu, Kristiina, Mikko, Jenni, Kati and Siniliina. I am also happy to have friends who have had shared interests, for example, in the fields of music, handicrafts or books. Thank you Kitarissimo!, Kourula family, and Kaija and Elina.

I owe my warmest gratitude to my family – Marjo, Kari, Reetta, Eero, Anneli, Liisa, Tuomo, Santtu, Elina, Lenni and Sauli – for their interest in my research topics and professional career. Your existence and all the really important things with you have been the foundation of the successful finalization of this thesis.

Lastly and most importantly: Roope, thank you for the scientific collaboration, love and support!

Turku, March 2023

Roosa Kallionpää

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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 Kallionpää RE, Valli K, Scheinin A, Långsjö J, Maksimow A, Vahlberg T, Revonsuo A, Scheinin H, Mashour GA, Li D: Alpha band frontal connectivity is a state-specific correlate of unresponsiveness during exposure to dexmedetomidine and propofol. *British Journal of Anaesthesia*, 2020; 125(4): 518–528.

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 Radek L, Kallionpää RE, Karvonen M, Scheinin A, Maksimow A, Långsjö J, Kaisti K, Vahlberg T, Revonsuo A, Scheinin H, Valli K: Dreaming and awareness during dexmedetomidine- and propofol-induced unresponsiveness. *British Journal of Anaesthesia*, 2018; 121(1): 260–269.

IV Kallionpää RE, Pesonen H, Scheinin A, Sandman N, Laitio R, Scheinin H, Revonsuo A, Valli K: Single-subject analysis of N400 event-related potential component with five different methods. *International Journal of Psychophysiology*, 2019; 144: 14–24.

1 Introduction

Our life consists of subjective experiences: perceptions, sensations, thoughts and feelings. These subjective experiences constitute our consciousness and make the world how it is for us (Nagel, 1974). Despite the major ethical implications of the topic, it is not known how consciousness is generated in the brain or how it could be measured objectively. Even if the neural correlates of consciousness were completely identified, the hard problem of consciousness would remain: why and how the experience arises from physical processes like neural activity (Chalmers, 1995). The inherent subjectivity of consciousness makes it complicated to even define consciousness unequivocally, although the conscious state can be defined as an ability to have subjective experiences. Conscious experiences can be either connected to or disconnected from the environment. While behavioral responsiveness is straightforward to detect, conscious experiences can also exist in the unresponsive state, and the subjective experiences can only be reported by the person having the experiences after regaining responsiveness.

General anesthesia, natural sleep and some disorders of consciousness represent examples of behaviorally unresponsive states where the presence of internal experiences is externally undetectable. The incidence of recalled connected consciousness during surgical anesthesia in the Western countries is typically reported as 0.005–0.18% (Pandit et al., 2014a; Sandin et al., 2000). In Finland, intraoperative awareness with later recall has been reported in 0.07% of outpatient operations and 0.13% of inpatient operations (Wennervirta et al., 2002). However, the occurrence of connected consciousness during general anesthesia may be much more common but obscured by the amnestic effects of anesthetics (Lennertz et al., 2023; Sanders et al., 2017). Also, around 40% of the patients with disorders of consciousness who are considered as unconscious may show signs of consciousness in a further standardized assessment (Schnakers et al., 2009). Although different tools and tests have been developed for the monitoring behavioral and physiological markers of consciousness, there is an acute need for an objective indicator of consciousness and better indices of anesthesia depth. A deeper understanding of the nature and the underlying mechanisms of the behaviorally unresponsive states is needed to develop better markers of connectedness and consciousness.

General anesthesia represents a unique possibility to reversibly study responsiveness and consciousness. While surgical general anesthesia is often achieved using a combination of several drugs, experimental anesthesia allows focusing on the isolated effects of certain anesthetics with various doses and without surgical stimulation. The comparison of several anesthetics acting through different molecular mechanisms and studying both responsive and unresponsive states at the same drug concentration may aid the identification of universal consciousness-related characteristics. The effects of anesthesia on the brain can be studied using a variety of different methods, such as functional magnetic resonance imaging (fMRI), positron-emission tomography (PET), magnetoencephalography (MEG) and electroencephalography (EEG).

EEG has a high clinical potential as it enables the on-line and on-site monitoring of the brain. EEG measures the extracranial scalp potentials that have their origin in postsynaptic and other contributing currents of thousands to millions of neurons (Buzsáki et al., 2012; Cohen, 2017). The effects detected on the scalp are widespread even if the sources were focal, and each electrode has been suggested to measure a spatiotemporally smoothed local field potential from an area of 10 cm^2 or more (Ahlfors et al., 2010; Buzsáki et al., 2012). The EEG is generally thought to originate from the cerebral cortex and more specifically from the pyramidal neurons (Hari and Salmelin, 2012) but also subcortical signals can be detected in scalp electrodes (Piastra et al., 2021; Seeber et al., 2019). Although EEG and MEG measure signals generated by the same sources in the brain, EEG is especially sensitive to radial and deep sources while MEG is most efficient with tangential sources and they therefore provide complementary information (Goldenholz et al., 2009; Hari and Salmelin, 2012; Piastra et al., 2021). Compared with fMRI- and PET-based brain imaging methods, EEG has a millisecond-level temporal resolution and is a cost-effective and easy-to-access method. In contrast to, for example, fMRI, EEG is a direct measure of brain electrophysiological activity (Drew, 2019; Ekstrom, 2010) and it is in some occasions more sensitive than fMRI (Curley et al., 2018).

The EEG consists of a wide frequency range of periodic fluctuations. The coherent oscillations convey communication between neuronal groups, and typically the oscillations of higher frequency are confined to a small neuronal space, whereas large networks are involved in slow oscillations (Buzsáki and Draguhn, 2004; Sauseng and Klimesch, 2008). EEG is typically roughly divided in frequency bands of delta (0–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (>30 Hz) oscillations (Fries, 2005, 2015; Sauseng and Klimesch, 2008). For example, the normal awake state is characterized by alpha EEG patterns that are important for consistent cognitive operations and especially the occipital alpha waves are prominent during wakefulness (Cohen, 2017; Palva and Palva, 2007; Vijayan and Kopell, 2012). Instead, anteriorly dominant alpha EEG patterns are characteristic in

the presence of anesthetic drugs potentiating gamma aminobutyric acid receptor A ($GABA_A$) signaling, such as propofol, and in certain pathological states of consciousness, such as alpha coma (Ching et al., 2010; Kaplan et al., 1999; Purdon et al., 2015). There are several ways to quantify the EEG based on the spectral content of oscillations, cross-frequency coupling, connectivity and event-related potentials.

In this thesis, two different anesthetic drugs, dexmedetomidine and propofol, are used to manipulate the consciousness and responsiveness of healthy volunteers. The aim is to shed light on the EEG-based neural correlates of anesthetic-induced unresponsiveness by measuring connectivity and event-related potentials and to explore the anesthetic-induced unresponsiveness as a subjective mental state by collecting verbal reports of the subjective experiences occurring during unresponsiveness, and by conducting memory tests measuring explicit and implicit memory for stimuli that were presented during unresponsiveness. In addition, the effect of the choice of analysis method on the detection rate of event-related potentials is examined to support solving the methodological challenges related to measuring the unresponsive state.

Connectivity is a tool to describe the interconnected organization of networks in the brain (He et al., 2019). Studies on connectivity examine neuroanatomical links between regions, statistical dependencies between signals from different areas, or causal influence between different brain regions. Fries (2005) was the first to propose that the communication between different brain regions can be inferred from phase delays. The phase synchronization at a specific frequency band can be used to measure the functional and directed connectivity. There is an ongoing discussion on the roles of the cortico-cortical and thalamo-cortical networks, and the connections between subcortical wake-promoting nuclei and the cortex in mediating consciousness (Mashour, 2014; Mashour and Hudetz, 2017).

Event-related potentials (ERPs) are voltage deflections that have a stable time-relationship to a reference event, such as a stimulus (Luck, 2014). ERPs have been associated with increased neural activity and phase locking of background oscillations (Fell et al., 2004; Telenczuk et al., 2010; Xu et al., 2016). An ERP component is neural activity generated in a specific neuroanatomical module, measured with EEG, when a specific computational operation is performed in the brain (Luck, 2014). Typically, the ERP components observed late after stimulus are related to more complex processing than the early components. Some ERP components have been studied in the presence of anesthetics, but they have been mainly early and automatic (Heinke et al., 2004a; Yppärilä et al., 2002). In the present thesis, the ERP component of interest is N400 that is observed 300–600 ms after a potentially meaningful stimulus. The N400 has been previously studied in other altered or pathological states of consciousness, such as sleep and disorders of

consciousness, but not during anesthetic-induced unresponsiveness. Ultimately, an index for consciousness should function similarly with each individual person. However, there are methodological challenges both in measuring and analyzing complex cognitive ERPs and these complicate comparisons of different studies.

The two EEG-based methods used in the thesis allow two different viewpoints on the anesthetic-induced state: the information flow in the resting-state measurements and stimulus-related cognitive processing. In addition, the subjective reports elucidate the contents of consciousness recalled after unresponsive states. A better understanding of the effects of anesthesia on the brain and the way that the consciousness fades away are essential for developing better anesthesia monitors and understanding the nature of the different unresponsive states that seem behaviorally similar.

2 Review of the literature

2.1 Consciousness

Phenomenal consciousness refers to the presence of subjective experiences that feel like something or have qualitative character (also known as qualia): there is something that it is like to be a conscious subject. According to the phenomenal criterion of consciousness, a person who is able to have experiences, such as perceptions, thoughts, and memories, is conscious. These experiences, also called the contents of consciousness, are not necessarily related to the external world but can be internally generated, like dreaming or hallucinations. Consciousness related to the detection of external, physical stimuli can also be termed awareness. The ensemble of phenomenal contents of consciousness constitutes the state of consciousness, and those contents may be reflected on by the person in the state – the ability that is called reflective consciousness. A conscious creature may be momentarily in unconscious state where there are no phenomenal experiences (Revonsuo, 2006). The unconscious state can be temporary (dreamless sleep or deep general anesthesia), long-lasting, or even permanent (coma or other disorders of consciousness).

2.1.1 The state of consciousness

Consciousness can be understood as a dichotomous phenomenon based on the presence of experiences: the person is either conscious or not. Also, the different states of consciousness can be defined by the relations of the contents or patterns of experience to the surrounding context (Revonsuo et al., 2009). In addition, consciousness can be considered as a graded phenomenon with different levels of consciousness (Bachmann, 2012; Laureys, 2005; Overgaard and Overgaard, 2010; Tononi and Koch, 2008). This view has its origin in the clinical medicine where the patients are evaluated with scales, like the Glasgow Coma Scale or indices for the depth of anesthesia (Section 2.2.3; Bruno et al., 2011). Also theoretical frameworks, like the Information Integration Theory and the related indices Perturbational Complexity Index (PCI) and Explainable Consciousness Indicator (ECI), describe

the state of consciousness in terms of one, graded object (Casali et al., 2013; Lee et al., 2022).

The one-dimensional view of the state of consciousness is appealing as it might allow comparisons between different pathological states and evaluating the distance of a particular state from normal wakefulness. However, the state of consciousness seems to be too complex to be represented on a one-dimensional scale as demonstrated by the altered states of consciousness. The altered states of consciousness are conditions where the neurocognitive background mechanisms of consciousness are likely to produce misrepresentations of the world, such as hallucinations, delusions, and memory distortions (Section 2.1.4; Revonsuo et al., 2009). The one-dimensional graded view of consciousness ignores the contents of consciousness (Bayne and Hohwy, 2016) that are essential in defining the different altered states. Recently, different multidimensional views have been presented (Bayne et al., 2016; Walter, 2021). Most of the models highlight the arousal and the richness of contents of consciousness. For example, Laureys (2005) and Bachmann and Hudetz (2014) emphasize the interplay between wakefulness ("level") and contents ("data"). Monti and co-workers (2009) suggest a three-dimensional model for assessing the patients with disorders of consciousness: awareness, wakefulness and voluntary mobility. Bayne and Howhy (2016) describe the states of consciousness by combining the contents of consciousness, the temporal and attentional structure of the experience, and the functionality of the experiencer. Sanz Perl and colleagues (2021) describe the dynamic stability and reversibility as the key dimension across states with different origins. Other dimensions of consciousness have been suggested to include executive and intentional functioning, reasoning, attentional control, memory consolidation, meta-awareness, vigilance, sensory richness, high-order object representation, and semantic comprehension (Walter, 2021).

One approach for classifying the states of consciousness is categorization based on responsiveness, connectedness and phenomenal consciousness (Sanders et al., 2012). These three measures can decouple in altered states of consciousness. Here, responsiveness is defined as behavioral activity in response to external stimulation, and connectedness as having experiences that are connected to the environment. Conditions that are behaviorally similar can differ based on connectedness and consciousness. For example, coma, locked-in syndrome, and natural sleep are behaviorally unresponsive conditions although the experiences in the three states are very different. In coma, the patient is not connected to the environment and has no (at least known) contents of consciousness. Locked-in syndrome is characterized by connectedness and awareness of the environment despite the unresponsiveness. In natural sleep, the person is typically disconnected from the environment despite occasionally having rich contents of consciousness in the form of dreams.

2.1.2 Neural correlates of consciousness

The neural correlates of consciousness can be defined as the minimally sufficient conditions for being in an overall conscious state rather than in an overall unconscious state (Hohwy, 2009). Furthermore, the neural correlates of consciousness can be seen as the minimal neural systems whose states correspond to specific states of consciousness, and a given state of a neural system is sufficient for the existence of the corresponding state of consciousness (Chalmers, 2000). In addition to the full neural correlates of consciousness that are related to the global state of consciousness, also content-specific correlates of consciousness can be studied (Chalmers, 2000; Koch et al., 2016). The neural correlates of the contents of consciousness are the minimum neuronal mechanisms jointly sufficient for any specific conscious percept (Koch et al., 2016). Both correlational and causal relationships between consciousness and the neural representational systems are often considered when studying the neural correlates of consciousness (Aru et al., 2012; Koch et al., 2016). As the causal relations are more relevant for the scientific explanation of consciousness than mere correlations, it has been suggested that the concept of "constitutive mechanisms of consciousness" could be used instead of "neural correlates of consciousness" (Revonsuo, 2006).

A variety of neurocognitive theories have been developed to describe the nature of consciousness (Northoff and Lamme, 2020; Seth and Bayne, 2022; Signorelli et al., 2021). Some of the theories that are currently undergoing empirical testing include the Global Neuronal Workspace Theory (Baars, 2005; Dehaene and Changeux, 2011), the Recurrent Processing Theory (Lamme, 2006, 2010), the Information Integration Theory (Tononi, 2004; Tononi et al., 2016), and higher order theories, like the Higher Order Thought Theory (Brown et al., 2019; Lau and Rosenthal, 2011). Many of these theories consider cortical processing as an essential contributor to consciousness, yet they highlight different cortical networks. The Global Neuronal Workspace Theory emphasizes anterior-posterior connections (Dehaene and Changeux, 2011; Mashour et al., 2020), the Recurrent Processing Theory highlights recurrent processing in the ventral occipitotemporal cortex (Boehler et al., 2008; Lamme and Roelfsema, 2000), higher order theories concentrate on the prefrontal cortex (Brown et al., 2019; Lau and Rosenthal, 2011), and the Information Integration Theory locates the correlates in the posterior cortex (Koch et al., 2016). In addition to the cortical regions, the roles of subcortical structures and thalamo-cortical networks have been highlighted by many theories of consciousness (Fuller et al., 2011; Llinás et al., 1998; Ward, 2011), and the thalamus has been reported to have an important role in controlling the state of consciousness in altered or pathological states of consciousness (Alkire et al., 2000; Uhrig et al., 2016; Schiff et al., 2007). For example, the disconnection and recovery of connectedness has recently been associated with the thalamus, anterior and posterior

cingulate cortex, and angular gyri (Scheinin et al., 2021). Also different localization-free approaches that take advantage of cell-level integration mechanisms (Aru et al., 2020), or of mathematical measures like network dynamics and configurations (Kim et al., 2016, 2018; Li et al., 2019; Moon et al., 2015) or chaos-theoretic views (Toker et al., 2022) are becoming increasingly popular. Further, the framework of predictive coding (Friston, 2010) has been suggested to set the background for many functions that are closely related to consciousness, like dreaming, semantic processing, or sensory connectedness (Hobson et al., 2014; Kuperberg et al., 2020; Sanders et al., 2021).

Several views combining the state-related and content-related correlates of consciousness have also been presented. The brain structures responsible for the state and contents are suggested to act jointly for conscious perception (Bachmann and Hudetz, 2014; Overgaard and Overgaard, 2010). Mashour and Hudetz (2017) describe the level of consciousness as a result of bottom-up processes, which are mediated through subcortical sleep-wake networks, and the contents of consciousness as a result of top-down processes mediated through thalamo-cortical and cortico-cortical networks. Both processes can be degraded by general anesthetics, and Mashour and Hudetz suggest that propofol and halogenated ethers affect both the level and contents of consciousness while dexmedetomidine degrades mostly the level and ketamine mostly the contents of consciousness. It has also been suggested that the state and contents of consciousness are linked by specific pyramidal neurons that are part of both cortico-cortical and thalamo-cortical loops (Aru et al., 2019).

2.1.3 The problem of measuring consciousness

Although consciousness is subjective by its nature, there is a constant need for measuring the state of consciousness objectively in different clinical conditions. The conscious detection of specific, externally presented stimuli can be expressed through behavioral signs, like pressing a button, verbal comments, or mental imagery, and some aspects of experiences can be studied with questionnaires. However, verbal reports are usually needed for accessing the detailed contents of consciousness. The subjective reports (Section 2.5) are not always reliable, and some aspects of the experience may be difficult to describe, but essentially, there are clinical conditions where the voluntary responses or verbal reports cannot be given. Therefore, associations between subjective experience and brain processes are studied to find neural correlates of consciousness that would enable objective monitoring of consciousness (Chalmers, 2013). In the absence of a perfect indicator for consciousness, clinical states are characterized with the help of surrogate measures. For example, disorders of consciousness are defined and monitored based

on motor and communicative tests, like the Coma Recovery Scale – Revised (Bruno et al., 2011; Seel et al., 2010). The depth of anesthesia can be monitored with behavioral and EEG-based measures (Sections 2.2 and 2.2.3) and further confirmed with delayed interviews (Section 2.5).

Determining the timing of an experience reported in a delayed interview is essential for associating an objective measurement with a subjective experience. Serial awakening paradigm is one of the approaches to study the experiences occurring during sleep or experimental sedation within a limited period of time using consecutive awakenings (Casey et al., 2022; Noreika et al., 2009; Siclari et al., 2017). This strategy enables within-state studies: the behaviorally or physiologically similar states may be associated with different types of experiences, which allows contrasting conscious and unconscious time periods. Currently, many efforts are focused on the search for differences in the brain signals between disconnected and unconscious states as determined by retrospective self-report (Casey et al., 2022; Nieminen et al., 2016; Siclari et al., 2017; Wong et al., 2020). In contrast, the disorders of consciousness are often studied by comparing different behaviorally defined diagnosis categories to find neural correlates of consciousness (Beukema et al., 2016). All of the above are examples of the calibration problem of consciousness, that is, the lack of means to prove that the retrospective reports or behavioral diagnoses are accurate reflections of a specific state of consciousness (Browning and Veit, 2020; Michel, 2023).

Many studies on the neural correlates of the state of consciousness are based on a between-subjects design (Scarpelli et al., 2015). In anesthesia studies, predefined doses inducing unresponsiveness in all participants are typically used, and differences between states are inseparable from differences merely related to the dose of the anesthetic. Systematic within-subject analyses can confirm and elaborate information on the potential neural correlates to ensure that the measures are truly associated with the state and not due to general drug-related effects or individual differences between participants. Importantly, trait-like individual characteristics may interfere with the measures that could potentially be used to monitor the state. For example, the anesthetic dose required to achieve a specific behavioral end-point varies between individuals (Chennu et al., 2016; Veselis et al., 2004; Warnaby et al., 2017) and two different anesthetic doses may result in comparable behavioral and self-reported state and cognitive performance (Hall et al., 2000). The individual differences of functional connectivity patterns measured in wakefulness are preserved under dexmedetomidine sedation (Liu et al., 2019) and the strength of the alpha band EEG networks at awake state has been associated with the sensitivity to lose responsiveness due to propofol infusion (Chennu et al., 2016). In another study, the cognitive and behavioral performance of participants receiving anesthetics could not be predicted based on the dose and showed heterogeneity even at single

concentration (Veselis et al., 2004). Also, the reporting frequency of dreams after physiological sleep varies between individuals (Blagrove and Pace-Schott, 2010) and a similar effect can be speculated to be associated with the report frequency after anesthetized states.

Although group-level studies can elucidate general trends to guide the development of further theories and future studies, only the measures that perform reliably at the individual-level can have clinical relevance in monitoring the state of consciousness (Mashour and Avidan, 2017). If subjective experiences were to be combined with objective measures to identify and develop monitors for consciousness, the individual level would be crucial. In order to draw conclusions on the current state of consciousness of a particular individual based on an objective indicator, it is essential to know the baseline level of the indicator in the normal awake state, behavior of the indicator in other altered states, and the effects of the methodological choices made in the process. For example, cognitive event-related potentials are not necessarily detected in all healthy individuals (Cruse et al., 2014; Rohaut et al., 2015; Sculthorpe-Petley et al., 2015). Many potential markers of consciousness tested for unresponsive patients are affected by, for example, age (An et al., 2022; Broderick et al., 2021; Federmeier and Kutas, 2005; Juottonen et al., 1996; Kaiser et al., 2020; Obert et al., 2021; Mah and Connolly, 2018) or comorbidities (Duncan et al., 2009; Kaiser et al., 2020), and the normative baseline groups are required for unresponsive patients for establishing threshold values. Patients with disorders of consciousness show particularly high variability in their brain activity since each patient has a disorder with different etiology and the measurements may be affected by fluctuations in arousal (Curley et al., 2018).

While the methods related to the analysis of verbal reports are relatively simple, the objective measurements aimed at tracking the neural correlates of consciousness often represent the newest and most complex technology and methodology available (Chalmers, 2013). New methods are endlessly introduced, and it may be impossible to compare the results of different studies with each other. The contribution of the methodological choices is particularly high in individual-level studies since the study material is typically smaller than in group-level settings. For example, the effect of the choice of an analysis method for single-subject ERPs has been a topic of vivid discussion (De Lucia and Tzovara, 2016; Gabriel et al., 2016; Naccache et al., 2016). There are numerous ways to analyze the ERPs at the individual level, which complicates comparisons between studies and evaluating the applicability of different methods for determining the state of consciousness. Establishing standardized pathways of measurements and analyses is needed for any measures that could guide clinical decisions.

The use of an active task or external stimulation to study unresponsive patients demonstrates one more problem of measuring of the state of consciousness (Storm

et al., 2017). Mental imagery tasks have demonstrated covert, preserved consciousness in patients who are behaviorally unresponsive due to severe disorders of consciousness (Cruse et al., 2011; Curley et al., 2018; Owen et al., 2006). Although the voluntary brain responses are an intriguing and important way to communicate with the unresponsive patients, the proportion of conscious patients may be substantially higher than the proportion of those who are capable to perform brain-based command following (Schnakers et al., 2009). The voluntary action requires understanding of the instructions, maintenance of attention, and capability of working memory. Consequently, the lack of command-following cannot be considered as evidence of the lack of consciousness (Hohwy, 2009). Also, in the active paradigms used in the context of anesthesia, the unresponsiveness detected with conventional methods or using the isolated forearm technique does not exclude consciousness during anesthesia, but the active paradigms can only confirm the presence of connected consciousness. In contrast to active task paradigms, the task-free measures may be more powerful in the diagnostics of disorders of consciousness (Bekinschtein et al., 2009; Kondziella et al., 2016; Stender et al., 2014). However, stimulation may be beneficial for the detection of the patient's cognitive processes or connected consciousness. The passive paradigms that engage attention through meaningful stimuli are successful prognostic markers in disorders of consciousness (Naci et al., 2014, 2017; Rohaut et al., 2015; Sokoliuk et al., 2021a). Stimulation during unresponsive states may provide additional information on connectedness or the reactivity of the brain in addition to the stimulus-free, resting-state measurements.

2.1.4 Altered and pathological states of consciousness

An altered state of consciousness is a condition with a qualitative and perceivable alteration in the overall pattern of mental functioning compared with the baseline awake state of consciousness (Tart, 1972), or a condition where the neurocognitive background mechanisms of consciousness are likely to produce misrepresentations of the world, like hallucinations, delusions, and memory distortions (Revonsuo et al., 2009). For example, sleep and dreaming and general anesthesia can be considered as altered states of consciousness. The origin of the alteration of the state, such as spontaneous occurrence or physical, psychological, pathological, or pharmacological induction can also be seen as a defining feature of an altered state (Vaitl et al., 2005). In some definitions, altered states of consciousness are described as temporary and reversible states (Revonsuo et al., 2009) but some others include also pathological and potentially permanent changes in consciousness (Cofré et al., 2020; Vaitl et al., 2005). Disorders of consciousness are pathological states that show a change in the state of consciousness compared with the earlier, healthy state of the

individual, but the recovery is typically slow or the state may be permanent. Since sleep and disorders of consciousness are typically unresponsive conditions and thus provide an interesting point of comparison for anesthetic-induced unresponsiveness, they are shortly reviewed below before focusing on general anesthesia (Section 2.2).

Physiological sleep is a natural and regularly occurring state during which disconnected experiences, i.e., dreaming may or may not occur. The sleep cycle consists of non-rapid eye movement (NREM) sleep stages N1, N2, and N3, and rapid eye movement (REM) sleep, and they can be identified based on the EEG, electro-oculogram (EOG), and electromyogram (EMG) signals (Berry et al., 2015). The EEG spectral patterns of different sleep stages constitute a continuum. The N1 stage is characterized by the loss of occipital alpha waves (Prerau et al., 2017). Slow delta oscillations, K-complexes, and sleep spindles (12–15 Hz) are typical in N2 sleep and N3 is dominated by slow delta oscillations (<4 Hz). In REM sleep, the EEG follows an activated pattern of mixed frequencies without K-complexes and sleep spindles (Akeju and Brown, 2017). Dreaming occurs in all sleep stages, with REM sleep being the most optimal for dream experiences to be recalled afterwards (Carr and Solomonova, 2019). NREM dreams are typically shorter, more fragmented, and more thought-like than REM dreams that are characterized by emotional and bizarre contents (Carr and Solomonova, 2019). Although the processing of external stimuli and especially self-relevant, emotionally salient stimuli and informative speech has been reported during N1 and N2 stages (Blume et al., 2017; Legendre et al., 2019), high-level parsing of the speech is disrupted in NREM and REM sleep (Makov et al., 2017). However, a recent report revealed on-line muscle-based responsive communication during REM sleep in a group of lucid dreamers demonstrating the conscious processing of stimuli during sleep (Konkoly et al., 2021).

Disorders of consciousness are states associated with alterations in arousal and/or awareness that are typically caused by cardiac arrest, traumatic brain injury, intracerebral hemorrhage, or ischemic stroke (Edlow et al., 2021). The diagnoses of disorders of consciousness are based on neurological evaluation that mainly utilizes behavioral criteria and emphasizes, for example, sensory, motor, and communicative skills (Seel et al., 2010). Recently, also neurophysiological and brain imaging methods have been recommended as complementary methods for establishing the diagnosis (Giacino et al., 2018; Kondziella et al., 2020). The distinguishing of the different disorders of consciousness is non-trivial and varying nomenclature and sub-division of states has been suggested (Curley et al., 2018; Hermann et al., 2021; Naccache, 2018; Zasler et al., 2019). A rough classification of the disorders of consciousness includes coma where both the consciousness and body functions related to the wakefulness-sleep cycle are absent; unresponsive wakefulness syndrome (UWS, previously vegetative state (VS) or apallic syndrome) where the wakefulness-sleep cycle, respiration, digestion, and thermoregulation are preserved

but the patient is considered unconscious due to the absence of communication or voluntary movement; and minimally conscious state (MCS, or cortically mediated state) where also signs of consciousness, such as visual pursuit, orientation to pain, or nonsystematic following of commands, can be observed (Bruno et al., 2013). The disorders of consciousness are characterized by various electrophysiological and neuroimaging features and some measures have been suggested to help in finding signs of consciousness in subacute and chronic conditions (André-Obadia et al., 2018; Bai et al., 2021; Kondziella et al., 2020; Schiff et al., 2014). The delta and alpha frequency bands are typically accentuated in the EEG of patients with disorders of consciousness (Bai et al., 2021). Based on the current knowledge, covert consciousness detected with volitional responses in fMRI or EEG, also called cognitive motor dissociation, is present in up to 15–20% of patients with disorders of consciousness (Edlow et al., 2021). Out of the patients diagnosed to have UWS/VS, 32–41% might be misdiagnosed because they show some signs of preserved consciousness in further evaluation, although the definition of the UWS/VS only assumes preserved autonomic and reflexive functions (Schnakers et al., 2009; Stender et al., 2014; van Erp et al., 2015; Wannez et al., 2017).

2.2 General anesthesia

General anesthesia is a reversible, drug-induced state that consists of unconsciousness, amnesia, analgesia, and akinesia combined with physiological stability (Brown et al., 2010). The American Society of Anesthesiologists (2019) defines general anesthesia as a state in which the patient is non-rousable even with painful stimulation in contrast to deep sedation where repeated or painful stimulation produces purposeful responses despite the exposure to anesthetics. Sedation can also be defined as a state characterized by diminished cognitive function due to hypnotic or sedative agents while respiratory and cardiovascular functions remain intact (Brown et al., 2010). In some contexts, the term general anesthesia is used to refer to all anesthetic-induced unresponsive states, whereas sedation is used to describe a responsive state under the influence of anesthetic agents. The most important field of application for general anesthesia is surgical anesthesia that is necessary for much of the modern medicine (Brown et al., 2018). Anesthetic agents can be administered as manually controlled continuous intravenous infusion, target-controlled infusion, as an intravenous bolus, or via inhalation (Joshi, 2021; Masui et al., 2010).

Clinical general anesthesia consists of induction, maintenance, and emergence periods (Joshi, 2021). The administration of a small dose of a hypnotic agent, such as propofol, induces sedation and makes the patient calm and rousable (Brown et al., 2010). When the dose is increased, irregular respiratory pattern appears and behavioral responsiveness, muscle tone, and many of the eye-related reflexes are lost

(Brown et al., 2010). Muscle relaxants can be administered at the end of the induction period, after which the patient is typically intubated. The maintenance of general anesthesia can be performed using hypnotic, opioid, muscle relaxant, sedative, and cardiovascular drugs, and the hypnotics can be administered as inhalation or intravenously (Brown et al., 2010; Joshi, 2021). The patients are monitored based on behavioral signs and an anesthesia monitor integrating information on, for example, heart rate, peripheral oxygen saturation, blood pressure, carbon dioxide concentration and mean alveolar gas concentration for volatile anesthetics (Ahonen et al., 2017). Different EEG-derived measures can be used for the adjustment of the depth of anesthesia. The ventilation and thermoregulation of the patient are also supported (Ahonen et al., 2017). Emergence from general anesthesia is marked by the return of spontaneous respiration, increases in the heart rate, blood pressure, and muscle tone, and behavioral responses to pain and tracheal intubation (Brown et al., 2010). The duration of the emergence period varies depending on the anesthetic agents, their dosing, individual's physiological characteristics, and the type and duration of the preceding operation.

2.2.1 Anesthetic drugs

General anesthesia can be induced using drugs that act through different molecular mechanisms. In the clinical setting, typically a balanced general anesthesia is favored, that is, smaller doses of multiple anesthetic agents are used to maximize the desired effects and to minimize the adverse effects (Brown et al., 2018). For example, the antinociception produced by opioids can be supported with dexmedetomidine as a part of multimodal anesthesia (Brown et al., 2018).

Out of the general anesthetic drugs used today, clinically the most significant agents include the intravenous hypnotic propofol and the inhaled gases desflurane, isoflurane, and sevoflurane. These drugs act primarily by modulating the gamma amino-butyric acid A ($GABA_A$) receptors in the synapses between the inhibitory interneurons and the pyramidal neurons of thalamus, brainstem, cortex, striatum, and spinal cord (Brown et al., 2018). In addition to $GABA_A$ receptors, desflurane, isoflurane, and sevoflurane also act through several other mechanisms (Alkire et al., 2008a; Franks, 2008).

Dexmedetomidine is an alpha-2 adrenergic receptor agonist that has effects on both arousal and nociception and its major field of application is in the intensive care (Brown et al., 2018). Dexmedetomidine decreases the arousal by downregulating the noradrenergic excitatory activation of preoptic hypothalamus, thalamus, basal forebrain, and cortex (Brown et al., 2018). Patients can be roused from dexmedetomidine-induced unresponsiveness which has been suggested to resemble natural sleep (Huupponen et al., 2008).

Ketamine acts through N-methyl D-aspartate (NMDA) receptors by inactivating excitatory arousal pathways (Brown et al., 2018). At low doses, ketamine binds to NMDA receptors on GABAergic inhibitory interneurons, which causes disinhibition of pyramidal neurons and cortical activation that may result in hallucinations (Brown et al., 2018). Higher doses of ketamine also block NMDA receptors of excitatory pyramidal neurons (Brown et al., 2018). The inactivation of excitatory arousal pathways from parabrachial nucleus and brainstem to the thalamus and basal forebrain is a major contributor of ketamine-induced decrease of arousal (Brown et al., 2018). Nitrous oxide and xenon are also NMDA receptor antagonists but they have little or no effect on $GABA_A$ receptors (Franks, 2008; Salmi et al., 2008).

2.2.2 Anesthetic-induced effects on the brain and electroencephalogram

Although the molecular targets of different anesthetic drugs are mostly known, the neural circuits responsible for the anesthetic effects have not yet been completely characterized. For example, the roles of bottom-up (mediated through subcortical sleep-wake networks) and top-down (mediated through cortico-cortical and thalamo-cortical networks) processes in the anesthetic-induced states are still disputed (Mashour, 2014; Mashour and Hudetz, 2017). Anesthetic agents may also differ in terms of the roles of different mechanisms in modulating the state of consciousness (Mashour and Hudetz, 2017). For example, propofol may affect both the bottom-up and the top-down mechanisms, whereas dexmedetomidine has been suggested to act mostly on the bottom-up processes (Mashour and Hudetz, 2017).

The reversible unresponsive states induced by general anesthetics and natural sleep share many features. Roughly, the anesthetics act both at subcortical and cortical brain areas but natural sleep is mainly induced by reduced subcortical excitation to the cortex (Akeju and Brown, 2017; Moody et al., 2021). The sedative effects of anesthetic drugs are partly mediated by the arousal-regulating nuclei in the hypothalamus and brainstem, for example, through the disinhibition of neurons in the ventrolateral preoptic nucleus or inhibition of locus coeruleus and awake-promoting nuclei in hypothalamus, such as the tuberomammillary nucleus (Långsjö et al., 2012; Moody et al., 2021). The thalamus has an important role in regulating consciousness (Alkire et al., 2000, 2008a; Kantonen et al., submitted; Mashour and Alkire, 2013; Scheinin et al., 2021). The central lateral thalamus and deep cortical layers have been shown to contribute to the regulation of consciousness: the stimulation of the central thalamus increases arousal during anesthesia and in disorders of consciousness and may cause reactivation of the cortex and modulation of feedforward and feedback connectivity (Bastos et al., 2021; Redinbaugh et al., 2020; Schiff et al., 2007). Also, the thalamus and the brainstem are among the first

areas activated upon emergence from general anesthesia and awakening from NREM sleep (Balkin et al., 2002; Kantonen et al., submitted; Långsjö et al., 2012; Scheinin et al., 2021).

The thalamus has been suggested to regulate the cortical communication through oscillatory activation (McCormick et al., 2015). For example, thalamic nuclei interact with the prefrontal cortex by modulating cortical gain and cortico-cortical functional connectivity (Phillips et al., 2021). During anesthesia, communication across brain regions is concentrated mainly in the structurally connected regions and slow-delta oscillations have been suggested to mediate the isolation of local cortical networks from the rest of the cortex (Lewis et al., 2012; Uhrig et al., 2018). The anesthetic-induced effects of brain connectivity are discussed in Section 2.3.2. Although the precise roles of frontal and posterior cortical areas are unclear in the context of consciousness (Boly et al., 2017; Mashour et al., 2022), there is evidence that the cholinergic stimulation of the prefrontal cortex can counteract the sevoflurane-induced unresponsiveness in rodents (Pal et al., 2018, 2020). In addition, the transition from wakefulness to NREM sleep is characterized by frontal deactivation (Maquet et al., 1997; Muzur et al., 2002; Ruby et al., 2021) and the stimulation of prefrontal cortex has positive effects on patients with disorders of consciousness (Angelakis et al., 2014; Thibaut et al., 2014, 2017).

Since the cortex and subcortical structures are highly interconnected, the changes in the neural activity of the thalamus and subcortical arousal centers are also reflected in the scalp EEG (Ching et al., 2010; Purdon et al., 2015; Seeber et al., 2019). Each anesthetic drug has distinct and dose-dependent EEG effects, which can be considered as evidence of multiple neural circuits being involved in modulating the state (Moody et al., 2021). Typical EEG signatures associated with propofol anesthesia include slow delta waves (0.1–5 Hz) and frontally highlighted alpha oscillations (8–14 Hz) (Akeju et al., 2014a; Purdon et al., 2015; Scheinin et al., 2018). In addition, an initial increase followed by a decrease in the spectral power of the beta band has been reported when the sedation deepens (McCarthy et al., 2008; Purdon et al., 2015; Scheinin et al., 2018). EEG markers typical for sevoflurane, isoflurane, and desflurane are oscillations in alpha, slow-delta, and theta bands, and nitrous oxide is associated with slow delta and beta-gamma oscillations (Purdon et al., 2015). At high doses, propofol, sevoflurane, isoflurane, and desflurane produce burst suppression pattern in the EEG (Moody et al., 2021). Dexmedetomidine-induced unresponsiveness is characterized by alpha or spindle activity (8–15 Hz), slow delta band oscillations (0–4 Hz), and decreased beta power (Akeju et al., 2016a; Purdon et al., 2015; Scheinin et al., 2018; Sleigh et al., 2018). Light dexmedetomidine sedation induces EEG activity typical for the N2 stage of NREM sleep, and deeper unresponsive dexmedetomidine sedation has similarities with N3 sleep (Akeju and Brown, 2017; Huupponen et al., 2008; Ramaswamy et al., 2021).

The effects of ketamine sedation are most prominent in high beta and gamma bands (>20 Hz) and higher doses are associated with altering gamma and delta (0.1–4 Hz) oscillations (Akeju et al., 2016b; Maksimow et al., 2006). Broad spectral changes due to anesthetics have been suggested to be related to disconnected consciousness, while more focal changes within the cingulate cortex may be associated with unconsciousness (Casey et al., 2022). The unresponsiveness induced by some anesthetic drugs can be eliminated with antagonist drugs, which also reverse the associated spectral changes (Ballesteros et al., 2020).

The delta power and especially its saturation to the individual maximal level has been suggested to have potential in monitoring propofol and sevoflurane anesthesia (Ní Mhuircheartaigh et al., 2013; Warnaby et al., 2017). The saturation of slow-wave activity has been suggested to indicate the loss of perception of external stimulation (Ní Mhuircheartaigh et al., 2013). The changes in the slow-wave activity show asymmetry between the induction of and emergence from anesthesia, and abrupt loss of slow-wave activity has been associated with undesired cognitive effects like confusion or delirium (Warnaby et al., 2017).

The alpha band has been of special interest in studies of the EEG correlates of different anesthetized states. Dose-independent decreases in the power of the broad alpha band (7–17 Hz) have been connected with nociception during surgical general anesthesia (Hight et al., 2019). The low level of frontal alpha power in response to propofol or sevoflurane is associated with an increased propensity for burst suppression pattern of EEG (Shao et al., 2020). Since intraoperative burst suppression is associated with postoperative delirium, low power of frontal alpha may be a marker of brain vulnerability in general anesthesia (Shao et al., 2020). Another alpha-related trait-like feature is the association of weak networks in the alpha band before sedation with an increased probability of propofol-induced loss of responsiveness at moderate sedative doses (Chennu et al., 2016). Low frontal alpha power is associated with rousability during dexmedetomidine and propofol sedation (Scheinin et al., 2018) and loss of evoked posterior alpha rhythms is associated with sensory disconnection during ketamine-induced unresponsiveness and NREM and REM sleep (Darracq et al., 2018). Coherent frontal alpha oscillations during propofol anesthesia have been suggested to indicate hypersynchronous communication between the thalamus and frontal cortex and to be associated with behavioral unresponsiveness (Ching et al., 2010; Vijayan et al., 2013) although opposite views have also been presented (Malekmohammadi et al., 2019). An alternative view suggests that flexible cortico-cortical communication is interrupted as a result of stereotypical alpha oscillations (Supp et al., 2011). The spectral power of propofol-induced frontal alpha is several folds higher than that of dexmedetomidine (Akeju et al., 2014a; Scheinin et al., 2018). Dexmedetomidine-induced alpha/spindle oscillations have been suggested to be generated by mechanisms similar to the

spindles in N2 sleep, that is, as a result of interaction of thalamic reticular GABAergic and thalamo-cortical relay cells (Akeju and Brown, 2017; Ballesteros et al., 2020; Huupponen et al., 2008; McCormick et al., 2015; Sleigh et al., 2011).

The mere increased spectral power of frontal alpha and delta does not guarantee the disconnection of consciousness, and therefore the more complex measures of EEG can provide additional information on the brain state (Gaskell et al., 2017). The phase-amplitude coupling of delta and alpha bands shows the frontal "trough-max" pattern in transitional states of propofol sedation, that is, the alpha amplitude is maximal at the trough of delta oscillations (Mukamel et al., 2014; Purdon et al., 2013; Scheinin et al., 2018). However, a broader "peak-max" pattern of alpha amplitude being maximal at the peak of delta is detected in deep propofol sedation (Mukamel et al., 2014; Purdon et al., 2013; Scheinin et al., 2018). The lack of peak-max pattern during general anesthesia correlates with responsiveness measured with isolated forearm technique more efficiently than the frontal alpha power (Gaskell et al., 2017). However, the phase of slow-delta oscillations does not modulate the amplitude of alpha oscillations during dexmedetomidine sedation (Scheinin et al., 2018).

2.2.3 Clinical and experimental indices for the depth of anesthesia

Clinical general anesthesia should be deep enough to suppress intra-operational awareness but excessive drug doses should be avoided as they may cause prolonged emergence period, inefficient early recovery, or postoperative cognitive dysfunction (Chan et al., 2013). The incidence of intraoperative awareness with later recall has typically been reported to range from 0.005% to 0.18% in western countries (Mashour et al., 2009, 2012; Pandit et al., 2014b; Pollard et al., 2007; Sandin et al., 2000; Sebel et al., 2004; Walker et al., 2016; Wennervirta et al., 2002), although also higher incidences have been reported (Errando et al., 2008; Ranta et al., 1998). The reported figures of intraoperative awareness with later recall are likely lower than the true incidence of connected experiences during the maintenance of general anesthesia (Kerssens et al., 2003; Sanders et al., 2017). In a large study performed in the UK and Ireland, the risk factors for spontaneously reported intraoperative awareness included neuromuscular blocking drugs, female sex, the age group of young adults, obesity, juniority of the staff, previous awareness experiences, out-of-hours surgery, emergency, and obstetric, cardiac, or thoracic surgery (Pandit et al., 2014b). Intraoperative awareness can cause immediate undesired feelings like helplessness, anxiety, and panic and it is a risk factor for late symptoms, such as sleep disorders, fear of future operations and post-traumatic stress disorder (Ghoneim et al., 2009; Whitlock et al., 2015). Better understanding of the neural

mechanisms of the anesthetics and online monitoring of the depth of anesthesia beyond the physiological markers and behavioral signs may help in titrating the optimal anesthetic dose. The monitoring should also detect those occurrences of intraoperative awareness that will not be remembered postoperatively (Sanders et al., 2016).

The isolated forearm technique allows the inspection of goal-directed responsiveness during general anesthesia despite of neuromuscular blocking agents. Consequently, the method has improved the understanding of the amnestic effects of anesthetics and the effects of akinetic drugs on the monitoring of the behavioral state during general anesthesia. The technique is based on isolating the patient's arm with a pressure cuff before the induction of a neuromuscular blocking drug (Tunstall, 1977). The continuous use of the isolated forearm method is limited to short operations and experimental settings due to the ischemia caused by the pressure cuff (Russell, 2013; Sleigh, 2013). However, a peripheral nerve stimulator can be used for monitoring the neuromuscular integrity of the hand, and the isolated forearm technique can be used for longer operations if the tourniquet is released approximately 20 minutes after the administration of the muscle relaxant and reapplied whenever additional muscle relaxant is needed (Russell, 1979, 2013; Russell and Wang, 2001). Even the regional use of an antagonist of neuromuscular blockade has been successfully piloted and referred to as the reversed isolated forearm technique (Hamp et al., 2016). However, in general, the isolated forearm technique is still quite rarely used in clinical practice (Sury et al., 2014). In a multicenter study, 4.6% of patients responded with the isolated forearm after tracheal intubation for surgical anesthesia and 42% of them reported having pain (Sanders et al., 2017). In another study, the preservation of connected consciousness after intubation was even more common among young patients (18–40 years), 11% of whom gave task-related responses with isolated forearm, and 49% of them reported pain (Lennertz et al., 2023). In an earlier meta-analysis, as much as 35% of patients participating in 22 different studies showed responsiveness during the induction or maintenance of general anesthesia (Linassi et al., 2018) and another review suggested that the percentage of those reporting pain would be 14% (Sanders et al., 2012). However, the responsiveness detected with the isolated forearm technique has rarely been associated with the postoperative explicit recall of the event (Linassi et al., 2018; Lennertz et al., 2023; Sanders et al., 2017).

Most of the commercially available anesthesia depth indices are based on processed EEG, are unidimensional, and have an index range that should correlate with the state of consciousness varying from wakefulness to unconsciousness. However, many of the present indices do not function properly or comparably with anesthetics with the different mechanisms of action (Abel et al., 2021; Xi et al., 2018). For example, if the index works well with the anesthetics acting primarily

through GABAergic signaling, such as propofol or sevoflurane, it may not perform equally well with alpha-2-adrenergic drugs like dexmedetomidine, or NMDA antagonists like ketamine (Hirota, 2006; Maksimow et al., 2006). Also, the use of multimodal anesthesia complicates the interpretation of agent-dependent indices. The depth-of-anesthesia indices should also perform reliably in individuals of different age despite the different spectral properties of children and elderly compared with young adults. However, the currently available indices are influenced by age (Obert et al., 2021). The commercially available EEG-based measures of anesthesia depth include Bispectral Index (Medtronic, Minneapolis, MN, USA), spectral entropy (Entropy Module, Datex-Ohmeda/GE Healthcare, Helsinki), Narcotrend (Narcotrend Group, Hannover, Germany), auditory evoked potentials (A-line AEP Monitor/2, Danmeter A/S, Odense, Denmark), and SEDLine (Masimo, Irvine, CA, USA). These methods are usually based on proprietary secret algorithms and manufacturer-provided threshold values. Head-to-head offline comparisons of different anesthesia depth indices have been presented only recently (Eagleman et al., 2021). The comparisons of different measures are also hampered by the constant further development of the algorithms while most of the studies demonstrating the clinical significance of these indices are from the early 2000s.

Bispectral index (BIS) can be measured with two or four channels of frontal EEG. The BIS algorithm applies, for example, Fast Fourier Transform to calculate the logarithmic power ratio of frequency bands 30–47 Hz and 11–20 Hz, and bispectrum in frequency bands 0.5–47 Hz and 40–47 Hz (Rampil, 1998). BIS is a unidimensional index whose values range from 100 to 0 and the target level during general anesthesia is between 60 and 40. Although BIS has performed well in many studies (Myles et al., 2004), a meta-analysis suggested that BIS-guided anesthesia reduces the risk for intraoperative awareness only slightly and does not differ from end-tidal concentration-guided anesthesia (Lewis et al., 2019). In another meta-analysis, definite awareness events were fewer in the BIS monitored group compared with the group that was monitored based on the clinical signs only (Messina et al., 2016). In one study with an unselected surgical population, the group monitored with BIS had a significantly lower incidence of intraoperative awareness with explicit recall than the group with no intervention, although BIS monitoring only non-significantly decreased the incidence of intraoperative awareness compared with anesthetic concentration protocols (Mashour et al., 2012). The use of the manufacturer-recommended BIS target levels may lead to sub-optimal depth of anesthesia, which can diminish the effect of BIS in comparison with other means of monitoring (Scheinin and Långsjö, 2013; Yli-Hankala and Scheinin, 2015).

The Entropy is based on frontal EEG and EMG measured with three electrodes and has two subindices: Response Entropy that ranges from 0 to 100 and State Entropy that varies between 0 and 91 (Vakkuri et al., 2004). State Entropy utilizes

the frequency band 0.8–32 Hz and Response Entropy is based on frequencies 0.8–47 Hz. The Entropy has good sensitivity and specificity to behavioral responsiveness and it correlates with drug concentration in clinical conditions (Schmidt et al., 2004; Vakkuri et al., 2004) but there are no large published studies exploring its ability to detect intraoperative awareness (Chhabra et al., 2016). When compared with each other, BIS and Entropy are both sensitive to certain artefacts and EEG patterns, and do not always agree (Aho et al., 2015).

The Narcotrend index has its origins in the visual classification of raw EEG (Kreuer et al., 2004). However, it fails to detect awareness observed with the isolated forearm technique (Russell, 2006). The A-line AEP algorithm is based on processed middle-latency evoked potentials (MLAEP) in response to repetitive auditory stimuli measured in a frontal electrode but information on the performance of the newest versions of the algorithm is insufficient (Huang et al., 2007; Nishiyama, 2013; Struys et al., 2002). SedLine Patient State index can take advantage of four electrodes but it fails to reliably detect the behavioral responsiveness of the patient (Schneider et al., 2003). Based on available evidence and expert consensus opinion, the British National Institute for Health and Care Excellence (NICE) has recommended the monitoring of anesthesia depth with either BIS, Entropy, or Narcotrend for patients receiving total intravenous anesthesia and for patients who are at an increased risk of unintended awareness or of excessively deep general anesthesia (National Institute for Clinical Excellence NICE Diagnostics Guidance, 2012). The results of a large multi-center trial later provided evidence to support the use of anesthesia monitoring based on processed EEG during total intravenous anesthesia with neuromuscular blocking drugs (Pandit et al., 2014b; Pandit and Cook, 2014).

Overall, the monitoring of the depth of anesthesia using EEG-derived measures can reduce the consumption of general anesthetics and shorten the recovery times (Bocskai et al., 2018; Gruenewald et al., 2021). The EEG-derived indices may reduce the risk of postoperative delirium, although only a statistically non-significant effect has been reported (Sumner et al., 2022). However, the currently available indices do not provide sufficient specificity and sensitivity for the detection of intraoperative awareness.

In addition to the clinically used and commercially available indices of anesthesia depth, anesthetic-induced unresponsiveness can be studied with other new or experimental methods. By improving our understanding of the anesthetic-induced unresponsiveness, these approaches can lead to better clinical monitoring of anesthesia depth and may also be applied in other altered and pathological states of consciousness, such as disorders of consciousness. Non-commercial methods have succeeded to demonstrate the preservation of task-related, volitional communication despite unresponsive state. For example, brain imaging can detect covert consciousness during anesthetic-induced unresponsiveness (Campbell et al., 2020;

Huang et al., 2018a). Several novel EEG-based indices have been suggested for the better monitoring of anesthetic depth, and many of them are related to revealing preserved complex brain processing with, for example, the tools of network science or machine learning (Abel et al., 2021; Eagleman and Drover, 2018; Lee et al., 2022; Ramaswamy et al., 2019). For example, the TMS-induced PCI has been suggested as a universal measure for distinguishing states of consciousness (Casali et al., 2013; Casarotto et al., 2016). Perturbational complexity differentiates wakefulness from unresponsiveness induced by propofol, midazolam or xenon, and correlates with the dose of propofol (Casali et al., 2013). Propofol anesthesia is associated with low PCI, and ketamine anesthesia shows high perturbational complexity (Sarasso et al., 2015).

2.2.4 Speech-related and semantic processing in anesthetized states

The sensory disconnection and the aberrations of further processing of stimuli have important roles when trying to understand the brain functioning in the presence of anesthetics. Semantic processing is closely associated with consciousness – for example, the lack of language comprehension is one of the criteria for UWS/VS, and the covert processing of speech and semantics is correlated with a favorable prognosis in disorders of consciousness (Coleman et al., 2009; Sokoliuk et al., 2021a). Knowing how changes in the state of consciousness affect semantic processing is essential to better understand intraoperative awareness during general anesthesia and the disorders of consciousness. Brain activity related to perceived speech may also be used as a model for speech production when constructing brain-computer interfaces for behaviorally unresponsive states (Moon et al., 2022). Recently, it has become possible to decode speech production of words and sentences from paralyzed individual's cortical activity with help of surface electrodes and machine learning models (Moses et al., 2021).

The cortical auditory processing of speech starts with acoustic-phonological processing at the primary auditory cortex at the middle part of the left superior temporal gyrus. The processing of word form continues in the anterior superior temporal gyrus accompanied by left perisylvian sources and the right temporal lobe within 100 ms after stimulus (Friederici, 2012). After that, the syntactic processing is continued in the anterior superior temporal gyrus and the superior temporal sulcus, left inferior frontal and premotor areas, and supramarginal gyrus (Friederici, 2012; Price, 2012). Lexical-semantic processing starts in the middle temporal gyrus, association cortices, anterior temporal lobe, posterior temporal lobe, angular gyrus, left lateral and medial superior frontal gyri, and ventral inferior frontal gyrus (Friederici, 2012; Price, 2012). Activation in the precuneus and the posterior cingulate cortex are associated with longer narratives (Friederici, 2012; Price, 2012).

Numerous studies have shown brain activation elicited by auditory stimuli during sedation or general anesthesia. Primary sensory processing is relatively well preserved in primary auditory, visual, and somatosensory cortices during anesthetic-induced unresponsiveness (Haider et al., 2013; Krom et al., 2020; Schroeder et al., 2016). The brainstem auditory evoked potentials (BAEP), that reflect the activation of the auditory nerve and brainstem, are relatively unaffected by anesthetic drugs (Pruvost-Robieux et al., 2022; Seubert and Herman, 2017). The MLAEP have their generators in the thalamus and the primary auditory cortex and show dose-dependent increases of the latency and decreases of the amplitude in response to many anesthetics (Plourde, 2006; Pruvost-Robieux et al., 2022; Seubert and Herman, 2017). Intracranially recorded auditory evoked potentials within 600 ms of the stimulus are suppressed in the prefrontal cortex already at responsive propofol sedation but evoked potentials in the auditory cortex do not degrade before the loss of responsiveness (Nourski et al., 2021). Also based on fMRI, propofol decreases auditory processing in a dose-dependent manner but primary cortical responses are partially preserved even in general anesthesia (Dueck et al., 2005; Plourde et al., 2006). Moderate and deep propofol and ketamine sedation allow the preservation or even amplification of brain activity in response to sound stimuli in macaques, and propofol has been suggested to induce partial functional disconnection between the auditory cortex and the subcortical regions (Uhrig et al., 2016). Mild dexmedetomidine and midazolam sedation but not propofol sedation decrease the fMRI activity seen in the auditory cortex in response to music (Frölich et al., 2017). In a rodent study, the effect of dexmedetomidine on the primary auditory cortex differed from propofol and isoflurane: the processing of animal vocalization stimuli was enhanced during dexmedetomidine sedation and decreased under propofol and isoflurane sedation, and the loss of responsiveness further accentuated the dexmedetomidine-induced effects (Banks et al., 2018).

A variety of auditory, non-semantic ERPs has been studied in propofol anesthesia. The amplitude of the negative ERP component observed 100 ms post-stimulus, N1, decreases at increasing doses of propofol (Haenggi et al., 2004; Simpson et al., 2002; Yppärilä et al., 2002, 2004a, 2004b). Some studies have also reported an increase in the latency of N1 during anesthesia (Yppärilä et al., 2002, 2004a). Propofol reduces but does not always completely abolish the mismatch negativity (MMN) effect that is observed as a difference between standard and deviant stimuli at 150–250 ms post-stimulus (Heinke et al., 2004a; Koelsch et al., 2006; Simpson et al., 2002; Yppärilä et al., 2002). The preservation of MMN and P3a (related to passive, task-independent attention switch) during deep sedation suggests that bottom-up attention and auditory sensory memory are functional although degraded during propofol anesthesia (Koelsch et al., 2006; Nourski et al., 2018; Yppärilä et al., 2002). The P3b, that requires task-related attention, is lost

during deep sedation (Koelsch et al., 2006; Nourski et al., 2018). The P3b can remain partially degraded and P3a may not be present at all during the recovery period, which suggests impaired attentional processes due to anesthetics (Koelsch et al., 2006). The local-global paradigm features MMN-like effects induced by local deviants and P3b-like effects induced by global deviants. In macaques, the processing of global deviants is preserved during propofol anesthesia although the processing of local deviants is degraded (Uhrig et al., 2016).

Also, the processing of word stimuli has been found to be preserved in light sedation. In one fMRI study, the processing of auditory word stimuli was comparable before and after propofol-induced loss of responsiveness although less efficient in the unresponsive state (Ní Mhuircheartaigh et al., 2013). The processing only changed after the increasing dosing caused the saturation of the slow delta (0.5–1.5 Hz) power of EEG, which the authors suggest as an indicator of isolation of the thalamo-cortical network from external stimulation. Recently, propofol-induced unresponsiveness has been shown to disrupt the connections of associative cortices in an experiment with simple auditory frequency stimuli and speech stimuli (Krom et al., 2020). In one study, sevoflurane degraded the brain responses elicited by repeated auditory word stimuli in a dose-dependent manner (Kerssens et al., 2005). The auditory processing of words and the habituation effect in response to repetition were preserved in the auditory, frontal, parietal, and occipital cortices under light sevoflurane sedation but all stimulus-related activation was lost in deep sedation (Kerssens et al., 2005). Furthermore, the activity elicited by words and other sounds differs in the superior temporal areas in propofol sedation and this differentiation is lost in general anesthesia (Plourde et al., 2006). Interestingly, scrambled words have been found to induce greater activity in the planum temporale compared with normal words in general anesthesia (Plourde et al., 2006).

The further comprehension of the meaning, measured as an fMRI difference between sentences including ambiguous and unambiguous words, degrades already at light propofol sedation in the inferior frontal and posterior temporal cortices (Davis et al., 2007). However, the differentiation of speech and signal-correlated noise in the temporal lobes is preserved both in light and deep sedation, although prefrontal and premotor responses to speech are lost in deep sedation (Davis et al., 2007). Another study found that responsive propofol sedation degraded the activation of the left inferior frontal cortex but not the activation of the left inferior temporal gyrus during a semantic decision task when the participants were able to respond accurately (Adapa et al., 2014). In accordance with the study of Davis and coworkers (2007), this study found that words induced higher activity in the left inferior temporal gyrus than non-speech sounds (Adapa et al., 2014). In another fMRI study, the frontal activation elicited by sentence stimuli was lost at unresponsiveness induced by propofol administration (Heinke et al., 2004b). The

sentence-related activation in the middle part of the superior temporal gyrus was initially preserved during unresponsiveness but lost after an additional dose increment (Heinke et al., 2004b). In a fourth propofol-based study, the task-related effects were preserved in the primary auditory cortex but lost in the inferior frontal gyrus and premotor areas during auditory word stimulation of unresponsive participants (Liu et al., 2012). Also the connectivity between the auditory cortex and higher-order areas was lost upon unresponsiveness (Liu et al., 2012). In another recent study, the processing of verbal stories was preserved in the auditory cortices but strongly degraded in the fronto-parietal regions during propofol-induced unresponsiveness which was suggested to be due to the disconnection between sensory and higher-order networks (Naci et al., 2018).

The findings regarding auditory and semantic processing in anesthesia show similarities with observations from NREM sleep and disorders of consciousness. During sleep, activity in the auditory thalamus and the primary auditory cortex remain unchanged or only mildly degraded but the regions related to language processing in the superior temporal gyrus show decreased activation, and the inferior frontal gyrus is silenced (Wilf et al., 2016). The differential processing of one's own name in comparison with other names is preserved during natural sleep, and the processing of speech by unfamiliar voices remains accentuated (Ameen et al., 2022; Perrin et al., 1999). Preferential processing of participant's own name and ability to follow task instructions also differentiates patients in MCS from those with UWS/VS (Schnakers et al., 2008). Preserved speech discrimination and processing of ambiguity have been observed in some patients in MCS and UWS/VS and it correlates with positive prognosis (Coleman et al., 2007, 2009).

In summary, auditory activation occurs in the brain during propofol and dexmedetomidine sedation (Davis et al., 2007; Frölich et al., 2017; Heinke et al., 2004b), although anesthesia may prevent higher-order processing of the sensory information (Liu et al., 2012). The discrimination of words and other sounds is preserved during light experimental propofol anesthesia although the processing of, for example, ambiguity is lost already at low doses (Adapa et al., 2014; Davis et al., 2007).

2.2.5 Memory in anesthesia

Memory loss, amnesia, is one of the purposes of general anesthesia. Testing the open, explicit recall is usually a part of the post-anesthetic procedure, for example in the form of the modified Brice questionnaire (Section 2.5.2). However, post-anesthetic explicit recall does not necessarily reflect the experiences during anesthesia because of the memory effects of the anesthetics (Sanders et al., 2017; Sandin et al., 2000). Even in an immediate interview after one hour of responsive or unresponsive

sedation with propofol, dexmedetomidine, sevoflurane, or S-ketamine, confirmed awareness reports are rare with an incidence of 1% (Radek et al., 2021). However, post-anesthetic memory traces of the verbal stimuli presented during anesthesia have been detected in many studies using different recognition tasks to test explicit or implicit memory (Deeprose et al., 2004, 2005; Iselin-Chaves et al., 2005; Kerssens et al., 2009; Lubke et al., 1999; Stonell et al., 2006). Anesthetics do not seem to affect the memorization of stimuli presented during the pre-anesthesia period (Hall et al., 2000; Pryor et al., 2010; Veselis et al., 1992, 2004).

Explicit memory refers to conscious memory for experiences that can be recollected or expressed to feel familiar (Gazzaniga and Heatherton, 2006). Explicit recall may be tested in open interviews after anesthesia or in cued recall or recognition tasks, such as the yes/no and forced choice tasks. Implicit memory refers to the unconscious influence of past experiences on behavior. Typically, implicit memory affects performance but not overt retrieval. Thus, to measure implicit memory, tests such as reaction times or word stem completion tasks can be used. Implicit memory traces formed under exposure to anesthetics have been detected in some studies (Deeprose et al., 2004, 2005; Flouda et al., 2013; Ghoneim et al., 2000; Lubke et al., 1999; Münte et al., 2003). A recent meta-analysis mainly focused on implicit memory during anesthesia but also included studies using only explicit recognition memory, and found that the memory formation was associated with an impaired overall physical condition (American Society of Anesthesiologists physical status classification, ASA, III–IV) (Linassi et al., 2021). Interestingly, the observations of the presence of implicit or recognition memory have been more common after general anesthesia than after deep sedation and premedication with benzodiazepines seems to decrease implicit memory formation (Linassi et al., 2021). Surgical stimulation increases the probability of later implicit memory traces (Deeprose et al., 2004).

Recognition memory is a form of retrieval of explicit memory and it can be divided into two processes – recollection and familiarity (Carlesimo et al., 2015; Scalici et al., 2017; Wais et al., 2006). During recollection, a stimulus that is judged as having been previously encountered cues the recall of specific details that are associated with the stimulus in memory. This may mean, for example, recollection of what one was thinking or feeling when the stimulus was previously encountered. Familiarity means that the recognition of a stimulus does not cue the recall of any additional detail, but the experience of remembering is based solely on the perceived memory strength of the recognized stimulus.

Different types of tasks can be used for testing the recognition memory, including the remember/know task, the yes/no recognition task and the forced choice task. Studies aiming at separating recollection and familiarity utilize the remember/know task where participants are instructed to respond “remember” if

they can recall contextual information about previous encounters of the stimulus (recollection) and "know" if they know that the stimulus has been encountered before but cannot retrieve its context (familiarity) (Kirwan, 2016). The yes/no task is based on the simple question of whether the stimulus has been previously encountered. In the forced choice task, the participant has to decide which of the alternatives has been encountered before. The yes/no task could be hypothesized to favor recollection memory in contrast to a forced choice test, yet familiarity and recollection have been observed to contribute equally in these two protocols (Bayley et al., 2008; Khoe et al., 2000).

Recognition memory for repeated word stimuli presented during surgical sevoflurane anesthesia has been observed postoperatively (Kerssens et al., 2009). In another study, the recognition memory for verbal stimuli presented during propofol-induced unresponsiveness was at the random level after recovery (Liu et al., 2012). At sedative concentrations, the high-performing subset of individuals receiving dexmedetomidine, propofol, or thiopental have been found to be able to encode 90% of the information in the long-term memory (Veselis et al., 2004). In the same study, sedation lowered the rate of recognition irrespective of the drug but propofol had a greater effect on the retrieval from the long term memory than dexmedetomidine or thiopental (Veselis et al., 2004). In some but not all studies, the repetition of stimuli during anesthesia has been found to increase the probability of later recall (Block et al., 1991; Bonebakker et al., 1996). Propofol and midazolam have been shown to affect the recollection and familiarity processes to a similar extent (Veselis et al., 2009). Dexmedetomidine has been suggested to have a greater effect on the familiarity process than on the recollection (Veselis et al., 2009) but such a difference was not detected in another study (Hayama et al., 2012). The loss of memory due to dexmedetomidine sedation is dose-dependent and has been suggested to be mostly associated with memory encoding, which is in contrast to propofol that mainly affects the retrieval of information from long-term memory (Hayama et al., 2012; Pryor et al., 2010; Veselis et al., 2008). However, in one study, the substantial loss in recollection performance immediately after the presentation of a word list during dexmedetomidine sedation was independent of the dose used (Hall et al., 2000).

In the absence of anesthetics, emotional content has a preferential memory trace over emotionally neutral material (Talmi, 2013). Dexmedetomidine degrades the memory on emotional and neutral stimuli similarly and the emotional stimuli presented during light dexmedetomidine sedation are memorized better than the neutral stimuli (Hayama et al., 2012). Emotional and neutral stimuli are processed at a comparable speed during dexmedetomidine sedation (Hayama et al., 2012). In contrast, propofol and sevoflurane degrade the recognition of emotional stimuli more than the recognition of neutral stimuli (Alkire et al., 2008b; Pryor et al., 2015). Both dexmedetomidine and propofol cause the degradation of the hippocampal response

to neutral and emotionally arousing stimuli already at sedative levels but have little effect on the amygdalar response during sedation (Hayama et al., 2012; Pryor et al., 2015). Because posttraumatic effects due to intraoperative awareness are possible without explicit recall (Wang et al., 2012; Whitlock et al., 2015), it would be important to better understand the memory traces related to neutral and affective stimuli during anesthesia.

2.2.6 The phases of losing consciousness – the Hierarchical Framework of Experiences

General anesthetics represent a possibility to manipulate the state of consciousness in a gradual and controlled manner, allowing the examination of the phases preceding the loss of consciousness. For example, Långsjö and co-workers (2012) suggested four schematic layers, all of which are required for behavioral responsiveness: consciousness, awareness and comprehension of stimuli, will and intention to respond, and ability to respond.

In the context of this thesis, I suggest that responsiveness, connectedness, and consciousness can provide a relevant framework for describing the qualitatively different phases associated with the anesthetic-induced loss of consciousness. This framework is hereafter shortened as the Hierarchical Framework of Experiences. The framework is not intended to be generalizable to other altered states of consciousness. The framework consists of four different phases induced by deepening sedation: 1. responsive state with connected consciousness, 2. unresponsive state with connected consciousness, 3. unresponsive state with internally-generated experiences, and 4. unresponsive and unconscious state (Figure 1). Thus, according to this framework, responsiveness is lost first, then the connectedness of the experiences, and finally experiences in overall. The framework describes the phases of losing abilities – responding, perceiving the surroundings, and experiencing. Obviously, unresponsiveness can also occur in the responsive state due to unwillingness to respond, and also disconnected experiences may occur during the connected states.

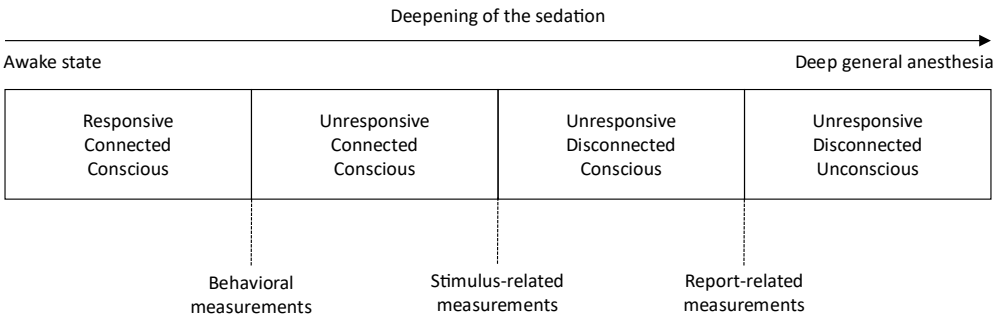

Figure 1. Framework of the characteristics related to losing consciousness in the context of general anesthesia. The four different phases can be differentiated using, for example, the methods shown at the bottom of the figure.

This framework is simplified and each of the four categories could be further dissected into subcategories. In reality, the shifts between the states are likely gradual instead of having sharp boundaries. Not all the states may always be experienced between the awake state and deep general anesthesia, or the phases may be too short to be measured. The phases associated with deepening anesthesia and their order may differ between anesthetic drugs in terms of, for example, to what extent the anesthetic induces dream-like content. The framework does not encompass the anesthetic-induced alterations in the contents of consciousness, such as hallucinatory experiences due to sedation in responsive state but the preserved possibility for responsiveness, connectedness, or consciousness. Although the framework is intended to depict the loss of consciousness, it might also describe the emergence from general anesthesia in a reversed order. It has been shown that responsiveness fluctuates during long anesthesia periods at the low drug levels (Kantonen et al., submitted), and a similar phenomenon might apply to connectedness and consciousness. The potential overlap of the hypnotic effect of anesthetic drugs and natural sleep may also affect the possible instability of the state during anesthesia.

The framework allows defining objective and measurable criteria for the different phases. Responsive and unresponsive states can be differentiated based on behavioral measurements. Connected and disconnected states in the presence of consciousness can be differentiated based on stimulus-related measurements requiring conscious processing or explicitly reported awareness reports. Out of the currently available measures, the disconnected but conscious state could be best differentiated from unconsciousness based on interview reports on subjective experiences.

However, these measurements may not enable a complete characterization of the individual's state. On one hand, responding with, for example, handle presses may become an automatized process that does not necessarily imply (connected)

conscious experiences (Gaskell et al., 2017). On the other hand, loss of interest or unwillingness to respond may cause unresponsiveness despite the ability to respond (Pandit, 2013). Since measuring specific contents of consciousness based on stimuli is not necessarily representative of the whole state of consciousness, the interview reports may also be important for differentiating the connected and disconnected states. Some of the cognitive processes decay earlier than others (Chennu and Bekinschtein, 2012; Wang et al., 2012), which may complicate the use of stimulus-related cognitive processing to index connected consciousness. Automatic brain responses can be present although higher processing is lost, which highlights the need for the careful selection of the test paradigm that involves the relevant processing in order to differentiate connected and disconnected states. Further, the anesthetics affect also unconscious processing, and the stimulus-related measure should not decay too early. The differentiation of the disconnected conscious and unconscious states is influenced by the limitations related to assessing subjectively reported experiences and is confounded by many biases, such as memory effect, willingness to report, and subjective effects in the interpretation of the reports (explored in Sections 2.1.3 and 2.5). Memory formation adds another layer of complexity that is relevant from the viewpoint of clinical practice. Memory encoding may or may not occur in the first three phases of the suggested framework. Some types of experiences, such as reflective consciousness, thoughts, or opinions, are difficult to assign in a specific phase of the framework.

2.3 Connectivity

In order to understand the functioning of the brain and its changes, it is essential to comprehend the complex network structure of the brain and the interactions between and within the networks (Fox et al., 2005). In the science of brain networks, the brain can be described at the macroscopic level as a small-world network where the nodes can be, for example, EEG or MEG sensors, sources reconstructed from electromagnetic signals, voxels of brain images, or broader structural or functional organizational units (Bassett and Bullmore, 2017; Liao et al., 2017). Originally, the brain networks were assumed to have symmetrical interactions between the different brain regions but currently the main topic of interest is in the directionality of the networks.

The key concept in the science of brain networks is connectivity that is a measure of the interdependence of activity in different brain regions. Connectivity can be defined as functional integration in the brain in contrast to the activation of a segregated brain region (Friston, 2011) and it can be studied using many methods, such as EEG, MEG, fMRI, and PET. Structural connectivity means the connectivity mediated by neuroanatomical links that can be measured using, for example,

magnetic resonance or diffusion tensor imaging (Cao et al., 2022). In contrast, functional connectivity measures the statistical dependency of electromagnetic or hemodynamic signals between different regions and its directed version is typically called directed connectivity. Functional connectivity differs from effective connectivity that can be defined as the causal influence between two neuronal systems (Friston, 2011).

2.3.1 Measurement of connectivity

The comparison of the studies on connectivity is complicated by methodological differences related to the choice of imaging or neurophysiological measurement modality, as well as to the task and stimulation used. When studying the state of consciousness, the resting-state and stimulus-related measures have been reported to reveal either critically different (Naci et al., 2018) or similar results (Bourdillon et al., 2020). For example, although most of the resting-state studies point out the importance of changes in the feedback connectivity during general anesthesia, especially the feedforward connections are highlighted when the brain is stimulated with TMS during anesthesia (Sanders et al., 2018). Naci and colleagues (2018) found that the loss of interaction between the sensory and fronto-parietal cortices was the key mechanism of disrupted processing of external stimuli in propofol anesthesia, but the resting-state measurements during anesthesia were characterized by decreased connectivity within those networks.

Among the several different methods to measure functional, directed, or effective connectivity using EEG or brain imaging, the simplest method to find statistical dependencies between signals is correlation in the time domain and coherence in the frequency domain (He et al., 2019). In fMRI studies, functional connectivity is traditionally measured based on correlation coefficient calculated over an entire scan or experimental condition (Friston, 2011; Lurie et al., 2020; Tagliazucchi and Laufs, 2015) but currently the field is moving towards dynamic and multidimensional connectivity measures. However, the new dynamic techniques have given rise to methodological challenges and functional questions, such as the effects of structured noise, the use of too short sliding windows, non-stationarity of BOLD signal, or the selection of region-of-interest (Basti et al., 2020; Hutchison et al., 2013; Lurie et al., 2020; Tagliazucchi and Laufs, 2015). The EEG-based techniques typically employ the phase synchronization of signals from two electrodes. There is a strong correlation between synchrony-based connectivity hubs of EEG and brain glucose metabolism detected with PET (Chennu et al., 2017). Optimal phase synchronization is thought to facilitate the communication between regions while an opposite phase difference suppresses it (Fries, 2005). Coherence is commonly used in the context of EEG although it is prone to errors related to zero-

lag sources (Bastos and Schoffelen, 2015; Palva et al., 2018; Vinck et al., 2011). Indeed, many of the EEG-based methods for studying connectivity are sensitive to the effects of volume conduction and common reference channel, and these problems can be approached using local referencing like current source density, source reconstruction, or using methods that are insensitive to zero-lag interactions (Bastos and Schoffelen, 2015). Many undirected measures related to coherence have been introduced, like phase locking value, phase coherence, imaginary coherency, pairwise phase consistency, or phase lag index (PLI) (Bastos and Schoffelen, 2015; He et al., 2019). The PLI is a measure of phase synchronization with a nonzero phase lag, which makes it less sensitive to volume conduction and the choice of reference electrode (Stam et al., 2007). In a refined version of PLI, the weighted phase lag index (wPLI), the phase-locking values are weighted by the magnitude of the imaginary component of the cross spectrum (Vinck et al., 2011).

To detect asymmetric connectivity, directed measures are needed. One example is directed phase lag index (dPLI) that is defined as the probability that the phase of one time series (EEG signal) lags the instantaneous phase of another signal (Stam and van Straaten, 2012). Other possibilities for studying directed connectivity are Granger causality that is based on linear autoregressive modeling of time-series, directed transfer function, partial directed coherence, phase slope index, and transfer entropy (Bastos and Schoffelen, 2015; He et al., 2019).

2.3.2 Connectivity in altered and pathological states of consciousness

Several studies have reported different connectivity patterns between anesthetic-induced unresponsiveness and wakefulness (Boly et al., 2012; Jordan et al., 2013; Ku et al., 2011; Lee et al., 2009, 2013a; Ranft et al., 2016; Untergehrer et al., 2014; Vlisides et al., 2017), mild and unresponsive sedation (Boly et al., 2012; Guldenmund et al., 2016; Lee et al., 2017a), or unresponsive sedation and recovery period (Ku et al., 2011; Lee et al., 2009, 2013a; Vlisides et al., 2017). Connectivity may therefore provide tools to monitor anesthetic-induced unresponsiveness and unconsciousness. However, since the experimental states compared in the previous reports have been obtained by using different anesthetic doses, changes related to unresponsiveness typically cannot be dissociated from the drug-induced effects. For example, in EEG-based studies, especially alpha band connectivity networks show decreased efficiency during propofol (Chennu et al., 2016; Lee et al., 2017b, 2013a), sevoflurane (Blain-Moraes et al., 2015; Kim et al., 2016) and ketamine (Blain-Moraes et al., 2014) sedation, yet it is unclear whether these changes are due to the drug itself or the state of consciousness. The comparisons are further complicated by the fact that connectivity may show asymmetry in neural dynamics between the loss

and recovery of responsiveness (Huang et al., 2021; Kim et al., 2018): in one study, the loss of responsiveness induced by propofol was associated with gradual changes in functional connectivity and in the timescale of neural processing but the emergence was associated with an abrupt restoration of the cortical speed of processing and an increase in subcortico-cortical connectivity (Huang et al., 2021). In addition, only a limited selection of drugs has been previously studied with no studies exploring the effects of dexmedetomidine on electroencephalogram-based measures of connectivity other than coherence (Akeju et al., 2014a, 2016a).

Fronto-parietal resting-state networks and temporo-parietal-occipital areas, also called the posterior hot zone, have been suggested to be essential for human consciousness (Bonhomme et al., 2019; Hudetz and Mashour, 2016; Ihalainen et al., 2021; Koch et al., 2016; Laureys and Schiff, 2012; Siclari et al., 2017). Especially the connectivity in certain resting-state networks, namely default mode network (DMN), salience network, central executive network, and dorsal and ventral attention networks have been studied during anesthesia. The connectivity-related mechanisms of loss of consciousness suggested in the literature include the disruption of thalamo-cortical and cortico-cortical connectivity within the fronto-parietal networks (Boveroux et al., 2010; Jordan et al., 2013; Schrouff et al., 2011), disruption of thalamo-cortical but not cortico-cortical connectivity (Akeju et al., 2014b), disrupted cortico-cortical but not thalamo-cortical connectivity (Boly et al., 2012; Monti et al., 2013; Murphy et al., 2011), disrupted frontal functioning (Guldenmund et al., 2016; Liu et al., 2017a, 2017b), and the loss of complexity of sparsely connected regions (Pappas et al., 2019). In some studies, the cortico-thalamic connectivity has been preserved at loss of responsiveness but changes have occurred in the subcortical network, including the putamen and amygdala (Mhuircheartaigh et al., 2010; Sanders et al., 2012). The decreased within-network activity in the frontal lobe and medial thalamus have been suggested to influence the reduction of the between-network communication (Golkowski et al., 2019). The suggested mechanisms related to anesthetic-induced states are controversial and complicated by differences in the methodology and terminology. For example, the feedforward projections are measured either from thalamus or cortex to different cortical structures and feedback projections may start from higher-order or lower-order cortex (Mashour, 2019a; Murphy et al., 2019). When studied separately, the thalamo-cortical connectivity has been preserved between the thalamus and the primary sensory areas although thalamic connections to the higher-order areas have been decreased during anesthesia (Boveroux et al., 2010; Murphy et al., 2019; Ranft et al., 2016).

The degradation of feedback signaling by anesthetics has been recently associated with the loss of both thalamo-cortical and cortico-cortical connectivity due to the decoupling of signaling at the apical dendrites of pyramidal neurons

(Suzuki and Larkum, 2020), giving rise to the Dendritic Integration Theory of consciousness (Aru et al., 2020). General anesthetics also cause reversible cortical-wide synchronization of pyramidal layer 5 neurons (Bharioke et al., 2022). As the layer 5 pyramidal neurons are the main source of the EEG signal, the EEG is an interesting method for studying the whole-brain effects of anesthetics. EEG-based studies on anesthetic-induced changes in connectivity have highlighted the fronto-parietal connections. The loss of frontal-to-parietal feedback connectivity has been reported in many studies (Lee et al., 2013a; Blain-Moraes et al., 2014; Jordan et al., 2013; Ku et al., 2011; Lee et al., 2009, 2013b; Boly et al., 2012; Lioi et al., 2019; Muthukumaraswamy et al., 2015; Ranft et al., 2016; Untergehrer et al., 2014; Vlisides et al., 2017; Wang et al., 2022), and also the suppression of parietal-to-frontal feedforward connectivity has been observed (Wang et al., 2022). The functional disconnection between the anterior and posterior brain structures measured with fMRI is associated with a reduction of frontal-to-parietal directed connectivity detected by EEG-based symbolic transfer entropy and with a reduction of frontal permutation entropy, which highlights the usefulness of the EEG-based frontal monitoring of anesthesia (Jordan et al., 2013; Ranft et al., 2016). The fronto-parietal loss of connectivity in anesthesia may be induced by cortico-cortical or thalamo-cortical changes or their combination (Hudetz and Mashour, 2016). Also other brain regions, such as the anterior insula, have been suggested to fragment the anterior-posterior connectivity (Warnaby et al., 2016). However, in a recent study, fronto-parietal feedback connectivity increased in propofol anesthesia and loss of both the parieto-frontal feedforward connectivity and effective connectivity within the temporo-parietal-occipital areas was related to propofol-induced unresponsiveness (Ihalainen et al., 2021).

Taking together the results obtained using the different methods, anesthetic drugs disrupt the functional connectivity between the anterior and posterior cortices and the anterior-to-posterior directed connectivity (Hudetz and Mashour, 2016). Anesthetics reduce (Boly et al., 2012; Jordan et al., 2013; Ku et al., 2011; Lee et al., 2009, 2013a, 2013b; Lioi et al., 2019; Untergehrer et al., 2014; Vlisides et al., 2017) or even reverse (Lee et al., 2013a; Lioi et al., 2019; Ranft et al., 2016) the dominant anterior-to-posterior information flow of the normal awake state, which may be due to a more prominent reduction in the feedback connectivity than in the feedforward connectivity (Ku et al., 2011; Lee et al., 2009, 2013b; Untergehrer et al., 2014). However, opposing views have also been suggested, for example, when evoked responses are studied instead of resting-state connectivity (Sanders et al., 2018) or methods based on Granger causality have been used (Maksimow et al., 2014; Nicolaou et al., 2012; Ryu et al., 2017).

Despite the growing evidence highlighting the loss of anterior-posterior connectivity in anesthetized states, the picture is not clear. Fronto-parietal

connectivity during anesthesia is not stable and therefore does not reliably reflect the state but the patterns of EEG connectivity alter dynamically during experimental isoflurane and surgical general anesthesia (Li et al., 2019; Vlisides et al., 2019). However, the connectivity patterns are more stable among children and adolescents (Puglia et al., 2022). The frontal-parietal connectivity measured with wPLI in the alpha frequency band does not correlate with the emergence from general anesthesia (Zierau et al., 2021). It has been shown that connectivity and phase-amplitude coupling within the structurally densely connected fronto-parietal network increase as a result of propofol anesthesia in non-human primates (Ma et al., 2019). This is in line with the previous results showing that connections tend to concentrate in the structurally connected regions during anesthesia and in disorders of consciousness (Demertzi et al., 2019; Uhrig et al., 2018), and long-distance connections are decreased more than the local ones (Schröter et al., 2012). Namely, the local synchronization may impede the communication between distant brain regions during unresponsiveness (Huang et al., 2018b). Also other studies have suggested the simplification of cortical connectivity dynamics as a sign of the anesthetic-induced unresponsiveness (Golkowski et al., 2019; Vlisides et al., 2019). This highlights the need for circuit-specific approaches in understanding the anesthetic mechanisms and in the monitoring of the patients (Lee and Mashour, 2018; Mashour, 2019b).

In addition to the connectivity between the anterior and posterior parts of the brain, the importance of the connectivity within the frontal lobe, an essential contributor in higher-order information processing, has been highlighted in the context of anesthesia. Propofol and sevoflurane decrease the activity and connectivity of the frontal lobe, showing early and large effects compared with the other parts of the brain in fMRI studies (Deshpande et al., 2010; Guldenmund et al., 2016; Liu et al., 2017a; Ranft et al., 2016). Nevertheless, prefrontal-frontal connectivity in the alpha frequency band measured using phase synchronization increases during surgical anesthesia (Puglia et al., 2022; Vlisides et al., 2019) and increased alpha frontal-to-prefrontal connectivity has also been reported in moderate and deep propofol sedation (Lee et al., 2017a). Both dexmedetomidine and propofol induce frontal coherence in the broad alpha band (Akeju et al., 2014a, 2016a; Purdon et al., 2013). However, another study reported frontally unchanged alpha band functional connectivity by propofol-induced unresponsiveness, yet the transitions between responsive and unresponsive states induced increased connectivity in the beta frequency band (Lee et al., 2017b). The importance of studying directed connectivity during anesthesia was highlighted by a study focusing on ketamine anesthesia that found no change in prefrontal-frontal alpha functional connectivity but the prefrontal-to-frontal connectivity was reduced (Vlisides et al., 2017). The frontal networks dominate in propofol anesthesia and the state of responsiveness

correlates more strongly with the changes in network topology than with the strength of connection (Lee et al., 2013a). Many of the different functional connectivity patterns observed during isoflurane anesthesia are predominantly localized in the prefrontal-frontal area (Li et al., 2019) and the hypersynchronous frontal theta-alpha activity is a dominant marker of anesthetic maintenance in children (Puglia et al., 2022). It seems that frontal cortical areas have an important role in the arousal-promoting networks (Mashour et al., 2022).

Many of the effects of anesthetics on connectivity generalize over different anesthetic drugs. For example, propofol and dexmedetomidine have been shown to reduce both local and global information transfer (Hashmi et al., 2017; Monti et al., 2013). However, some of the anesthetic effects on connectivity may be agent-specific, and less is known about dexmedetomidine than about propofol or halogenated ethers. For example, dexmedetomidine has been found to disrupt the cortico-cortical fronto-parietal connectivity less than other anesthetics (Akeju et al., 2014b). Propofol and volatile agents affect cortico-cortical connections in addition to the potential thalamo-cortical disruption (Boly et al., 2012; Boveroux et al., 2010; Monti et al., 2013; Palanca et al., 2015; Ranft et al., 2016). Akeju and co-workers (2014b) suggested that dexmedetomidine impairs thalamo-cortical resting-state connectivity similarly to NREM sleep (Picchioni et al., 2014). In another study, the decrease of thalamo-cortical connectivity was smaller in dexmedetomidine-induced unresponsiveness than in N3 sleep or in propofol-induced unresponsiveness (Guldenmund et al., 2017). Also, individual differences in functional connectivity patterns are especially prominent in fronto-parietal networks and relatively independent of the dexmedetomidine sedation (Liu et al., 2019).

Thalamo-cortical and cortico-cortical disconnections have also been reported during sleep (Guldenmund et al., 2017; Massimini et al., 2005; Spoormaker et al., 2010) and in disorders of consciousness (Bai et al., 2021; Boly et al., 2011; Crone et al., 2014; King et al., 2013; Laureys and Schiff, 2012; Lehembre et al., 2012). The disruption of long-range connectivity along the anterior-posterior axis has been suggested to correlate with the severity of the disorders of consciousness (Bai et al., 2021; Boly et al., 2011; Laureys and Schiff, 2012; Lehembre et al., 2012) and the EEG-based connectivity can be used as a prognostic factor (van den Brink et al., 2018). Disruption of anterior-posterior connectivity has been reported also in NREM sleep (Chow et al., 2013; Tagliazucchi et al., 2013). Unresponsive propofol anesthesia and N2 and N3 sleep are characterized by alpha band connectivity particularly within the prefrontal cortex in contrast to the high wPLI within the temporal lobe in wakefulness, N1 and REM sleep, and in responsive propofol sedation (Banks et al., 2020). Dream-report related and dreamless NREM sleep are not differentiated by fronto-parietal EEG connectivity at low frequencies (<4 Hz) but reduced phase-locking is associated with dream content (Lee et al., 2019). In addition, decreased local posterior connectivity in

the delta frequency band correlates with conscious experiences during sleep (Lee et al., 2019). In another study, different NREM sleep stages were not separated by alpha band functional connectivity (Imperatori et al., 2021). However, functional alpha connectivity did discriminate wakefulness and REM sleep: whole-brain measurements showed high alpha connectivity in the awake state and low alpha connectivity during REM sleep (Imperatori et al., 2021).

2.4 N400

The N400 component is a negative event-related potential peaking around 400 ms after stimulus. The N400 was first reported in 1980 by Kutas and Hillyard in the context of reading senseless sentences (Kutas and Hillyard, 1980). Since then, the N400 has been found to be elicited by all potentially semantic stimuli including linguistic stimuli, such as stories, sentences, word pairs, and pseudowords, and non-linguistic stimuli, like drawings, photos, gestures, faces, environmental sounds, and odors (Ganis et al., 1996; Ganis and Kutas, 2003; Grigor et al., 1999; Holcomb, 1993; Kelly et al., 2004; Kutas, 1993; van Berkum et al., 1999; van Petten and Rheinfelder, 1995; Voss and Paller, 2006). The N400 has been suggested to reflect the processing of meaning, and its amplitude is inversely proportional to the contextual fit of a stimulus. Therefore, the amplitude of the N400 component is larger for unexpected than for expected stimuli, and the difference between the two conditions is termed the N400 effect. For example, N400 is elicited by all words of a sentence but the amplitude decreases gradually along with the building of the context (Kutas and Hillyard, 1984). N400 can be elicited by stimuli in different sensory modalities and by mixtures of different modalities (D'Arcy et al., 2004).

2.4.1 Processes reflected by N400

N400 is an ERP component with a long duration and it is typically studied in the time window that starts 200–300 ms and ends 600–800 ms post-stimulus (Figure 2; Cruse et al., 2014; Duncan et al., 2009; Revonsuo et al., 1998). The early part of the negative deflection may be due to the combination of the phonological mismatch negativity and N400 (D'Arcy et al., 2004). The type of the stimulus affects the duration of the N400: sentence stimuli induce stronger and longer N400 effect than mere manipulation of lexical characteristics, like word frequency or relatedness (Duncan et al., 2009; Kutas, 1993). In experiments studying N400, the EEG is typically referenced to mastoid average or linked earlobes and the peak N400 effect is observed in centro-parietal midline electrodes (Duncan et al., 2009). However, the amplitude of the N400 component is larger and spatially more broadly distributed than that of many other ERP components (Van Petten and Luka, 2006).

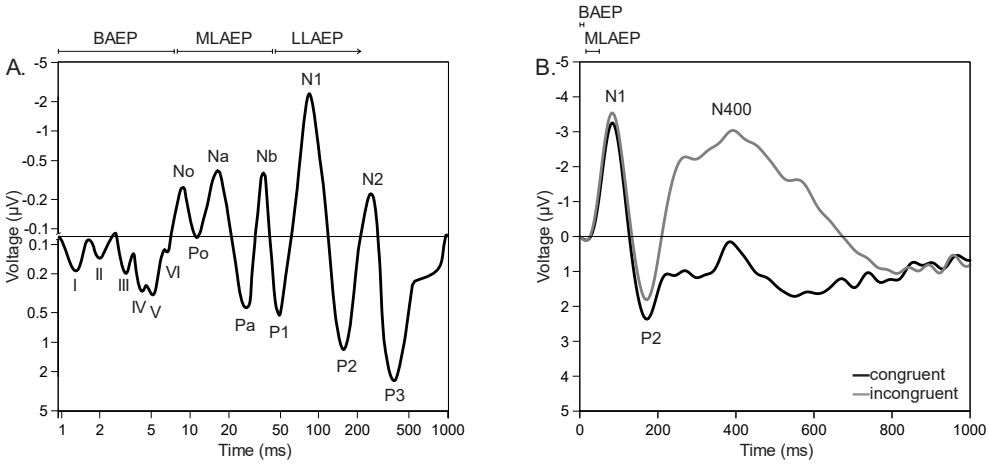

Figure 2. The time scale and size of the N400 ERP component compared with the auditory evoked potentials used in clinical contexts, such as neurophysiological diagnostics and intraoperative monitoring. A. A schematic representation of the waveform of an auditory evoked potential recorded at vertex (Cz) in response to a brief sound. The latency and the voltage are presented with a logarithmic scale. Abbreviations: BAEP, brainstem auditory evoked potentials; MLAEP, middle-latency auditory evoked potentials; LLAEP, long-latency auditory evoked potentials. Drawn based on Hillyard and Kutas (1983), Kumar et al. (2000), Pockett (1999), and Trainor (2007). B. A typical auditory event-related potential waveform recorded at vertex in response to semantically congruent and incongruent speech stimuli. A group-level average is shown. The latency and the voltage are presented with a linear scale. The time windows of the BAEP and MLAEP responses corresponding the panel A are shown. Different evoked and event-related potentials require different types of stimulation paradigm, recording and preprocessing for an optimal measurement.

In addition to semantic relations, N400 effect has also been detected separately for associative relations (Cruse et al., 2014; Koivisto and Revonsuo, 2001; Rhodes and Donaldson, 2008). In addition, both the discourse-level information and the general knowledge of the world modulate N400 (Boudewyn et al., 2012; Hagoort et al., 2004; Hald et al., 2007; Mitchell et al., 1993; van Berkum et al., 1999). The expectancy of the stimulus has an important role in inducing the N400 effect (Lau et al., 2013) and it can be measured with, for example, cloze probability. The cloze probability is obtained using a cloze test where a normative group of participants is, for example, asked to fill in the missing last word of partial sentences with the word that first comes to their mind. The amplitude of N400 component is strongly correlated with the cloze probability of stimuli (Kutas and Hillyard, 1984). An unexpected last word elicits a larger N400 component in high-cloze sentences than in moderate-cloze sentences (Thornhill and Van Petten, 2012). In addition, the N400 component is smaller for unexpected synonyms of the most expected word than for unrelated, unexpected words (Thornhill and Van Petten, 2012). In contrast, N400 effect has not been found in response to violations of general social norms which

suggests that N400 does not reflect pure expectancy (Weimer et al., 2019). Also, the N400 is not affected by the physical properties of a stimulus, such as the size of the letters of a visual stimulus, or grammatical errors (Kutas and Hillyard, 1980, 1983). In most N400 studies, the stimuli include expectancy-related, semantic, and associative relations at the same time, which is the case also in natural language (Cruse et al., 2014; Rabs et al., 2022).

The roles of automated and controlled processing in the formation of N400 have been a matter of debate since 1980s. Masking and degradation studies have shown that the N400 effect can be detected for word pairs or word lists in conditions preventing the conscious perception (Coulson and Brang, 2010; Daltrozzo et al., 2012a; Deacon et al., 2000; Kiefer, 2002), and N400 effect has also been detected if the prime or target word has been presented during the attentional blink (Luck et al., 1996; Rolke et al., 2001). However, N400 effect has not been detected in all masking paradigms (Brown and Hagoort, 1993), masked effect has been smaller compared to that elicited by non-masked stimuli in almost all studies (Coulson and Brang, 2010; Daltrozzo et al., 2012a; Kiefer, 2002), and the attentional blink reduces the amplitude of N400 (Rolke et al., 2001). Also, N400 effect can only be detected for masked single words and not for masked or degraded sentence stimuli, which suggests that the sentence-level processing giving rise to N400 is not automatic (Daltrozzo et al., 2012a; Mongelli et al., 2019).

A task that requires responding increases the amplitude of N400 effect (Cruse et al., 2014; Erlbeck et al., 2014), and N400 effect has been reported to disappear if the task is to ignore the stimuli, which suggests the involvement of controlled processing and the need for selective attention (Erlbeck et al., 2014). However, a distracting task does not prevent N400 effect (Relander et al., 2009). In some studies, the spatial attention has been a prerequisite for N400 both in visual and auditory modalities (Bentin et al., 1995; McCarthy and Nobre, 1993) and the task-related top-down control and time-related selective attention notably increase the N400 effect (Kiefer and Brendel, 2006; Kiefer and Martens, 2010). In some studies, N400 effect has been detected only when the task is semantic and not with a morphological task requiring attention (Chwilla et al., 1995), but others have reported N400 effect elicited without a semantic task (Ford et al., 1996; Hohlfeld et al., 2015; Holcomb, 1988; Kutas and Hillyard, 1989; Relander et al., 2009). It has also been suggested that the processing related to visual and auditory stimuli differs in terms of the required amount of controlled processing (Anderson and Holcomb, 1995; Boudewyn et al., 2012; Holcomb and Neville, 1990). The temporal unfolding and strong bottom-up attention in the auditory modality may also affect the processing (Anderson and Holcomb, 1995; Boudewyn et al., 2012; Ford et al., 1996).

In the field of linguistics, there is a long history of polarization in describing N400 in terms of lexical access (Deacon et al., 2000; Delogu et al., 2019; Lau et al.,

2009) or semantic integration (Brown and Hagoort, 1993; Daltrozzo et al., 2012a; Mongelli et al., 2019; van Berkum et al., 1999). In addition, there are multiple theories and models regarding the functional basis of N400 component. N400 has been suggested to reflect, for example, the retrieval from semantic memory according to the retrieval-integration model (Brouwer et al., 2017), semantic inhibition (Debruille, 2007), semantic binding (Federmeier and Laszlo, 2009), implicit prediction error (Hodapp and Rabovsky, 2021; Rabovsky and McRae, 2014), probabilistic update of semantic representations (also known as sentence gestalt model) (Hodapp and Rabovsky, 2021; Rabovsky et al., 2018), semantic predictive coding (Bornkessel-Schlesewsky and Schlesewsky, 2019; Kuperberg et al., 2020), or attentionally sensitized automatic semantic processing (Kiefer and Martens, 2010). To summarize, N400 can be seen to reflect the difficulty of activating the representation of a semantic stimulus. It seems plausible that N400 reflects both automatic and integrative processes (Nieuwland et al., 2020; Rabovsky et al., 2018) or N400 reflects automatic processing but is strengthened by top-down controlled processes (Kiefer and Martens, 2010).

Based on MEG, fMRI, scalp-level or intracranial EEG, and lesion studies, the sources of N400 are located in the (left) temporal cortex, more precisely in the superior and middle temporal gyri, superior temporal sulcus, and anterior medial temporal lobe including, for example, amygdala and hippocampus (Elger et al., 1997; Halgren et al., 2002; Kuperberg et al., 2003; Lau et al., 2008; McCarthy et al., 1995; Rämä et al., 2010; Van Petten and Luka, 2006). The activation spreads to the frontotemporal cortex by the time that N400 reaches its peak amplitude (Halgren et al., 2002). Also, the activation of the left inferior frontal gyrus has been detected in most of the fMRI experiments (Lau et al., 2008; Van Petten and Luka, 2006; Zhu et al., 2019). Although there is no clear consensus, this has been suggested to contribute to both N400 and late positive (LP) component via the ease of retrieval, the following of the task, or the integration with the knowledge of the world. The brain areas responsible for N400 are the very same that are activated when integrating individual words to sentences (Sokoliuk et al., 2021b). N400 may provide a more sensitive method to study semantic processing than fMRI (Geukes et al., 2013).

Due to its flexible properties in terms of sensory modality, task, and the type of stimuli, N400 has potential in brain computer interfaces (Dijkstra et al., 2019, 2020). The N400 can be used to test general knowledge of the world (Hagoort et al., 2004) or some field-specific content, like familiarity with a specific fictional universe (Troyer and Kutas, 2020). However, the signal-to-noise ratio has been highlighted as a limiting factor for the use of N400 (Dijkstra et al., 2020). Also, the N400 effect cannot be detected in all healthy individuals (Cruse et al., 2014; Daltrozzo et al., 2009; Hinterberger et al., 2005; Kotchoubey, 2005; Rohaut et al., 2015; Sculthorpe-Petley et al., 2015), and the known test-retest probabilities within the same

individuals are high but imperfect (Kiang et al., 2013; Besche-Richard et al., 2014; Martín-Loeches et al., 2017). Although the N400 responses are elicited by natural, continuous speech (Broderick et al., 2018; Holcomb and Neville, 1991), the size of the effect can be maximized with careful experimental design. For example, the amplitude of the N400 component decreases when the same stimulus is repeated multiple times (Van Petten et al., 1991), which highlights the need for unique stimuli if aiming at the largest possible N400 effect.

2.4.2 N400 in altered states of consciousness and in clinical conditions

Studying the N400 ERP component in altered states of consciousness is of interest since the preservation of semantic processing may suggest the presence of also other kinds of information processing. Semantic processing has been suggested as a necessary but insufficient condition for consciousness (Schoenle and Witzke, 2004). Although the awareness of a stimulus might not be necessary for the elicitation of N400, it is possible that N400 effect degrades along with the state of consciousness and cannot be detected in unconscious individuals (Beukema et al., 2016).

In addition to the normal awake state, group-level N400 effect has been detected in N2 and REM sleep for word pairs and sentences (Brualla et al., 1998; Daltrozzo et al., 2012b; Ibáñez et al., 2006; Perrin et al., 2002). In one study, no EEG-based N400 effect but a residual MEG-based mN400 effect was found for arithmetic operations during combined N2 and REM sleep stages but the effect was not statistically significant in either of the two sleep stages alone (Strauss and Dehaene, 2019). No study has combined N400 analysis with dream report results, and it is thus unclear whether N400 can be detected in a state devoid of experiences. The reduced alertness due to complete sleep deprivation decreases the amplitude of the N400 component for both congruent and incongruent stimuli (López Zunini et al., 2014). However, partial sleep deprivation does not affect the N400 (Tavakoli et al., 2015).

The only previous anesthetic-related study on N400 used intracranial EEG measurements in the anterior medial temporal lobe (Grunwald et al., 1999). The participants were in an alert and active state but exposed to ketamine for analgesia before visual word lists were presented. The N400 component elicited by new words diminished and the N400 repetition effect disappeared as a consequence of ketamine.

The N400 has been studied extensively among patients with disorders of consciousness, with a special interest in finding information to support the diagnostics or prognostic evaluation. In single-subject analyses, the detection rate of N400 effect is associated with the severity of the disorder of consciousness. The N400 effect has been detected in 0–32% of patients with UWS/VS diagnosis (Beukema et al., 2016; Erlbeck et al., 2017; Kotchoubey, 2005; Kotchoubey et al.,

2005; Rohaut et al., 2015; Schoenle and Witzke, 2004; Steppacher et al., 2013), in 0–44% of patients with MCS diagnosis (Beukema et al., 2016; Erlbeck et al., 2017; Kotchoubey et al., 2005; Rohaut et al., 2015; Steppacher et al., 2013), and in 14–73% of communicative patients with brain damage (Kotchoubey, 2005; Kotchoubey et al., 2005; Schoenle and Witzke, 2004). In the same studies, the detection rate of the N400 effect has been 42–88% among healthy participants (Beukema et al., 2016; Kotchoubey, 2005; Rohaut et al., 2015). In addition, many studies have aimed at developing N400-related single-subject paradigms for the subsequent use in disorders of consciousness. In these studies, the prevalence of N400 effect has been 73–92% at the highest in healthy participants (Cruse et al., 2014; Mah and Connolly, 2018; Sculthorpe-Petley et al., 2015). The features that predict the absence of N400 effect among patients with disorders of consciousness include flat EEG or dominant diffuse delta (1–2.5 Hz) activity, lack of preserved theta or slow alpha activity (4–9 Hz), hypoxia-related brain damage, and temporal lobe lesions (Kotchoubey, 2005; Kotchoubey et al., 2005; Rämä et al., 2010). The peak amplitude of the N400 elicited by incongruent stimuli diminishes along with the increasing severity of the disorder according to different coma scales (Balconi and Arangio, 2015) and some studies have reported a delayed N400 peak latency for incongruent stimuli in disorders of consciousness (Balconi et al., 2013; Balconi and Arangio, 2015).

Importantly, the presence of the N400 effect correlates with a positive prognosis in disorders of consciousness, which suggests that it may reflect processes relevant to consciousness (Rohaut et al., 2015; Steppacher et al., 2013). Among patients with a diagnosis of UWS/VS or MCS, the presence of N400 has been found to predict becoming communicative within a year of the measurement (sensitivity 50%, specificity 90%, positive predictive value 67%, negative predictive value 83%) (Rohaut et al., 2015). In a longer-term follow-up of 2 to 14 years, the UWS/VS patients with a visually detected N400 effect became communicative with a 60% sensitivity, 97% specificity, 86% positive predictive value, and 90% negative predictive value (Steppacher et al., 2013). Among the MCS patients with N400, the respective numbers for recovery were 40%, 100%, 100%, and 61% (Steppacher et al., 2013). The P3a, P3b, MMN, and LP ERP components have also been linked to the positive prognosis of the patients (Rohaut et al., 2015; Chennu and Bekinschtein, 2012) but N400 has also been detected in some patients without P3 (Kotchoubey et al., 2005; Schoenle and Witzke, 2004). These results are in line with a recent study that tracked covert speech perception based on EEG-level synchronization (inter-trial phase coherence) among patients with disorders of consciousness and found that taking the comprehension response into account improved the accuracy of prognosis relative to only relying on clinical characteristics (Sokoliuk et al., 2021a). Steppacher and co-workers (2013) proposed that the uncommunicative patients with preserved N400 may specifically benefit from linguistic stimulation as a treatment. They

suggested that if N400 effect can be detected, the awareness-related brain regions are not deeply damaged, or they can recover.

Other clinical conditions where N400 has been suggested to have diagnostic value include schizophrenia and other psychotic disorders. In these conditions, the N400 component for incongruent words is diminished and the magnitude of the N400 effect correlates positively with a favorable course of the disorder (Besche-Richard et al., 2014; Jackson et al., 2014). A decreased N400 effect has been reported in individuals with Alzheimer's disease, which may be associated with deficits in accessing semantic representations and in remembering the preceding context (Revonsuo et al., 1998). However, the results vary depending on the phase of the Alzheimer's disease and the strength of the context of the stimuli (Duncan et al., 2009). Also age, for example, may change the processing strategies of semantic information (An et al., 2022; Broderick et al., 2021; Federmeier and Kutas, 2005).

2.5 Subjective reports

2.5.1 Subjective reports as a research method

Subjective reports are currently the only method to access more deeply the experiences of another person, including the internally generated contents of consciousness. Some theories of consciousness even define reportability as a necessary requirement for a conscious experience (Baars, 2005; Dehaene and Changeux, 2011). The nature of the acquired verbal reports depends on introspection, memory, ability to communicate, motivation, and cooperativeness of the participant but also on many aspects of the reporting environment, like questions presented, modality of the report, and time relative to the period with experiences in question. Therefore, when dream-related contents of consciousness are targeted, actually dream recall-related phenomena are studied (Zhang and Wamsley, 2019), and the same distortion holds true with the experiences from other unresponsive states, like general anesthesia. After the report has been given, the analysis of the report is affected by who analyzes it and what kind of tools are used for quantifying the experiences. For example, the reports from natural sleep or mind-wandering are generally more positive if rated by the experiencer than an external rater (Sikka et al., 2014, 2021). To achieve a truthful picture of the experiences of another person, they need to be interviewed and reports analyzed carefully from different angles with a sufficient number of phenomenal categories in order to avoid missing the presence of experiences, for example, because of asking only about one predicted type of experiences like dreaming (Windt et al., 2016).

2.5.2 Subjective reports in altered states of consciousness

The median recall rate of dream experiences is 45% from NREM sleep and 85% from REM sleep (Nielsen, 2000). In general, dreams from NREM sleep are more thought-like, conceptual, simpler, and less intense than the dreams in REM sleep (Martin et al., 2020). However, both NREM and REM dream reports become longer and include more bizarre content later during the night (Fosse et al., 2004; Stickgold et al., 2001). Dreams reported after awakening from the early night NREM sleep are typically brief and static unlike the late night NREM experiences that resemble dreaming during REM sleep (Cicogna et al., 1998; Noreika et al., 2009). Dream reports from natural sleep are affected by the environment where the report is given: laboratory dreams differ from dreams collected at home (Sikka et al., 2018; Waterman et al., 1993). When the dreams are studied in the sleep laboratory, the incorporation of the laboratory into the dreams is common in all sleep stages (Picard-Deland et al., 2021). In sleep studies, the incorporation of external signals, like verbal stimuli or odors, has been reported to affect the overall valence of the dream content (Hoelscher et al., 1981; Schredl et al., 2009). The lag between awakening and the dream report should be as short as possible to diminish memory loss and reconstruction bias (Aspy et al., 2015; Putois et al., 2020). In addition, the reporting should not be too laborious to avoid the biased reporting of only the most salient experiences due to the loss of motivation (Zadra and Robert, 2012).

The experiences reported after anesthetic-induced unresponsiveness and early-night NREM sleep are comparable in terms of the content and report frequency (Valli et al., submitted). The Brice questionnaire is a widely used test for accidental awareness and other experiences during general anesthesia. The participant is asked whether they can recall anything between the anesthetic induction and the emergence and whether there were unpleasant experiences (Brice et al., 1970). In Brice's original study, casual questions on dreaming were presented immediately after emergence from anesthesia, and a structured questionnaire was presented at 24–48 hours and 7–8 days after the operation. A modified Brice questionnaire has been reported to detect accidental awareness during general anesthesia more often than unstructured post-operative discussion (Mashour et al., 2013). When accidental awareness is measured based on spontaneous reports to healthcare professionals, the incidence of awareness during anesthesia is much lower than based on Brice's questionnaire (Pandit et al., 2014b, 2014a; Walker et al., 2016). This highlights the importance of postoperative interviews and direct questions about the experiences occurring during anesthesia (Leslie, 2007). However, repeating the questions multiple times or testing up to one month after the general anesthesia may lead to false memories (Cook and Pandit, 2015). Yet, it is also possible that the intraoperative awareness may be recalled only later after the operation and several delayed interviews may be needed to reveal it (Cascella, 2020). There are many

variations of Brice's questionnaire and their effects on the results have not been formally compared (Cook and Pandit, 2015).

In a surgical setting, the interviews are conditional on the medical status of the patient, the duration and depth of the anesthesia, and the anesthetic drugs used. In studies among surgical patients, the time between the emergence and the interview vary considerably. When patients have been interviewed as soon as possible after emergence from clinical general anesthesia, the incidence of dream experiences has ranged 21–53% (Brandner et al., 1997; Chen et al., 2021; Errando et al., 2008; Kim et al., 2011; Leslie et al., 2007, 2009; Yoshida et al., 2021). In contrast, the incidence of dream experiences has been 3.2–4.2% in studies with the interview performed at a later time during the day of operation (Leslie et al., 2005; Samuelsson et al., 2008a; Xu et al., 2009). Since the anesthetic drugs have strong amnestic effects already at sedative levels, it has been suggested that dreaming in the context of surgical general anesthesia would only occur during the emergence period, just before arousal (Leslie and Skrzypek, 2007; Leslie et al., 2009).

In a study with experimental anesthetic-induced unresponsiveness, the recall rate of subjective experiences after emergence was 74% for dexmedetomidine, 37% for propofol, 60% for sevoflurane, and 70% for xenon (Noreika et al., 2011). Another experimental study using dexmedetomidine, propofol, sevoflurane, and S-ketamine found that dreams were reported in 68%, 31%, 25%, and 44% of the successful interviews immediately after one-hour sedation, respectively (Radek et al., 2021). Memory incorporation of the study environment was present in 26%, 0%, 13%, and 11% of the interviews but immediate interviews did not reveal any cases of awareness although most of the participants were responsive at some point during the sedation (Radek et al., 2021). In another experimental study, 80% of the participants receiving dexmedetomidine and 74% of the participants receiving propofol reported experiences from the unresponsive period (Valli et al., submitted). Interestingly, there was a substantial number of discrepancies between an immediate question about dreaming and a full interview although the full interview was performed only an average of 7.5 minutes after the immediate question (Valli et al., submitted). The incidence of dreaming under anesthesia may or may not be related to insufficient dosing of the anesthetics (reviewed by Leslie and Skrzypek, 2007). The results regarding the association of dreaming with anxiousness and satisfaction with the anesthetic care are also inconsistent (Leslie et al., 2005; Cascella et al., 2017). Dreaming under anesthesia has been correlated with frequent dreaming during sleep at home (Leslie et al., 2009). One study has reported an increased rate of intraoperative awareness among the patients with dreaming during anesthesia and the topic needs further investigation (Samuelsson et al., 2008a).

The most typical experiences in spontaneous reports of intraoperative awareness are auditory perception, sensation of paralysis and pain, and different feelings of

anxiety (Ghoneim et al., 2009). The dreams reported after general anesthesia or sedation are mainly pleasant, simple, and related to everyday events (Kim et al., 2011; Leslie and Skrzypek, 2007). The dreams reported after deep propofol sedation have been suggested to resemble the typical natural dream content of the same persons (Cascella et al., 2017). However, the hospital environment or the operating room may be part of the scenery of the dreams (Kim et al., 2011; Leslie et al., 2005). In addition, the incorporation of the conversations or other events from the anesthetized period into the dream content has been reported (Leslie and Skrzypek, 2007; Leslie et al., 2007) and visual suggestive stimulation just before anesthetic induction may affect the postoperatively reported dream content (Gyulaházi et al., 2016).

Some studies have suggested neural correlates of dreaming and remembering dreams during natural sleep. For example, Siclari and co-workers (2017) found that reports of dream experiences correlate with the suppressed low-frequency (1–4 Hz) and increased high-frequency (20–50 Hz) EEG activity in the posterior cortical regions including the medial and lateral occipital lobe, precuneus, and posterior cingulate gyrus, that is, in the so called posterior hot zone. Interestingly, the suppression of low EEG frequencies was also observed during sleep if the participant gave a white report, that is, reported to have dreamed but did not remember the contents of the dream, which suggests that the EEG activity of the posterior areas does not solely reflect the ability to report dream contents. Instead, the ability to report the contents of a dream was associated with increased high-frequency power in the medial and lateral fronto-parietal areas compared with the white reports. The thought-like content of dreams during REM sleep correlated with high-frequency power in the frontal regions, and perceiving-like content correlated with posterior high-frequency activity. However, the results of Siclari and colleagues (2017) could not be replicated in another study using serial awakening paradigm and blinded EEG analysis without source modelling (Wong et al., 2020) and their study has been criticized for misconceptualization (neural correlates of dreaming vs. neural correlates of dream reports) (Ruby, 2020). The association of EEG spindles and NREM dreaming is unclear: dreaming has been associated both with decreased power in the frequency band of 12–15 Hz (Chellappa et al., 2011) and with more frequent and accelerated spindles (Siclari et al., 2018). No difference in the complexity of the EEG signal has been observed between dreaming and dreamless sleep (Aamodt et al., 2021). However, during dreaming, the TMS-evoked EEG activation resembles the respective activation in the awake state more than the activation observed during dreamless sleep (Nieminen et al., 2016). High functional connectivity within DMN shortly after awakening and the occurrence of P3a ERP during sleep and wakefulness have been suggested as trait-like correlates of high probability of dream recall (Eichenlaub et al., 2014; Vallat et al., 2020).

The neural correlates of dreaming during anesthesia have been much less studied. The association of dreaming with commercial indices of anesthesia depth is unclear (Eer et al., 2009; Leslie et al., 2007, 2009; Matus et al., 2021; Noreika et al., 2011; Samuelsson et al., 2008b). In one study, the dreamers showed decreased spindle activity (~11 Hz) and increased gamma power (30 Hz) in EEG just before emergence from propofol or desflurane anesthesia (Leslie et al., 2009). In a recent study using serial awakening paradigm, occipital EEG delta power differed between dreaming and unconscious state with dexmedetomidine but not with propofol or in natural sleep (Casey et al., 2022). The disconnection of consciousness was observed as broad spatial and spectral changes over the brain and unconsciousness was associated with focal decreases in beta/delta activity in the anterior and posterior cingulate cortices (Casey et al., 2022).

3 The aims of the present thesis

The overall aim of this thesis was to find EEG-based correlates of anesthetic-induced altered states of consciousness. The states of consciousness occurring during deepening sedation were approximated using certain experimental states constituted by the presence and amount of anesthetic drug, behavioral responsiveness, and the order of phases of the experiment. The same experiment was studied from four different angles that reflect different types of brain processing: interplay between major brain areas, semantic processing, recognition memory, and subjective experiences. The primary threshold state used in this study was the minimally unresponsive state, termed loss of responsiveness, where the participant had received an individually titrated drug dose that was just enough to induce unresponsiveness to the behavioral task. In addition, also the sedative but responsive state and the state measured during a higher drug dose (presumed to induce loss of consciousness) were studied. In addition to the pre-anesthesia baseline and responsive sedation, an important point of comparison for unresponsiveness was the recovery of responsiveness measured during the same drug dose.

The study design aimed at differentiating responsiveness and the state of consciousness from drug dose, which is a general problem in studies using anesthesia to modify consciousness. The changes associated with unresponsiveness instead of the anesthetic concentration itself can be assumed to be reversed by the recovery of responsiveness during constant dosing. The brain correlates of responsiveness are important because surgical anesthesia typically includes, in addition to the hypnotic agent and analgesics, paralyzing or muscle relaxant drugs that interfere with the behavioral responsiveness. The combination of EEG-based measures and subjective reports of the contents of consciousness help to construct a multifaceted view of the unresponsive states induced by two different anesthetic drugs, dexmedetomidine and propofol. The two drugs differ in terms of their mechanisms of action, pharmacokinetics, typical applications (surgical operations vs. sedation in intensive care unit), physiological effects, and rousability. The use of dexmedetomidine and propofol allows distinguishing the consciousness-related phenomena and agent-specific phenomena.

In addition to studying the correlates of anesthetic-induced altered states of consciousness, the aim was to explore and compare different methods for the analysis of complex cognitive event-related potentials at the single-subject level using N400 as an example. The single-subject analyses are a prerequisite for any clinical use of cognitive ERPs. The optimal method would be as sensitive as possible and take into account the inter-individual differences between patients. Five different analysis methods were compared: visual inspection of averaged ERPs, analysis of variance of time-windowed amplitude averages, cluster-based nonparametric testing, Bayesian regression analysis, and techniques based on continuous wavelet transform. EEG measurements from the awake state were analyzed using several different analysis methods to study the concordance of the different approaches.

In summary, the aim of the study was to find EEG-based correlates that would differentiate behavioral states and increase understanding of brain functioning at different behavioral endpoints of general anesthesia. Specifically, the main objectives of the present thesis were to:

1. study whether the anterior-posterior and prefrontal-frontal functional and directed connectivity are associated with unresponsiveness (Study I).
2. test whether semantic processing, measured using the N400 ERP component, can be preserved during anesthetic-induced unresponsiveness, and whether the processing is different during dexmedetomidine and propofol sedation (Study II).
3. describe and quantify the subjective experiences occurring during anesthetic-induced unresponsiveness (Study III).
4. explore how dexmedetomidine and propofol affect memory for the semantic and emotional stimuli presented during anesthesia (Studies II and III).
5. study the effect of the choice of offline analysis method on the detection rate of event-related potential effects at the single-subject level with N400 as an example (Study IV).

4 Materials and methods

The Studies I–IV are based on two different experiments: the awake experiment where 79 participants were tested in awake condition and the anesthesia experiment where 47 of the participants of the awake experiment received either dexmedetomidine (n=23) or propofol (n=24) (Table 1). Both experiments were performed in the Intensive Care Unit of the Department of Perioperative Services, Intensive Care and Pain Medicine, Turku University Hospital, Turku, Finland.

Table 1. Summary of the data included in Studies I–IV.

STUDY	TOPIC	PARTICIPANTS	EXPERIMENT	DATA
I	connectivity	47 (23 dexmedetomidine, 24 propofol)	anesthesia	Stimulus-free 2-min epochs
II	N400 ERP	47 (23 dexmedetomidine, 24 propofol)	awake and anesthesia	Sentence stimulus blocks from the anesthesia experiment Sentence stimulus blocks from the awake experiment as a baseline Sentence recognition memory testing from the awake and anesthesia experiments
III	subjective experiences	47 (23 dexmedetomidine, 24 propofol)	anesthesia	Interviews Emotional sound recognition memory testing
IV	performance evaluation of N400 analysis methods	79	awake	Active and passive sentence stimulus blocks

4.1 Ethical permissions

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (24.6.2013) and the Finnish Medicines Agency Fimea (14.6.2013). The study was preregistered in ClinicalTrials.gov (Identifier NCT01889004). Written informed consent was acquired from all participants according to the Declaration of Helsinki.

4.2 Participants

A total of 79 healthy male participants were recruited to participate in the study. The recruitment advertisements were sent to the student email lists of University of Turku, Åbo Akademi University and Turku University of Applied Sciences with a short information sheet and contact details. All participants were interviewed before enrollment in the study and laboratory tests including drug screening, electrocardiogram (ECG), and a hearing test were performed. The participants were 20–30 years of age (median 23 years), healthy according to the criteria of the American Society of Anesthesiologists (ASA I), and right-handed by self-report. The criteria for inclusion were fluent Finnish language and normal hearing as determined with Entomed SA 50 screening audiometer (Entomed MedTech AB, Malmö, Sweden). The exclusion criteria were smoking, substance abuse, susceptibility for nausea, somatic illness, drug allergy, cardiac arrhythmia, and history of psychiatric disorder. Ongoing medications were also considered as a reason for exclusion.

The awake and anesthesia experiments described in this thesis are the first two experiments of a study series including a total of five experiments. Only men were studied because the subsequent experiments included positron emission tomography and subjected the participants to radiation exposure.

All the participants attended the awake experiment. The 47 participants with the most prominent N400 effect based on visual inspection continued to the anesthesia experiment. Five more participants were selected but declined to attend. The selection was made to avoid anesthetizing participants without a detectable N400 effect in awake state. The sample size was based on the experience from previous studies with a similar design (Kaskinoro et al., 2011; Långsjö et al., 2012).

The mean age of the participants who attended the anesthesia experiment was 23.7 years (range 20 to 30 years); their mean height was 180 cm (range 165 to 198 cm) and weight 79.5 kg (range 53 to 122 kg). For the anesthesia experiment, the participants were randomized to receive either dexmedetomidine (n=23) or propofol (n=24) using the permuted blocks technique.

Handedness for responses was balanced across participants so that 41 participants in the awake experiment and 24 participants in the following anesthesia experiment responded to the congruent and familiar sentences with the right hand

and to the incongruent and novel sentences with the left hand. The other 38 participants in the awake experiment and the 23 participants in the anesthesia experiment used the opposite hands for responding. The handedness assigned to a participant was maintained across the experiments and balanced across the two treatment groups.

4.3 N400 stimuli

The N400 stimuli were 680 Finnish auditory high-cloze probability sentences: 10 for practicing, 300 to be used in the awake experiment, 310 to be used in the anesthesia experiment, 30 for the memory test in the awake experiment, and 30 for the memory test in the anesthesia experiment.

Twenty psychology students were asked to fill in the missing last word of a set of sentence bodies with a word that first comes to mind and fits the context. Different inflections and clear synonyms were combined under the most common form. The sentences that had a cloze probability equal to or higher than 50% were included in the study.

Out of the 680 sentences, 370 were randomly assigned to be transformed to semantically incongruent sentences by changing the last word of each sentence. The remaining 310 sentences were kept unchanged and constituted the set of congruent sentences. The sentence bodies of the incongruent sentences were combined with context-incompatible last words whose number of syllables, word class, inflection, and lemma frequency (Laine and Virtanen, 1999) were as similar to the original congruent last word as possible. The semantically incongruent last word preferably also had a different first phoneme than the semantically congruous high-cloze word. For example, “This soup needs a bit more salt” was changed to “This soup needs a bit more garbage”. The resulting incongruent sentences did not differ from their original counterparts with respect to the lemma frequency and the length of the last word (Wilcoxon Signed Rank test; $P>0.05$). In addition, the congruent and incongruent sentences did not differ in terms of the word count or the lemma frequency and the length of the last word (Mann-Whitney U; $P>0.05$ for all).

The stimuli were recorded by a female native Finnish speaker. A 1 s silent pause was recorded before the last word of the sentence to avoid mixing of the phonetic cues of the last word with the second to last word. The amplitude of the sentences was normalized and the pause before the last word was adjusted to 1000 ms (Ford et al., 1996).

Each sentence was followed by a 1000 ms pause and a response cue that was a 100 ms sine sound (frequency 554 Hz, rise and fall time 5 ms). The delayed responding was employed to avoid the contamination of the N400 component

occurring after the last word with the response-related activity (van Vliet et al., 2014). The inter-stimulus interval was 2.3 s.

The sentences were assigned into blocks that did not differ from each other based on the lemma frequency of the last word, the length of the last word, or the sentence word count (Kruskal-Wallis H, $P>0.05$). Congruent and incongruent sentences were randomly ordered, and their presentation order was the same for all participants. Two blocks of 150 sentences (half congruent, half incongruent) were allocated for the awake experiment (B1 and B2) and three blocks of 100 sentences (half congruent, half incongruent) were prepared for the anesthesia experiment (B3, B4, and B5).

Ten sentences (5 congruent, 5 incongruent) constituted the responsiveness test for the anesthesia experiment. The responsiveness test was used to guide the stepwise anesthetic dose increments and to control the responsiveness of the participants during the relatively long states with pseudo-steady state drug concentration.

Sixty incongruent sentences served as novel sentences in the recognition memory test. The memory test consisted of 20% of the incongruent sentences that had been presented previously during the experiment and the same number of novel incongruent sentences. The five incongruent sentences of the responsiveness test were also included in the recognition test of the anesthesia experiment. In the recognition test, the participants were asked to indicate with the response handles whether the sentence felt familiar or not within the 2.3 seconds after the response cue. The use of the response cue allowed the measurement of reaction times.

4.4 Emotional stimuli

Three emotionally unpleasant stimuli of 6 seconds were selected from the International Affective Digitized Sound Library (Bradley and Lang, 2007). The test stimuli were a puppy in distress, a baby crying, and car horns in a traffic jam. The test stimuli were as similar as possible in terms of their pleasantness, arousal and dominance scores. For each test sound, four other sounds were selected as control stimuli for the memory test: four animal-originated stimuli for the puppy sound, four human-originated stimuli for the baby sound, and four sounds of human artifacts for the traffic sound. The control stimuli were matched with the three test stimuli based on their pleasantness, arousal and dominance scores. In the recognition test, the participants were asked to indicate with the response handles whether the sound felt familiar or not within the 2.3 seconds after the response cue. The use of the response cue allowed the measurement of reaction times.

4.5 Interview questions

The interview questions for the anesthesia experiment were prepared based on the Brice questionnaire and a previous study (Brice et al., 1970; Noreika et al., 2011). The interview questions presented after each recovery of responsiveness were:

1. Did you dream during unresponsiveness? (Orig. Näitkö unta nukutuksen aikana?)
   - Yes:
     a) Describe your dream with as many details as possible. (Orig. Kuvaile untasi niin tarkkaan kuin pystyt.)
     b) Open questions based on the response of the participant, e.g. “Do you remember any more details? How was the environment? Do you remember anything else?”
   - No: Are you sure that you did not dream during unresponsiveness? (Orig. Oletko varma, ettet nähnyt unta nukutuksen aikana?)
2. Do you feel that you dreamed during unresponsiveness but you have already forgotten the dream? (Orig. Tuntuuko sinusta siltä, että näit unta nukutuksen aikana, mutta olet jo unohtanut sen?)
3. Did you experience anything related to the research environment during unresponsiveness? (Orig. Koitko mitään tähän huoneeseen liittyvää nukutuksen aikana?)
   - Yes:
     a) Describe your experiences with as many details as possible. (Orig. Kuvaile kokemuksesi niin tarkasti kuin muistat.)
     b) Open questions based on the response of the participant, e.g. “Do you remember any more details? How did it look/sound/feel like? Do you remember anything else?”
4. Did you hear anything (else) during unresponsiveness? (Orig. Kuulitko minkäänlaisia (muita) ääniä nukutuksen aikana?)
   - Yes:
     a) Describe the voices/sounds with as many details as possible. (Orig. Kuvaile ääniä niin tarkasti kuin muistat.)
     b) Open questions based on the response of the participant, e.g. “How were the sounds like? Can you describe the voice or tone of the person that talked? What was the talk about?”

5. Did you sense anything else during unresponsiveness? (Orig. Aistitko mitään muuta nukutuksen aikana?)
    - Yes:
        a) Describe your sensation with as many details as possible. (Orig. Kuvaile aistimuksesi niin tarkasti kuin muistat.)
        b) Open questions based on the response of the participant, e.g. “How was the pain and where was it?
6. Do you remember anything else that you have not already mentioned (Orig. Muistatko nukutuksen ajalta jotakin muuta, josta et ole vielä kertonut?)

Additional questions only presented after ceasing the infusion (state ROR3) were:

7. What is the last thing you remember before falling asleep for the first time? (Orig. Mikä on viimeinen asia, jonka muistat ajalta ennen kuin nukahdit ensimmäisen kerran?)
8. What is the first thing that you remember after awakening? (Orig. Mikä on ensimmäinen asia, jonka muistat heräämisen jälkeen?)

Participants were informed about the interview questions before the experiment. The interviews were recorded and transcribed for content analysis.

4.6 EEG recording and equipment

Throughout the experiments, EEG was recorded at 64 channels according to the 10-10 electrode system. An active electrode cap (EasyCap GmbH, Herrsching, Germany), NeurOne 1.3.1.26 software (Mega Electronics Ltd., Kuopio, Finland), and Tesla #MRI 2013011 and #MRI 2013012 amplifiers (Mega Electronics Ltd.) were used. Four additional electrodes were used for the measurement of horizontal and vertical eye movements with bipolar montage (EOG). The EEG was referenced online to FCz and the ground electrode was AFz. The sampling rate was 1000 Hz with a low-pass filter having a half-amplitude threshold of 360 Hz (transition band: 250–498 Hz) and a high-pass filter of 0.16 Hz (6 dB/octave).

The stimuli and instructions were presented via headphones using the Presentation 17.0 stimulus delivery and experimental control software system (Neurobehavioral Systems Inc, Berkeley, CA, USA).

In the anesthesia experiment, a Harvard 22 syringe pump (Harvard Apparatus, Holliston, MA, USA) connected to the Stanpump software (by Steven L. Schafer, M.D., http://www.opentci.org/code/stanpump) was used for drug administration. Dexmedetomidine (Dexdor 100 μg/ml, Orion Pharma, Finland) was administered using the pharmacokinetic parameters reported by Talke and co-workers (Talke et

al., 2003). Propofol (Propofol Lipuro 10 mg/ml, B. Braun, Germany) was administered using the pharmacokinetic parameters published by Marsh and colleagues (Marsh et al., 1991).

A Datex-Ohmeda S/5 anesthesia monitor (Datex-Ohmeda Division, Instrumentarium Corp., General Electric Co., Helsinki, Finland) and a portable computer running the S5 Collect software (Collect version 4.0, GE Healthcare, Finland) were used to record and restore the vital parameters in the anesthesia experiment. The pulse oximetry plethysmograms and ECG were monitored throughout the study. Blood pressure was measured in the beginning and at the end of the anesthesia experiment to avoid possible cuff pain and related rousing effects during the experiment. End-tidal carbon dioxide was registered with a dual-operating nasal cannula also used for oxygenation.

4.7 Experiments

4.7.1 Awake experiment

At the beginning of the experiment, the phases of the experiment were described to the participant in writing and also orally while attaching the electrodes. The participant was also told that his memory for the stimuli will be tested in the end of the experiment. Pre-recorded instructions were presented via headphones every time when the task of the participant changed during the experiment.

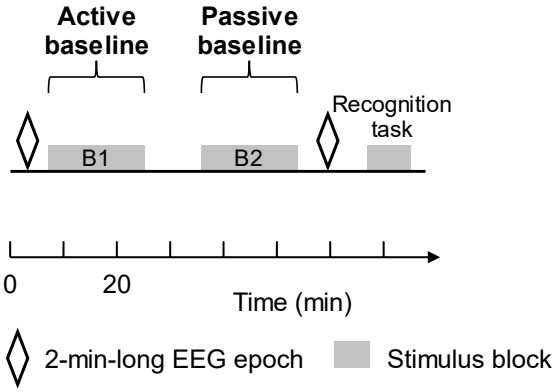

Figure 3. The awake experiment. Two blocks of sentence stimuli (B1 and B2) were presented and followed by a recognition memory task. Two stimulus-free 2-min-long epochs were recorded before and after the sentence blocks.

The outline of the experiment is depicted in Figure 3. The participant rested eyes closed on a bed with response handles in his hands. First, a stimulus-free baseline was recorded for 4 minutes (2 minutes eyes open and 2 minutes eyes closed). The N400 experiment started with 10 sentences that allowed the participant to practice responding to the sentences, followed by 150 sentences (stimulus block B1). The task was to indicate with the response handles whether the sentence was congruent or incongruent (active paradigm). After a small break, another set of 150 sentences (stimulus block B2) was presented and the participant was instructed to carefully listen to the sentences without responding (passive paradigm). After the sentence blocks, another stimulus-free baseline of 2 minutes was measured with eyes closed. Finally, the yes/no recognition task was performed to test the memory of the participant for the recognition of the sentences. The participants were instructed to indicate with the response handles whether each sentence felt familiar or new after the response cue.

4.7.2 Anesthesia experiment

Forty-seven participants from the awake experiment attended the anesthesia experiment a median of 26 days (range 6 to 109 days) after their awake experiment. The participants fasted overnight before the experiment. They were not allowed to use alcohol or any drugs during the 48 hours preceding the experiment.

In the beginning of the experiment, the participant was given thorough instructions about the phases of the study and his tasks. The main task of the participant was to respond to the sentence stimuli similarly as in the awake experiment and to answer the interview questions. The participant was also told that his memory for the stimuli will be tested in the end of the experiment. He was advised to lie eyes closed. The participants were not informed about the emotional sound stimuli presented during the experiment. Blood sample was drawn at the end of each target concentration step.

Both forearms of the participants were cannulated. After attaching the ECG, EEG, and EOG electrodes, the experiment started with a 4-minute-long baseline recording with 2 minutes eyes open and 2 minutes eyes closed (Figure 4). The instructions to respond to the sentence stimuli were given and ten sentences were presented for practicing. After that, the same 150 sentence stimuli that were presented in the active paradigm of the awake experiment were played. After the baseline block, the participant was informed about the beginning of the administration of the anesthetic. He was also told that sentence stimuli will be presented, and he will be asked to respond to the stimuli and to open the eyes at some point. Pre-recorded instructions were presented via headphones every time when the task of the participant changed during the experiment.

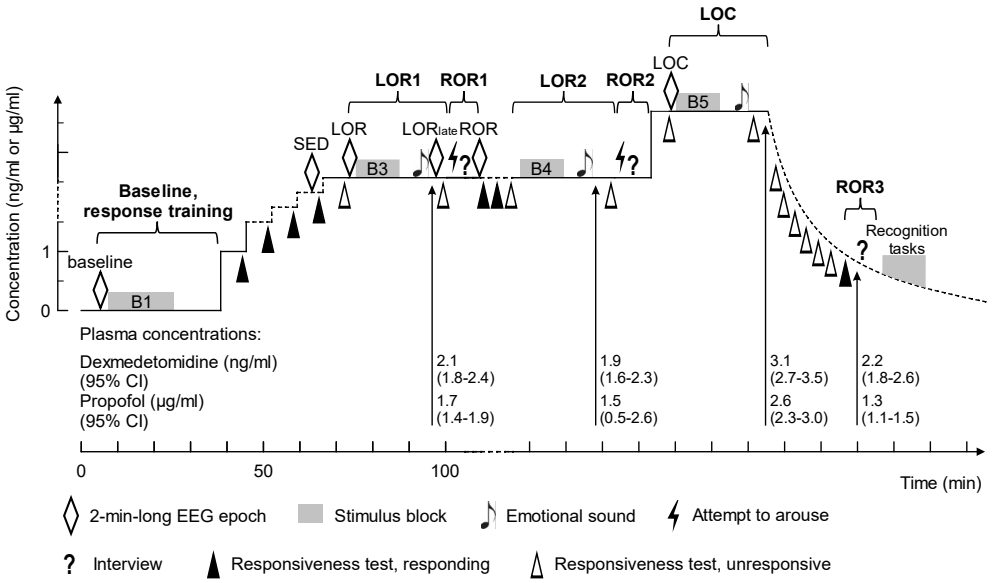

Figure 4. The anesthesia experiment. Sentence stimuli were presented in four blocks (B1, B3, B4 and B5). The average measured drug plasma concentrations in states LOR1, LOR2, and LOC are depicted in the figure. Abbreviations: CI, confidence interval; LOC, presumed loss of consciousness; LOR, the epoch in the beginning of LOR1 state; LOR1, the first loss of responsiveness; LOR2, the second loss of responsiveness; LOR_{late}, the epoch at the end of LOR1 state; ROR, the epoch from the ROR1 state; ROR1, the first recovery of responsiveness; ROR2, the second recovery of responsiveness; ROR3, the third recovery of responsiveness; SED, epoch from the last responsive sedation.

The anesthetic infusion was started with a target plasma concentration of 1.0 ng/ml with dexmedetomidine and 1.0 µg/ml with propofol. Five minutes after starting the infusion, the responsiveness test was presented. If the participant responded to at least one sentence, the pseudo-steady-state concentration of the anesthetic was increased. The stepwise increments with responsiveness test five minutes after each increment were continued as long as the participant responded to the stimuli. The first increase was 0.5 ng/ml in the dexmedetomidine group, and the following steps were 0.25 ng/ml. In the propofol group, the first increase was 0.5 µg/ml and the next steps were 0.25 µg/ml.

When the participant responded to none of the sentences in the responsiveness test, he was defined to be in the first state of loss of responsiveness (LOR1). Then, 100 sentence stimuli (stimulus block B3) and one emotional stimulus were presented during the pseudo-steady-state infusion. There was a 2-min break between different types of stimulation. The participant was attempted to be roused during the constant anesthetic infusion by calling him twice by name and mildly shaking his shoulder. If the participant woke up, he was defined to have reached the first return of responsiveness (ROR1). The participant was interviewed while maintaining the

constant infusion. After the interview, he was left unstimulated for five minutes and the second LOR-ROR cycle of a responsiveness test, 100 new sentence stimuli (stimulus block B4), an emotional sound, an attempt to rouse, and an interview was performed to achieve LOR2 and ROR2. If the participant did not wake up after LOR1 or LOR2, the subject was considered non-rousable and the experiment continued to the next phase.

Finally, the plasma target concentration was increased to 1.5-fold to achieve the state of presumed loss of consciousness (LOC) and, 5 minutes after the dose increase, the responsiveness test, 100 new sentence stimuli (stimulus block B5), and an emotional sound were presented. The drug infusion was ceased, and the responsiveness test was played repeatedly until the participant started to respond. If the participant did not regain responsiveness within 30 minutes after ceasing the anesthetic infusion, he was roused. After the return of responsiveness (ROR3), the participant was interviewed, and the recognition of the sentences and the emotional sounds was tested. After the termination of the experiment, the participant stayed under the surveillance of the anesthetic personnel until he could be discharged.

4.8 Analyses

4.8.1 Preprocessing of EEG

The electroencephalogram signal was preprocessed using the MATLAB R2013b (Mathworks Inc, Natick, MA, USA) and the EEGLAB 13_4_4b toolbox. The EEG was initially resampled to 250 Hz. After that, the preprocessing of EEG was performed as described in Table 2.

Table 2. The preprocessing of EEG in different studies. Abbreviations: EEG, electroencephalogram; FIR, finite impulse response; ICA, independent component analysis; SD, standard deviation.

STUDY	REFERENCE	HIGH-PASS AND LOW-PASS FILTERING	SEGMENTATION	BASELINE CORREC-TION	ARTIFACT REMOVAL	INTERPOLA-TION OF ARTIFACTU-OUS CHANNELS
STUDY I (CONNECTIVITY)	mastoid average (TP9 and TP10) in wPLI and dPLI analysis, spline Laplacian in coherence analysis	-, cross-spectral density evaluated with multitaper method and statistical analysis of the connectivity values performed in the alpha band of 8 to 14 Hz	2 min, 1 min 50 s after artifact removal	-	max 10 s of EEG was removed based on visual inspection	yes (mean 1.20, median 1, range 0–10)
STUDY II (N400 IN ANESTHESIA)	mastoid average (TP9 and TP10)	non-causal Blackman-windowed sinc FIR filter, half-amplitude threshold 0.5 Hz for high-pass and 20 Hz for low-pass (transition band width 1 Hz for high-pass and 4 Hz for low-pass, passband ripple 0.02%; stopband attenuation -74 dB)	−1000 to 1000 ms relative to the last and first word	−1000 to 0 ms	epochs with absolute value of amplitude exceeding 150 μV or amplitude changes greater than 100 μV within 80 ms were excluded	yes (mean 0.23, SD 1.05 channels per participant in the anesthesia experiment)
STUDY IV (N400 IN SINGLE PARTICIPANTS)	mastoid average (TP9 and TP10)	non-causal Blackman-windowed sinc FIR filter, half-amplitude threshold 0.1 Hz for high-pass and 20 Hz for low-pass (transition band width 0.2 Hz for high-pass and 4 Hz for low-pass, passband ripple 0.02%; stopband attenuation -74 dB)	−1000 to 1500 ms relative to the last words of the sentences. In addition, epochs of the same length were randomly generated from the 2 min stimulus-free periods of the study for the Bayesian method	−200 to 0 ms	artifactuous epochs were removed using visual inspection with the help of ICA, another ICA was used to remove eye movements by removing eye-related components	yes (mean 0.67, median 0, range 0–7 channels per participant)

4.8.2 Analyses of connectivity (Study I)

For the connectivity analysis, six stimulus-free 2-min epochs of EEG were segmented from the different phases of the anesthesia experiment: baseline (eyes closed), SED (from the last responsive sedation), LOR (from the beginning of LOR1 state, after responsiveness test), LOR_{late} (from the end of LOR1 state just before the rousal attempt), ROR (from ROR1 state, after the interview), and LOC (from the beginning of LOC state) (Figure 4). The LOR and LOR_{late} epochs were both included to control the stability of the relatively long state of loss of responsiveness. The epochs were preprocessed as described in the Table 2. Since the coherence analysis is sensitive to the volume conduction effect, surface Laplacian transform was applied to the EEG signal before the computation of coherence (Perrin et al., 1989).

Functional connectivity was estimated using magnitude squared coherence and weighted phase lag index (wPLI) (Vinck et al., 2011). Directed connectivity was assessed with directed phase lag index (dPLI) (Stam and van Straaten, 2012).

Spectral coherence is the most traditional measure for quantifying phase-synchrony of EEG and can be seen as a linear (squared) correlation coefficient between two signals in the frequency domain: its maximum value 1 indicates complete correlation between signals and its minimum value 0 means that the signals are not correlated (Nunez and Srinivasan, 2006). The coherence is highly affected by volume conduction effects but the volume conduction can be mitigated using the surface Laplacian transform (Bastos and Schoffelen, 2015; Srinivasan et al., 2007). In practice, EEG coherence mostly depends on the consistency of phase differences between electrodes (Srinivasan et al., 2007).

The phase lag index (PLI) is a measure of phase synchronization with a nonzero phase lag (Stam et al., 2007). The wPLI is a refined version of PLI. In contrast to PLI, the phase-locking values of wPLI are weighted by the magnitude of imaginary component of the cross spectrum (Vinck et al., 2011). The wPLI measures the instantaneous phase-locking of two EEG signals by accounting for only nonzero phase lead/lag relationships. If the phase of one signal consistently leads or lags the phase of another signal, wPLI reaches its maximal value of 1. If the phase lead/lag relationship is random and there is no phase locking, wPLI gets the value 0.

The dPLI is a measure of directed connectivity and it describes the asymmetry of lead/lag relationship of the phases of two signals (Stam and van Straaten, 2012). The absolute value of dPLI equals PLI. In this study, the modified version of dPLI is used with a scale between –1 and 1: if one signal consistently leads the phase of another signal, dPLI is 1, and in the inverse case, dPLI is –1. If neither of the two signals is leading on average, dPLI is 0. Both wPLI and dPLI are robust with respect to volume conduction and reference montages (Stam and van Straaten, 2012; Vinck et al., 2011).

For the calculation of the connectivity measures, the EEG epochs were divided into 2-s nonoverlapping windows and the cross-spectral density was estimated using the multitaper method from each window with a time-bandwidth product of 2 and the number of tapers of 3 (Bokil et al., 2010). The averaged coherence, wPLI, and dPLI values were estimated as a function of frequency based on these repetitions using a custom-written function adapted from the Fieldtrip toolbox (Oostenveld et al., 2011). The shuffled-data method was used to control for spurious conclusions about the existence and the direction of coupling (Papana et al., 2011). A series (N=20) of shuffled signal pairs were generated and used to calculate the coherence, wPLI, and dPLI measures. The means of the resulting shuffled values were subtracted from the raw values to obtain the final estimates of functional and directed connectivity.

The analysis was focused on the anterior and posterior areas (Figure 5 A), where anesthetic-induced changes have previously been reported (Jordan et al., 2013; Ku et al., 2011; Lee et al., 2009, 2013a; Ranft et al., 2016; Untergehrer et al., 2014; Vlisides et al., 2017). The anterior area was a region of special interest (Lee et al., 2009, 2017a; Li et al., 2019; Vlisides et al., 2017, 2019), and it was further sub-divided into prefrontal and frontal areas (Figure 5 A). The coherence, wPLI, and dPLI values were calculated for each pair of channels between the regions of interest – between the anterior and posterior regions, and between the prefrontal and frontal regions – and then averaged. The positive values of dPLI indicated a dominant phase-lead relationship from-front-to-back (anterior-to-posterior or prefrontal-to-frontal) and the negative values of dPLI reflected the dominant direction of connectivity from-back-to-front (posterior-to-anterior or frontal-to-prefrontal). For statistical comparisons, the coherence, wPLI, and dPLI were calculated for each epoch of interest in the alpha frequency band (8−14 Hz) that has previously shown prominent changes related to anesthetic-induced unresponsiveness (Blain-Moraes et al., 2014; Chennu et al., 2016; Kim et al., 2016; Lee et al., 2013a; Supp et al., 2011; Vlisides et al., 2017).

To compare the predictive capacity of connectivity measures with spectral power, the absolute spectral power of the alpha band was analyzed in the frequency range of 8–14 Hz. Surface Laplacian transform (spherical spline interpolation) was applied to the signals (Perrin et al., 1989), and a spectrogram was calculated with the multitaper method using the Chronux toolbox (http://chronux.org/) with a window length of 4 s and 2 s overlap, time-bandwidth product of 2, the number of tapers of 3, and the spectral resolution of 1 Hz (Bokil et al., 2010). All the windows were averaged to compute the segment-wise alpha power for each participant. Finally, averaging was done over all the anterior channels (Figure 5 A).

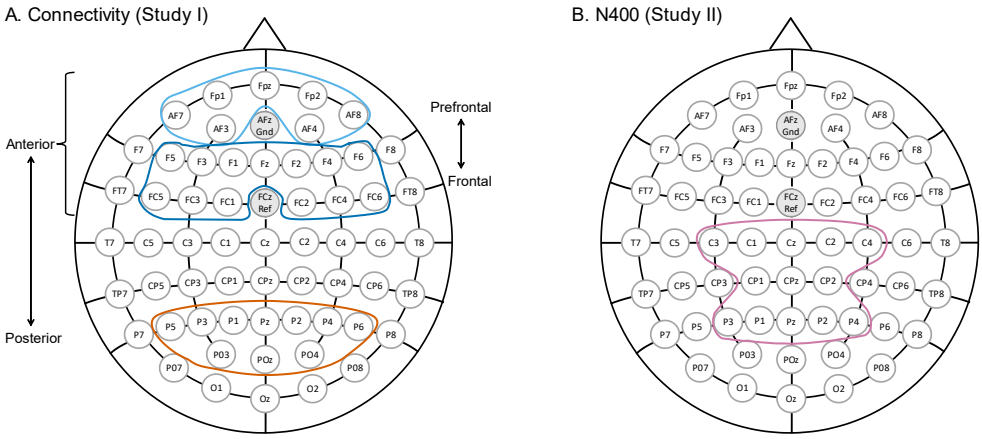

Figure 5. The channel sets of interest in Studies I (A.) and II (B.). A. The channels of interest in the connectivity study were the anterior area (electrodes Fp1, Fpz, Fp2, AF7, AF3, AF4, AF8, F5, F3, F1, Fz, F2, F4, F6, FC5, FC3, FC1, FC2, FC4, FC6), prefrontal (Fp1, Fpz, Fp2, AF7, AF3, AF4, AF8), frontal (F5, F3, F1, Fz, F2, F4, F6, FC5, FC3, FC1, FC2, FC4, FC6), and posterior area (P5, P3, P1, Pz, P2, P4, P6, PO3, POz, PO4). B. The N400 ERP was calculated in the centroparietal channels Cz, C1, C2, C3, C4, Pz, P1, P2, P3, P4, CPz, CP1, and CP2.

Two-way repeated-measures analysis of variance implemented in the SAS/STAT, PROC MIXED (version 9.4, SAS Institute Inc., Cary, NC, USA) was used to compare the epochs from different states and the two-tailed *P* values <0.05 were considered statistically significant. State was defined as a within-factor and treatment (dexmedetomidine or propofol) as a between-factor. Since the ROR1 state was not achieved in all of the participants, two separate analyses were performed. First, the epochs with increasing anesthetic concentration (BL, SED, LOR, and LOC) were compared and all participants were included. Second, the epochs measured during the constant dosing (LOR, LOR_{late}, and ROR) were compared and only the participants with data from ROR1 were included. The significance of the state-by-treatment interaction was used to guide the post-hoc analyses. If the *P* value of the interaction was <0.05, the dexmedetomidine and propofol groups were analyzed separately in the pairwise comparisons between the states. If the interaction was not statistically significant, the dexmedetomidine and propofol groups were combined and the pairwise comparisons between the states were adjusted for the treatment. The post-hoc tests were corrected using the Bonferroni method.

Prediction probability (P_K) was used to measure the capability of the connectivity measures (coherence, wPLI, dPLI) and the anterior alpha power to differentiate the unresponsive and responsive states (LOR, LOR_{late}, and ROR epochs) and the four states with increasing drug concentration (baseline, SED, LOR, and LOC epochs) (Smith et al., 1996a, 1996b). Prediction probability is the multi-class version of AUC

(area under the receiver operator characteristics (ROC) curve) and it has been originally designed to test the performance of different indicators of the depth of anesthesia. If P_K is 1.0, the measure predicts the observed state correctly, and if P_K is 0.5, the prediction power of the measure is at the chance level. The P_K and its standard error (SE) were estimated using the jack-knife method with the PKMACRO algorithm implemented in Microsoft Excel (Smith et al., 1996a). The P_K values were compared with the random level of 0.5 and between the different measures using Bonferroni-corrected paired t-tests with PKDMACRO algorithm (Smith et al., 1996a).

4.8.3 Analyses of N400 ERP in different awake and anesthetized states (Study II)

After the preprocessing steps (Table 2), the N400 component and N400 effect were calculated for the congruent and incongruent last words and the first words of the sentence stimuli. The last words of the sentences were designed to induce the N400 effect between congruent and incongruent conditions whereas the first words of the sentences only induce the N400 component. Amplitude averages were calculated in the presumed N400 time window 300 to 600 ms after stimulus (Kutas and Hillyard, 1980) and in the prestimulus control time window from –600 to –300 ms. The control time window was used to take into account the baseline variation occurring within 300 ms. The amplitude averages were computed separately for each stimulus block of each participant, and for congruent, incongruent, and first word conditions in each of the electrodes in the centroparietal region (Cz, C1, C2, C3, C4, Pz, P1, P2, P3, P4, CPz, CP1, and CP2) (Figure 5 B). If less than 20 stimuli per condition remained after preprocessing, the case was excluded from the analysis. Linear mixed-effects regression analysis with random slopes for subject and channel was used for the statistical analysis. If the model did not converge, the random slope for channel was reduced to random intercept.

N400 component was computed by comparing the N400 time window with the control time window. N400 effect was calculated by comparing the N400 time window after congruent and incongruent last words. Unresponsive states were compared with the active baseline from the awake experiment (block B1) and the results were Bonferroni corrected. The latency of N400 component was defined as the most negative value 200 ms to 800 ms post-stimulus in the signal averaged over the 13 centroparietal channels using the jack-knife method (Miller et al., 1998). A statistically significant N400 effect or component was defined by $P<0.05$. The statistical analyses were performed with the R 3.3.2 software and lmerTest 2.0-33-package (Kuznetsova et al., 2017).

4.8.4 Systematic content analysis of interviews on subjective experiences under exposure to anesthetics (Study III)

The transcribed interview reports were coded to different categories based on their content by two independent raters. The raters performed the coding independently according to a coding manual. If the two raters disagreed, they discussed until agreement was achieved, or a third judge decided which one of the suggested categories should be selected. The reports were coded in three different stages (Figure 6): the relation of the report to the unresponsiveness period, the overall type of the experiences in the unresponsiveness report, and further qualities of the experiences (modality and complexity). The modified Subjective Experiences During Anesthesia (SEDA) microlevel scale was used for the modality analysis and simplified Orlinsky scale for the complexity analysis (Noreika et al., 2011; Orlinsky, 1962). The psychometric properties, such as validity and reliability, of the simplified Orlinsky and the modified SEDA scales have not been formally evaluated (Cook and Beckman, 2006). However, the reliability of the scales, measured as inter-rater agreement, has been high in previous studies (Noreika et al., 2009, 2011; Radek et al., 2021; Valli et al., submitted).

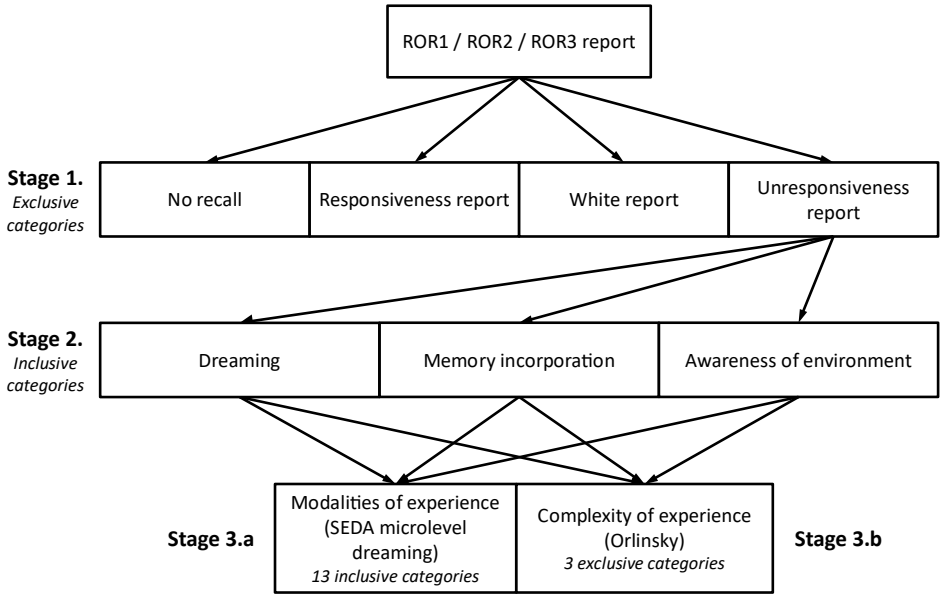

Figure 6. The schema of coding of the experience reports. The reports were coded in three stages: 1. availability and overall content of the report, 2. content related to the connectedness of the experiences (type of experiences in the unresponsiveness report), and 3. further qualities of the experiences (modality and complexity).

In the first stage, the aim was to categorize the reports into those with and without unresponsiveness-related experiences. Unresponsiveness reports refer to the reports with experiences that have most probably occurred during the unresponsive period. Responsiveness reports refer to the reports with only experiences that have taken place before the unresponsive period or after recovery, or to the reports without any experiences related to the anesthesia experiment, such as descriptions of experiences from past surgeries. White reports refer to the occasions where the participant reported having had experiences during unresponsiveness but could not recall any content. If the participant was interviewed but could not recall any experiences, the interview was classified as a no recall report.

In the second stage, the unresponsiveness reports were further classified based on the overall content type of the experiences. The dreaming category was selected for purely hallucinatory content, defined as internally generated experiences that were not related to the research environment or the experiment. Memory incorporation category was selected for the content that reflected memory incorporation of the research environment, such as realistic experiences related to objects or persons that have been present or events that have occurred during the anesthesia session. However, the timing of the experiences could not be specified to unresponsiveness periods, but the experiences might have reflected memory incorporation from the time before the start of the experiment or from the responsive periods of the experiment. The awareness category was selected if the participant reported experiences related to events that only occurred during the unresponsive period, such as stimuli that were presented only during unresponsiveness, and of which that participant had no prior knowledge. One report could include content of all the three categories.

The stage 3a was designed to categorize the complexity of the experiences based on the modalities present in the reports using SEDA microlevel scale (Noreika et al., 2011). The scale consists of categories for basic subjective sensory percepts, affective states, and cognition. A single report may include a large number of separate micro-level experiences from different modalities, and each experience was classified only under one SEDA class. If the report contained experiences from multiple stage 2 categories, the classification was separately performed for each category. The 13 different modalities were visual, auditory, gustatory, olfactory, interoception (hunger, thirst), kinesthesia (balance and movement), touch, pain or temperature, positive moods or emotions, negative moods or emotions, cognition (thoughts, memories, reflection), out-of-body experiences, and sense of presence.

In the stage 3b, the perceptual complexity was evaluated using a simplified version of the Orlinsky scale (Orlinsky, 1962). In the Orlinsky scaling, the scene is defined as one percept encompassing another. The reports were categorized into three classes based on the most complex experience within each of the stage 2

categories with experiences. The static category (combining the original Orlinsky categories 1–3) was chosen for isolated, fragmentary percepts or for several percepts that do not contain perceptual information about a more general scene of the experience. The scenery category (the original Orlinsky category 4) was selected for the reports where one perceptual experience encompasses another, but there is no change within a single scene. The dynamic category (combining the original Orlinsky categories 5–7) was selected for complex percepts where a temporal progression occurs between several interconnected experiences within a scene or between scenes.

The inter-rater agreement of the coding was evaluated with Cohen's κ. The distributions of the data were mostly skewed, and nonparametric tests were used. The differences in the number and content of experience reports were tested with Mann-Whitney U, Fisher's Exact test, Chi Squared test, and Kruskal-Wallis test. SPSS 24.0 (IBM, Armonk, NY, USA) and SAS System 9.4 were used for the analysis.

4.8.5 Analyses of recognition tests (Studies II and III)

Sentence recognition was measured using the discriminability measure *d'* and response bias criterion *c* based on signal detection theory (Wickens, 2002; Hautus, 1995). The discriminability measure *d'* is the distance between the means of the target and distractor distribution. Values greater than 1.0 indicate good recognition performance. The response bias criterion *c* reflects the internal criterion of judgement when the participant is not sure about the correct answer. If the participant requires high degree of familiarity to indicate the stimulus as 'familiar', there is a conservative response bias ($c>0$), and if a low degree of familiarity is needed for the response 'familiar', there is a liberal response bias ($c<0$).

The *d'* was calculated with the log-linear correction for extreme proportions (Hautus, 1995). A participant was excluded from the analysis of a particular state if more than 50% of the responses corresponding a specific experimental state were missing. Two-tailed t-test was used to test whether *d'* and *c* differed from 0, i.e., whether the sentence was recognized and whether there was a response bias. The reaction time for responses was measured from the response cue to the response and responses faster than 100 ms were ignored. The natural logarithm of reaction time was analyzed with linear mixed-effects regression with a random intercept for participant. The analysis was performed with R 3.3.2 software and lmerTest 2.0-33-package (Kuznetsova et al., 2017).

To study the recognition of emotional sounds, logistic regression analysis with generalized estimating equations method (GEE-estimation, dependent observations) was used to analyze the effects of stimulus type (familiar/new), state, and drug on

the reported recognition of the stimulus. In another model, the correctness of the response was studied with state and drug as explanatory variables. The interactions were initially included and the non-significant interactions were subsequently dropped out. The results are reported as the geometric mean and its 95% confidence interval.

Linear mixed model with random intercept was used for testing the reaction times of the recognition task for emotional sounds. Natural logarithm transformed reaction times were tested with three different sets of explanatory variables. In the first model, the main effects of state and drug were included. In the second model, the main effects of state, drug, and the type of stimulus (familiar/new) were included. In the third model, state, drug, and correctness of the response were included. In all models, interactions were initially included, and if the interactions were not statistically significant, the models were reduced to main effects only. SAS System 9.4 was used for the analysis of emotional sounds.

4.8.6 Analyses of N400 ERP at single-subject level in the awake experiment (Study IV)

Five different analysis methods were selected for a comparative analysis of the N400 ERP at single-subject level: visual inspection of averaged ERPs, analysis of variance (ANOVA) of time-windowed amplitude averages, cluster-based nonparametric testing, Bayesian regression analysis, and techniques based on continuous wavelet transform. The visual inspection of averaged voltage-amplitude curves allows to flexibly take into account the individual differences in the topography, latency, and form of the ERP component of interest and interactions with other ERP components. The ANOVA of amplitude averages allows accounting for the inter-trial variation although the assumptions made in the selection of the channels of interest and the time window affect the results and must be based on previous information (Kriegeskorte et al., 2009; Luck, 2014). The cluster-based mass univariate approach is especially useful when there is no strong a priori information on the spatiotemporal location of the effect of interest. In the cluster-based testing, a non-specific null hypothesis is tested: the test statistics are controlled for multiple comparisons at the level of each cluster but do not provide information about the effect in individual electrodes and time points (Groppe et al., 2011; Maris, 2012; Maris and Oostenveld, 2007). A newly developed Bayesian regression method is based on modeling the voltage-amplitude curve using a linear model and the method can take the background EEG signal into account (Pesonen et al., 2019). The Bayesian regression method is especially useful if there is strong spatiotemporal a priori information and a suitable observation model for the voltage-amplitude curve. The Studentized continuous wavelet transform (t-CWT) is a feature extraction method that can be

used in combination with classification algorithms for ERP analysis even at the single-trial level (Bostanov, 2015). There are several different ways to estimate and control the classification error in t-CWT and the method can be used both for analyzing the complete ERP curves and for extracting single ERP components.

A total of 79 EEG measurements from the awake experiment (Figure 3) were analyzed with all five methods. The EEG from awake experiment was preprocessed as described in Table 2. In addition to the stimulus-related epochs, 150 epochs of 2.5 s were randomly selected from the stimulus-free baseline measurements recorded before (75 epochs) and after (75 epochs) the stimulus blocks. These 150 epochs were used to model the background EEG in the Bayesian regression method.

The analyses were performed separately for each participant and in the two paradigms (active and passive) with the parameters described in Table 3. Briefly, visual inspection was performed by three individual raters from 27-channel ERP waveform figures including the superimposed average curves related to congruent and incongruent last words. If all three raters agreed on the presence of N400 effect, N400 effect was considered to be present. This approach resembles the clinical routine for ERP analysis in many hospitals (Gabriel et al., 2016; Kotchoubey, 2015; Steppacher et al., 2013).

The second method was ANOVA of voltage-amplitude averages in a pre-determined time window, which is the most common ERP analysis method at group-level (Dien and Santuzzi, 2005). The previously published information of the spatiotemporal location of the N400 effect was utilized (Kutas and Hillyard, 1980). The amplitude averages in a time window were calculated for each trial. Repeated measures ANOVA was used to determine N400 effect as the difference between the congruent and incongruent signals in the N400-specific time window in the centro-parietal channels (Kotchoubey et al., 2005).

The third method was cluster-based nonparametric approach that allows testing of adjacent time points and electrodes and controlling the multiple comparisons error with cluster-level statistics (Maris and Oostenveld, 2007). The cluster-based testing utilized the trial-wise sample points in every time point and electrode. The testing was based on finding a cluster of spatiotemporally adjacent sample points. Specifically, one-tailed independent samples t-tests were performed between the congruent and incongruent conditions in the time window of 200–800 ms after stimulus (Cruse et al., 2014). Spatiotemporally adjacent samples were clustered by summing their t-values if a significant effect was simultaneously detected in two or more neighboring channels. The t-value of the cluster was compared with the t-value distribution of 1000 random permutations to obtain a Monte Carlo estimate of the cluster *P* value.

Table 3. Parameters of different analysis methods in Study IV. Abbreviations: ANOVA, analysis of variance, t-CWT, Studentized continuous wavelet transform.

METHOD	TIME WINDOW WHERE THE EFFECT WAS TESTED	CHANNELS	TEST PARAMETERS	SOFTWARE	CRITERIA OF THE PRESENCE OF N400 EFFECT
VISUAL INSPECTION	appropriate time window between 200–1000 ms	27 channels evenly distributed over the scalp: Fp1, Fp2, F3, Fz, F4, FC5, FC1, FCz, FC2, FC6, T7, C3, C1, Cz, C2, C4, T8, CP5, CP1, CPz, CP2, CP6, P3, Pz, P4, O1, O2	-	plotting with Brain Vision Analyzer 2.0 (Brain Products GmbH, Gilching, Germany)	agreement of 3/3 raters
ANOVA IN A TIME-WINDOW	300–600 ms	13 channels from the centroparietal area: Cz, C1, C2, C3, C4, Pz, P1, P2, P3, P4, CPz, CP1, CP2	repeated measures from the 13 electrodes (trial as the statistical unit and measurements from different electrodes as repeated measures)	SPSS Statistics 22 (IBM Corp., Armonk, NY, USA)	$P<0.05$ for the difference of amplitude averages
CLUSTER-BASED METHOD	200–800 ms	all 64 channels	neighboring channels had a maximum distance of 40 mm in the standard head model	FieldTrip toolbox (Oostenveld et al., 2011) for MATLAB	at least one cluster with $P<0.05$

(Table 3 continued)

METHOD	TIME WINDOW WHERE THE EFFECT WAS TESTED	CHANNELS	TEST PARAMETERS	SOFTWARE	CRITERIA OF THE PRESENCE OF N400 EFFECT
BAYESIAN REGRESSION	time window of 300–600 ms was used for N400 probability, 0–800 ms was used for the model, time points 0–296 ms were assumed not to differ between the stimulus types and 300–800 ms were assumed to differ	13 channels from the centroparietal area: Cz, C1, C2, C3, C4, Pz, P1, P2, P3, P4, CPz, CP1, CP2	Gaussian prior and posterior distributions	Bayesian regression toolbox (Pesonen et al., 2019) for MATLAB	the probability of a negative N400 effect within a time window 300–600 ms was >95%
T-CWT **- SPLIT-HALF 50%/50%** **- SPLIT-HALF 80%/20%** **- GROUP HOLD-OUT** **- INDIVIDUAL HOLD-OUT** **- INDIVIDUAL BIASED**	300–600 ms	13 channels from the centroparietal area: Cz, C1, C2, C3, C4, Pz, P1, P2, P3, P4, CPz, CP1, CP2	cutoff scale 50 ms corresponding to the cutoff frequency of 20 Hz, log-grid sampling rate 15 points per scale, fade-in time 20 ms, fade-out time 200 ms, eigenvalues that represented 99% of variance in principal component transformation were retained, a priori error rate based on the actual number of trials in each condition	MATLAB package t-CWT 2.01 (Bostanov, 2015)	Hotelling's T2 test $P<0.05$ for split-half and group hold-out methods, binomial P from test for classification error rates for individual hold-out, uncorrected P from Hotelling's T2 test for individual biased method

The fourth method was the Bayesian regression method where Bayesian inference was used in combination with linear regression (Pesonen et al., 2019). The Bayes' theorem is based on a priori information that is used to construct the prior distribution, and a likelihood function that models the observations. The posterior distribution of the model parameters in the condition of the observed data is the product of likelihood function and the prior distribution. Here, the voltage-amplitude curve in the time window of 0–800 ms was modelled using linear regression, and the posterior distribution was found for the parameters that define N400 component for each subject at each of the 13 channels. The stimulus-free background EEG signal was assumed to represent a stationary Gaussian process with moments evaluated from the stimulus-free epochs. The early part (0–296 ms) of the ERP curve was assumed to be identical between the congruent and incongruent conditions, and the latter part (300–800 ms) was assumed to differ between the conditions. The Gaussian posterior distribution was evaluated in closed form using the assumptions and Gaussian prior distribution for the parameters. The participant-level posterior distribution was evaluated from channel-level posterior distributions by assuming a common additive N400 component in the investigated centro-parietal channels. The N400 effect was present if the probability of a negative N400 effect within the N400-specific time window (300–600 ms) was >95%.

The fifth method was the continuous wavelet transform in combination with Student's t-tests (t-CWT). The t-CWT is an ERP analysis method that is based on the feature extraction of the ERP trials and the classification of the test trials based on a linear discriminant function model that is created using training data from different conditions (Bostanov, 2004, 2015; Bostanov and Kotchoubey, 2006). Here, five variants of the t-CWT method implemented in t-CWT 2.01 package (Bostanov, 2015) were utilized. The alternative methods divide the data to training and test sets differently. The training set is used to form the linear discriminant functions and the test set is classified. The t-CWT individual split-half classification was based on dividing the trials in the training and test sets in the proportions of 50%/50% or 80%/20%. The presence of N400 effect was defined based on the Hotelling's T2 test. The group hold-out t-CWT was based on excluding one participant at a time from the trial set and the N400 was defined based on the Hotelling's T2 test. In the individual hold-out method, one trial was excluded at a time and classified using the model constructed based on the remaining trials. Binomial test was used to assess whether the classification error rates were better than the chance classification error rates defined by the a priori ratios of the congruent and incongruent trials. The individual biased method reuses the same data for training and testing and would require an appropriate correction of the accumulation chance bias. However, since the randomization test correction was not readily included in the t-CWT 2.01 package, no correction of the accumulation chance bias was performed. Out of all

the t-CWT methods, the individual split-half method and the group hold-out method allowed the correction of Hotelling's T2 test results for repeated tests with the tools implemented in the t-CWT 2.01 package and could be utilized without additional data and were therefore most comparable with the other methods in the study.

The participants with the N400 effect detected with different methods were visualized using approximately area-proportional Euler Diagrams that were drawn with Biovenn (Hulsen et al., 2008). The performance of different methods was evaluated quantitatively by comparing epoch characteristics and qualitatively by visual classification. To avoid excessive multiple comparisons, the t-CWT method with its alternative testing approaches was excluded from the quantitative and qualitative assessments.

The quantitative comparisons included the N400 effect size and its maximum and median values computed from the difference waves of each individual; the standard deviation, kurtosis, and skewness of the time window-averaged amplitudes over trials to evaluate the distribution of voltages in different trials; and the standard deviation, kurtosis, and skewness of the sample points averaged over trials to evaluate the distribution of voltages within trials. All analyses used data from the Cz channel. In addition, the maximum and average of global field power (GFP) (Lehmann and Skrandies, 1980) were calculated separately for congruent and incongruent trials using average referenced data. All quantitative analyses were restricted to the time window from 300 to 600 ms. The participants with and without a significant N400 effect according to each method were compared using independent samples t-tests. Moreover, the participants with no N400 effect detected with any method were compared to those with a significant effect according to at least one method. Since each quantitative feature was tested five times in the two paradigms, a Bonferroni corrected α-level of 0.005 was used.

For the qualitative comparison of the analysis methods, the average waveforms were classified based on six features (Table 4). The classification was performed by one rater in a randomized order using the same N400-average-figures that were used in the context of the visual inspection method.

Table 4. Features evaluated qualitatively from each ERP average waveform

FEATURE	LEVELS
TIMING	typical / early / late / inconsistent
TOPOGRAPHY	typical / local / frontal / inconsistent
LENGTH OF EFFECT	typical / short / long / inconsistent
MORPHOLOGY	typical / typical but rough / multiple-peaked / flat / flat but rough / inconsistent
ALPHA SYNCHRONIZATION	not prominent / strong
OVERALL SIGNAL QUALITY	normal / noisy

5 Results

5.1 The numbers of participants in each experimental state

All of the 79 participants successfully completed the awake experiment. In the active setting, the participants responded to a median of 100% (range 90–100%) stimuli, and the median proportion of correct responses was 100% (range 96–100%).

In the anesthesia experiment, all 47 participants reached LOR1 state. Four dexmedetomidine participants and three propofol participants lost responsiveness with the lowest targeted concentration step (1.0 ng/ml or 1.0 µl/ml, respectively) and thus did not have any responsive sedative states before LOR1. Two propofol anesthesia sessions were discontinued due to snoring and mild apnea: one during LOR1 and another after LOR1. In the dexmedetomidine group, 18/23 were rousable after LOR1, and among the participants receiving propofol, there were 10/23 successful awakenings. LOR2 was observed in all 18 participants receiving dexmedetomidine but in only 4 cases in the propofol group. All 18 participants in the dexmedetomidine group and two participants receiving propofol could be roused to ROR2 interview. The LOC was achieved in 23 participants receiving dexmedetomidine and 22 participants receiving propofol. Two participants in both drug groups required an additional increment of dose to reach LOC state. Finally, all the 23 and 22 participants in the dexmedetomidine and propofol groups, respectively, were interviewed in ROR3. The awakenings during constant anesthetic infusion were more frequently successful with dexmedetomidine than with propofol (Fisher's Exact test P=0.033 in ROR1 and P=0.026 in ROR2). Eight participants from the dexmedetomidine group and one participant in the propofol group needed to be roused to ROR3 state after awaiting the spontaneous recovery for 30 minutes. The drug concentrations targeted and measured at each stage and associated adverse events have been previously reported (Scheinin et al., 2018) and the measured concentrations are summarized in Figure 4.

In one propofol experiment, there was a problem in anesthetic infusion in LOC after N400 block. In one dexmedetomidine experiment, EEG data is only available until the beginning of LOR2 state due to technical problems in the recording computer. Sufficient numbers of good-quality trials were required for including a

participant in the N400 analyses (Section 4.8.3) and the numbers of participants are therefore smaller than in the connectivity analyses. The numbers of participants in different experimental states and analyses are shown in Table 5.

Table 5. The numbers of participants contributing data to each study: For anesthetized states, the numbers are shown as n of dexmedetomidine participants + n of propofol participants = total number of participants. The epoch names refer to the EEG epochs used in connectivity analyses.

STATE (EEG epoch)	**STATE ACHIE-VED**	**STUDY I: CONNEC-TIVITY**	**STUDY II: N400**	**STUDY II: SEN-TENCE RECOG-NITION**	**STUDY III: EXPE-RIENCES**	**STUDY III: SOUND RECOG-NITION**	**STUDY IV: N400 AWAKE**
BASELINE (baseline)	79	23+24=47	23+24=47	23+24=47	-	-	79
LAST RESPONSIVE SEDATION (SED)	19+21=40	19+21=40	-	-	-	-	-
LOR1 (LOR)	23+24=47	23+24=47	22+(21 to 22)=43 to 44*	20+23=43	-	23+23=46	-
LOR1 (LOR_{late})	23+23=46	23+23=46	-	-	-	-	-
ROR1	18+10=28	-	-	-	18+10=28	-	-
LOR2	18+4=22	-	17+3=20	13+4=17	-	18+4=22	-
ROR2	18+2 =20	-	-	-	18+2=20	-	-
LOC (LOC)	23+22=45	22+22=44	(21 to 22)+(16 to 17)=37 to 39*	21+22=43	-	23+21=44	-
ROR3	23+22=45	-	-	-	23+22=45	-	-

* The number of participants varies for different types of stimuli (congruent and incongruent last words and first words).

5.2 Alpha band frontal connectivity as a state-specific correlate of unresponsiveness (Study I)

The statistical analyses of the present study focused on the connectivity in the alpha frequency band that has been highlighted in the previous literature on connectivity during anesthesia (Blain-Moraes et al., 2014; Chennu et al., 2016; Kim et al., 2016; Lee et al., 2013a; Supp et al., 2011; Vlisides et al., 2017). The alpha band also showed the largest changes in connectivity in the present study. The connectivity was analyzed between the anterior and posterior areas and within the anterior area (prefrontal-frontal). Topographic analysis showed marked state-dependent changes in the anterior areas with both drugs.

When states associated with different anesthetic concentrations were compared, the anterior-posterior connectivity differed between states in terms of coherence (P=0.002), wPLI (P=0.051), and dPLI (P<0.001) (Figure 7). Functional connectivity, measured with coherence and wPLI, showed a transient and mostly non-significant decrease in sedation and LOR1 especially in the propofol group but returned back to baseline-level in LOC. The dPLI analysis suggested that the direction of the phase lead-lag relationship turned from anterior-to-posterior net information flow seen in baseline to posterior-to-anterior dominance in LOC. The overall levels of wPLI and dPLI but not coherence differed between the two treatments (Figure 7).

Within the anterior area, the prefrontal-frontal coherence, wPLI, and dPLI differed between the states associated with different anesthetic concentrations (P<0.001, Figure 7). With both drugs, coherence and wPLI strongly increased in response to the increasing concentration, which, based on dPLI, stemmed from the switch of the prefrontal-to-frontal phase lead-lag-relationship in baseline to frontal-to-prefrontal in the sedated states. Propofol induced larger differences between the states than dexmedetomidine based on wPLI and dPLI but not based on coherence (interaction of state and treatment: coherence P=0.406; wPLI P=0.004; dPLI P=0.005). The dominant direction of connectivity differed already between baseline and responsive sedation in the propofol group (P=0.041), and the dominance of frontal-to-prefrontal connectivity was strengthened with the increasing dose and the loss of responsiveness in both treatment groups (P<0.001 for SED vs. LOR and for SED vs. LOC).

There were no major differences in the anterior-posterior connectivity between the epochs associated with the same anesthetic concentration (LOR, LOR_{late}, ROR) in either dexmedetomidine or propofol group (Figure 8). Importantly, anterior-posterior connectivity measured with coherence, wPLI, or dPLI did not significantly differ between the ROR epoch and the two epochs originating from the LOR1

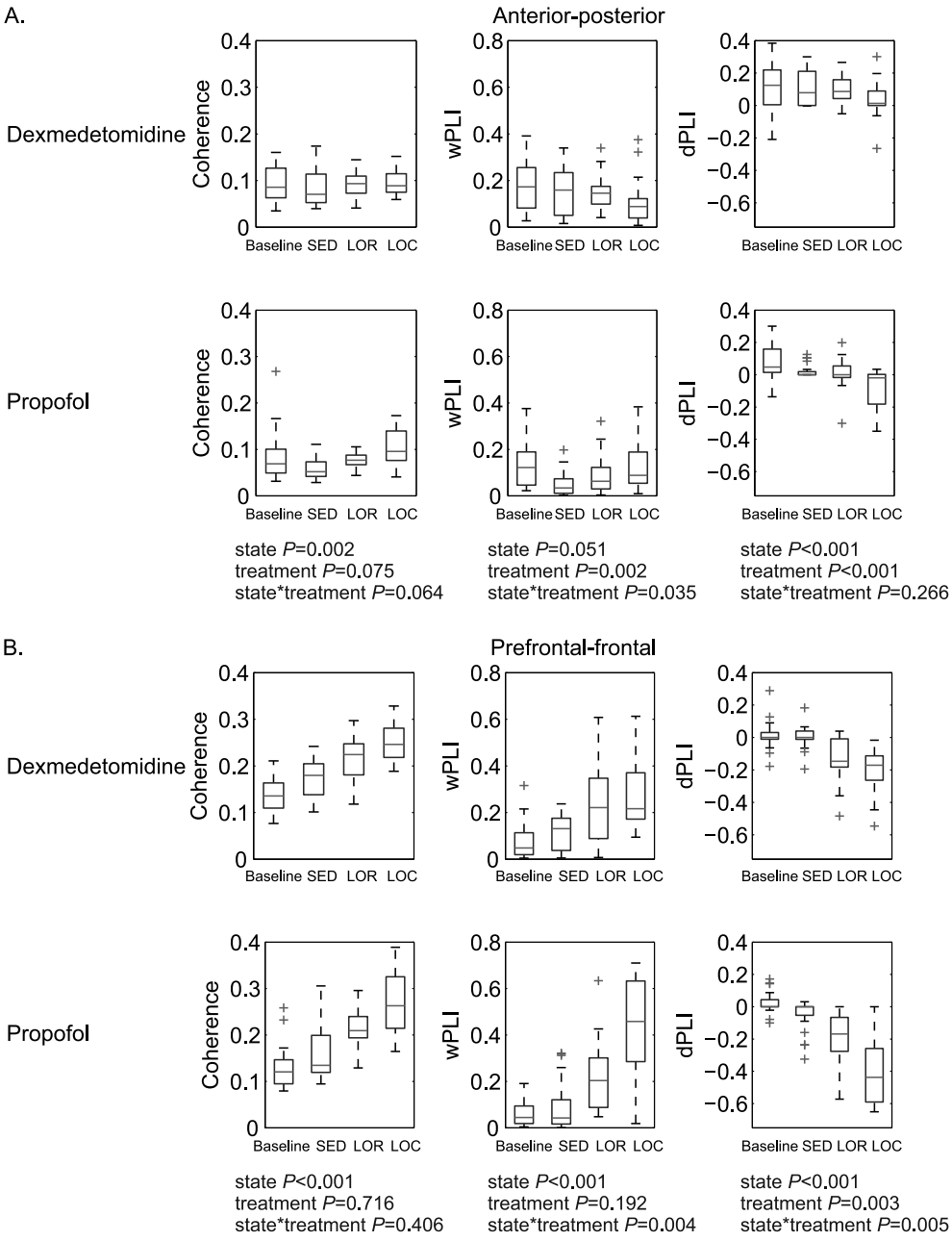

Figure 7. Connectivity values (coherence, wPLI, and dPLI) of the epochs associated with increasing drug concentration in A. anterior-posterior region and B. prefrontal-frontal region illustrated with Tukey boxplots.

state. Thus, there was no effect of responsiveness when the drug concentration remained constant. The levels of the wPLI and dPLI measures observed during the constant concentration of the anesthetics differed between dexmedetomidine and propofol (main effect of treatment P=0.012 and P<0.001, respectively).

As opposed to the anterior-posterior connectivity measures, the prefrontal-frontal coherence, wPLI, and dPLI distinguished ROR from the LOR and LOR_{late} (Figure 8). Notably, the phase lead-lag relationship measured with dPLI reverted from the frontal-to-prefrontal dominance in LOR and LOR_{late} to prefrontal-to-frontal direction in ROR. The differences between the two LOR1-originating epochs indicated that the unresponsive period was not completely stable despite the constant target concentration, but the connectivity values shifted towards LOC values during the state.

The coherence, wPLI, and dPLI were also tested in prefrontal-posterior and frontal-posterior areas to ensure that there is no bias caused by the use of a broad anterior area in the anterior-posterior analysis, and the results were very similar to the anterior-posterior results (data not shown).

Prediction probability (P_K) values were calculated to compare the connectivity measures with each other and with the anterior alpha spectral power. The anterior-posterior connectivity did not discriminate LOR and ROR states (P_K 0.53–0.67; P values 0.176–1). When the states associated with an increasing anesthetic concentration were considered, the coherence (P_K=0.66, P=0.006) and dPLI (P_K=0.73, P<0.001) values of anterior-posterior connectivity differentiated the states above the chance level in the propofol group.

In contrast to the anterior-posterior measures, the anterior alpha power, wPLI, and dPLI distinguished LOR and ROR states (P_K range 0.74 to 0.88, P<0.05 for all). Coherence could not separate the LOR and ROR states at a statistically significant level in the dexmedetomidine group (P_K 0.71, P=0.065) although a significant prediction probability was detected in the propofol group (P_K 0.83, P<0.001). All four measures were able to differentiate the states with increasing anesthetic concentration (baseline, SED, LOR, LOC) as indicated by P_K values (P_K range 0.61 to 0.86, P<0.05 for all). There were no statistically significant differences in the P_K values between the different measures in the LOR–ROR comparison with either of the two drugs, or in the baseline–SED–LOR–LOC comparison with propofol. In the dexmedetomidine group, the connectivity measures had higher P_K values (range 0.76 to 0.83) than the alpha spectral power (P_K=0.61) in the analysis of increasing drug concentration (P<0.05 for all). Overall, the correlation between the anterior alpha power and prefrontal-frontal connectivity was fairly high across the different drug concentrations especially in the propofol group.

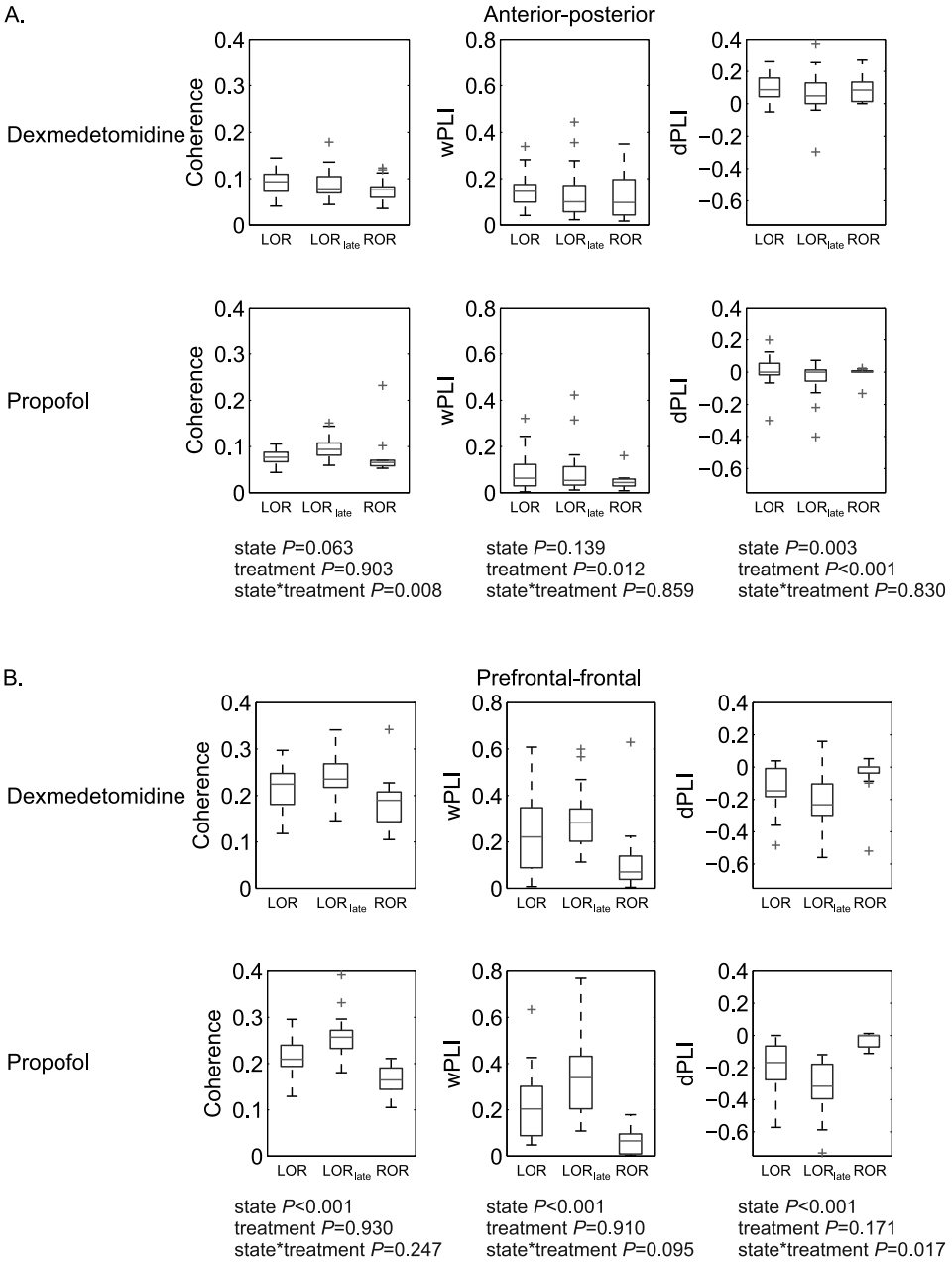

Figure 8. Connectivity values of the epochs with constant drug concentration in A. anterior-posterior region and B. prefrontal-frontal region illustrated with Tukey boxplots.

5.3 Semantic processing in anesthetic-induced unresponsiveness (Study II)

In both active and passive awake baseline, the first and the incongruent last words of the sentences elicited an N400 component significantly more negative than the corresponding control time window (Figure 9). The N400 component elicited by the incongruent last words was more negative than the component resulting from the congruent last words (P<0.001), that is, the N400 effect was observed. The latencies of the N400 components elicited by the first and the incongruent last words were 441 ms (95% CI, 373–509) and 382 ms (95% CI 332–431) in the active baseline, respectively. In the passive baseline, the corresponding latencies were 416 ms (95% CI 401–432) and 414 ms (95% CI 323–504).

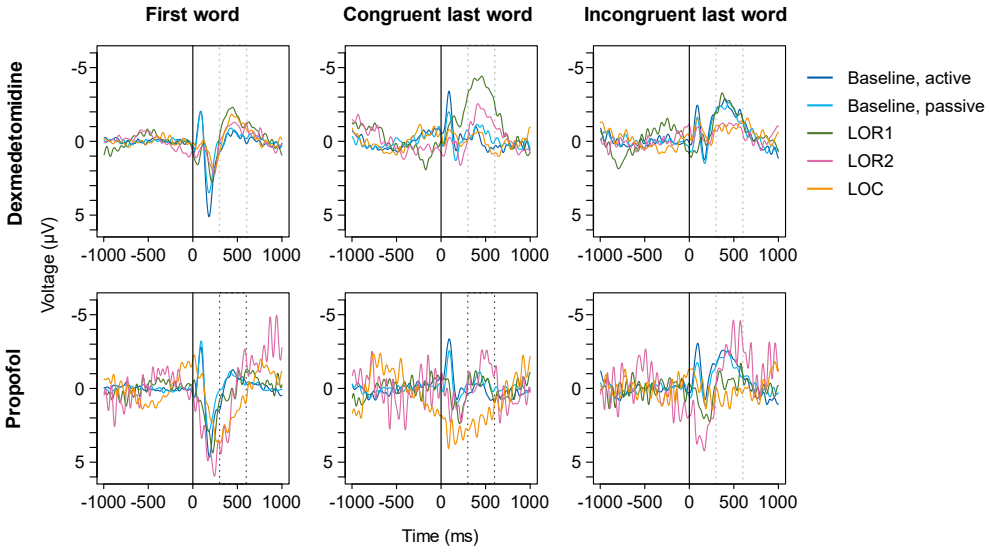

Figure 9. N400 components elicited by different stimuli in electrode C4. The limits of the time window of interest (300–600 ms) are highlighted with grey dashed lines. In the dexmedetomidine group, the numbers of participants in each condition were 23 in baseline, 22 in LOR1, 17 in LOR2, 22 for the first words in LOC, and 21 for the last words in LOC. In the propofol group, there were 24 participants in baseline, 22 for the first words in LOR1, 21 for the last words in LOR1, 3 in LOR2, 16 for the first words in LOC, and 17 for the last words in LOC.

The N400 effect disappeared in dexmedetomidine-induced unresponsiveness already in LOR1 state. However, a negative deflection with a timing and topography compatible with the N400 component persisted, and the N400 component was observed for the first and last words of sentences in the dexmedetomidine group. The N400 component elicited by the first words of sentences differed between the states (main effect of state P=0.021 for the comparison of active baseline, LOR1, LOR2,

LOC) and was more negative in the LOR states than in the active baseline (LOR1 P=0.043 and LOR2 P=0.052). The N400 component elicited by the congruent last words was also significantly different between the four states (main effect of state P<0.001) and was more negative in all the unresponsive states than in the active baseline (LOR1 P<0.001, LOR2 P=0.014, and LOC P=0.019). The N400 component observed in response to the incongruent last words of sentences did not, however, differ between the active baseline and the unresponsive states (P=0.316). Thus, the N400 component elicited by all the three types of words (first, congruent last, incongruent last) during dexmedetomidine-induced unresponsiveness resembled the N400 component elicited by incongruent words in the awake baseline. In the dexmedetomidine group, the latency of N400 component varied between 360 ms (95% CI 134–586 ms) for the congruent last words in LOC and 462 ms (95% CI 200–724 ms) for the incongruent last words in LOR2.

Propofol administration resulted in high-amplitude oscillations that dominated even the average ERP waveforms, which limits the interpretation of the results. In addition, the LOR2 state was achieved with only four participants receiving propofol, and only three of them had a sufficient amount of the ERP data available after the preprocessing steps. During the propofol-induced unresponsiveness, the average amplitudes observed in the N400 time window were consistently more negative than those in the control time window, but statistically significant N400 effect and component were mostly not detected. Although a statistically significant ERP was detected on a few occasions, such as in response to incongruent last words in LOR1 (P=0.017), the results were not consistent across stimulus types or states. However, interestingly, the N400 effect was detected in LOR2 (P<0.001), but the data were only available from three participants. Restricting the LOR1 analysis to these same three participants yielded no observable N400 component. Stratifying the analyses by the reporting of experiences was not feasible, since only 0–6 participants per drug reported no experiences from each state (Section 5.5).

5.4 Familiarity of the sentences and emotional sounds presented during sedation (Studies II and III)

The memory trace of emotional sounds (anesthesia experiment) and incongruent sentences (awake and anesthesia experiments) was studied with a yes/no recognition task.

The participants anesthetized with dexmedetomidine recognized the emotional sounds heard during unresponsiveness better than the participants anesthetized with propofol (P=0.02, interaction of stimulus and treatment). The recognition rate of the familiar sounds was 41.7% and the false alarm rate was 26.8% in the

dexmedetomidine group (odds ratio for the familiar sounds after adjustment for state 1.75, 95% CI 1.19–2.79). In the propofol group, the recognition rate was 15.2% for familiar sounds and the false alarm rate was 21.9% (odds ratio for the familiar sounds after adjustment for state 0.67, 95% CI 0.35–1.28). None of the participants mentioned hearing the emotional sounds in the interviews. In the recognition task, the responses to the familiar stimuli (mean 627 ms, 95% CI 551–713 ms) were faster than to novel stimuli (715 ms, 95% CI 647–792 ms; P=0.02 after adjustment for state and drug).

The sentences heard during the active baseline of the awake experiment were recognized at an average rate of 87% and, with a false alarm rate of 7.7%. In the passive baseline, the respective numbers were 71% and 13%. Accordingly, the discriminability measure *d'* clearly showed the recognition of the stimuli with values of 2.5 (95% CI 2.3 to 2.7) in the active baseline and 1.7 (95% CI 1.4 to 2.0) in the passive baseline. The reaction times were shorter for the correct responses than for the misidentified sentences, but the response times did not differ between familiar and novel sentences in the awake experiment. Dexmedetomidine and propofol significantly disrupted the sentence recognition (P<0.001 for comparison with the active baseline) and the *d'* ranged from 0.0 to 0.1 in the unresponsive states (95% CI –0.3 to 0.4). The sentences heard during unresponsiveness were recognized at a rate of 21% with a false alarm rate of 18%. The reaction times did not differ significantly between the correct responses and the misidentified sentences. Throughout the experiment, there was a conservative response bias which means that the stimuli were reported as novel when unsure (except the active baseline). The five sentences that were part of the responsiveness test were recognized at a rate of 32% in the dexmedetomidine group and at a rate of 42% in the propofol group. The responsiveness test was repeated a median of 3 times (range 0–11) in responsive and 11 times (range 2–27) in unresponsive state. The number of the times of hearing the responsiveness test when the participant was either responsive or unresponsive did not correlate with the recognition of the sentences.

5.5 Subjective experiences reported after unresponsiveness (Study III)

The inter-rater reliability between the two raters for the stage 1 categorization of the report types (origin of the experiences) was 92.9%, κ=0.887 (P<0.001). For the stage 2 coding of the unresponsiveness-related experiences as dreaming, memory incorporation, or awareness of the environment, the inter-rater reliability was 98.6%, κ=0.973 (P<0.001). The two raters assessed the SEDA categories for the modalities of the experience (stage 3a) similarly in 84.0% for the dream reports, 93.3% for the memory incorporation reports, and 89.7% for the awareness reports. The inter-rater

reliability of the complexity measured with the Orlinsky scale (stage 3b) was 85.7%, κ=0.754 (P<0.001).

There were 93 successful awakenings followed by an interview: 59 in the dexmedetomidine and 34 in the propofol group. Out of the interviews, 28 were from ROR1 after LOR1, 20 from ROR2 after LOR2, and 45 from ROR3 after LOC state. Most of the reports (84%) were classified as unresponsiveness reports and most of them contained experiences from more than one stage 2 category: dreaming, memory incorporation, and awareness of environment (Figure 10). There were more successful awakenings from LOR1 and LOR2 states induced by dexmedetomidine than from those induced by propofol (Fisher's Exact test, P=0.033 for LOR1 and P=0.026 for LOR2). Most of the participants reported subjective experiences originating from the unresponsive period (90% of the dexmedetomidine participants and 74% of the propofol participants) and there was no difference between the two drugs in the proportions of reports with unresponsiveness-related content (unresponsiveness-related content vs. other stage 1 categories, Fisher's Exact test, P=0.076). However, when all the four stage 1 categories were compared, the distribution of reports with no recall, responsiveness-related content, white report, or unresponsiveness-related content differed between the drugs (Fisher's Exact test, P=0.001): the proportion of reports with experiences from the unresponsive period was higher among the participants receiving dexmedetomidine than among the participants receiving propofol, while the proportion of reports with wake-related experiences was higher in the propofol group.

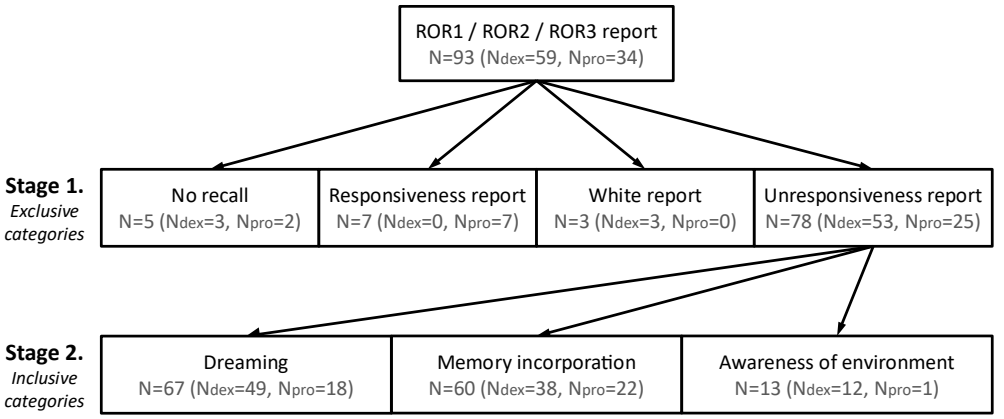

Figure 10. The distribution of the interview reports from the 93 successful awakenings in analysis stages 1 and 2. N_{dex} = number of reports related to dexmedetomidine, N_{pro} = number of reports related to propofol.

Most of the unresponsiveness-related experiences were either dreaming or memory incorporation of the research environment. Out of the unresponsiveness reports from ROR1, ROR2, and ROR3, 88.0%, 80.0%, and 86.8% included dream content, respectively. Memory incorporation was included in 88.0% of the unresponsiveness reports in ROR1, 53.3% in ROR2, and 78.9% in ROR3, and awareness was observed in 16.0%, 26.7%, and 13.2% of the unresponsiveness reports of the respective states. Participants in the dexmedetomidine group had more dreaming than those receiving propofol in ROR1 (100% vs. 62.5%, Fisher's Exact test, P=0.024) and in all RORs combined (92.5% vs. 72.0%, P=0.022). Awareness of the research environment was present in 13 reports (16.7%). When these reports were compared with experiment logs and EEG recordings, all the cases were related to brief arousals from the unresponsive state. Thus, no awareness of the environment was observed during complete anesthetic-induced unresponsiveness. Awareness of the research environment was more common in the dexmedetomidine group than in the propofol group (12 reports vs. 1 report, Fisher's Exact test, P=0.051). The only awareness report in the propofol group originated from the ROR3 state. The awareness reports of the participants receiving dexmedetomidine were evenly distributed in ROR1, ROR2, and ROR3 states, 4 reports in each.

When the unresponsive experimental states achieved in each participant were further grouped based on the reports to connected, disconnected, unconscious, and unknown, there were 13 unresponsive periods with connected experiences (unresponsiveness report with awareness content), 65 periods with disconnected experiences (unresponsiveness report without awareness content), and 12 periods suggestive of unconsciousness (no recall or responsiveness-related report). In 24 unresponsive periods, the status remained unknown (no awakening, no successful interview or white report). Out of the 12 potentially unconscious unresponsive periods, only 3 were from the dexmedetomidine group and all of them were from ROR2. The remaining 9 cases were from the propofol group and were recorded in ROR1 (N=2), ROR2 (N=1), or ROR3 (N=6)

The participants receiving dexmedetomidine had to be roused to the ROR3 state more often than those in the propofol group (Fisher's Exact test, P=0.010). All but one person in the propofol group regained responsiveness spontaneously. In the dexmedetomidine group, the time from the end of drug administration in LOC to awakening correlated with the measured drug concentration in LOC (Spearman's correlation coefficient 0.84). There were no statistically significant differences in the proportions of unresponsiveness reports and other types of reports (no recall, responsiveness report, white report) between the participants who were roused and the participants who woke up spontaneously (P=1.000).

The modality and complexity of the experiences did not differ between the two drugs and the results are therefore reported with the drugs combined (Table 6, Table

7). The dream experiences were mostly visual (89.6%) and many of them (32.8%) included auditory perceptions. The kinesthetic and cognitive experiences were broadly present in the dream reports. The reports showing memory incorporation contained mostly auditory (65.0%) and visual (36.7%) experiences. The experiences related to temperature or pain were present in one fifth of the reports with memory incorporation and they were mostly related to cannulation or injection of the anesthetic. The dream experiences were classified relatively evenly to static, scenery, and dynamic categories but the memory incorporation reports were mostly static (84.5%). The awareness experiences were primarily static, and they included mostly auditory (53.8%) or kinesthetic (23.1%) experiences or sense of presence (23.1%).

Table 6. The modality (stage 3a) of experiences in unresponsiveness reports. In total, there were 67 dream reports, 60 memory incorporation reports, and 13 awareness reports.

	DREAM REPORTS CONTAINING A SPECIFIC MODALITY, N (%)	**MEMORY INCORPORATION REPORTS CONTAINING A SPECIFIC MODALITY, N (%)**	**AWARENESS REPORTS CONTAINING A SPECIFIC MODALITY, N (%)**
SENSORY-PERCEPTUAL			
VISUAL	60 (89.6%)	22 (36.7%)	1 (7.7%)
AUDITORY	22 (32.8%)	39 (65.0%)	7 (53.8%)
GUSTATORY	2 (3.0%)	0 (0.0%)	0 (0.0%)
OLFACTORY	0 (0.0%)	0 (0.0%)	0 (0.0%)
INTEROCEPTIVE	1 (1.5%)	1 (1.7%)	0 (0.0%)
KINESTHETIC	18 (26.9%)	17 (28.3%)	3 (23.1%)
TACTILE	3 (4.5%)	10 (16.7%)	2 (15.4%)
PAIN, TEMPERATURE	2 (3.0%)	12 (20.0%)	2 (15.4%)
AFFECTIVE STATES			
POSITIVE	14 (20.9%)	4 (6.7%)	0 (0.0%)
NEGATIVE	10 (14.9%)	2 (3.3%)	1 (7.7%)
COGNITION	22 (32.8%)	9 (15.0%)	2 (15.4%)
OUT-OF-BODY EXPERIENCE	0 (0.0%)	0 (0.0%)	0 (0.0%)
SENSE OF PRESENCE	2 (3.0%)	6 (10.0%)	3 (23.1%)

Table 7. The perceptual complexity and dynamics (stage 3b) of experiences in unresponsiveness reports. In total, there were 67 dream reports, 60 memory incorporation reports, and 13 awareness reports. Some of the reports only contained thoughts or memories without any perceptual content and thus 64 dream reports, 58 memory incorporation reports, and 12 awareness reports could be classified with Orlinsky scale.

	DREAM REPORTS, N (%)	MEMORY INCORPORATION REPORTS, N (%)	AWARENESS REPORTS, N (%)
STATIC REPORT	24 (37.5%)	49 (84.5%)	11 (91.7%)
SCENERY REPORT	22 (34.4%)	9 (15.5%)	0 (0.0%)
DYNAMIC REPORT	18 (28.1%)	0 (0.0%)	1 (8.3%)

Considering the presence of experiences of different content types (dreaming, memory incorporation, and awareness of environment) within single reports, most of the reports included both dreaming and memory incorporation (49/78, 62.8%). All of the reports demonstrating awareness also included dreaming (11/13, 84.6%) and/or memory incorporation (9/13, 69.2%). The median number of different modalities was 2 (range 1 to 8) in dream reports, 2 in incorporation reports (1 to 5) and 1 in awareness reports (1 to 3).

5.6 Combined results from the anesthesia experiment (Studies I–III)

The results from the anesthesia experiment (Studies I–III) are summarized in Table 8. The most prominent changes from baseline to the anesthetic-induced unresponsiveness were the loss of N400 effect, the increased amplitude of N400 component elicited by congruent words in the dexmedetomidine group, the increase in the prefrontal-frontal functional alpha connectivity, and the decrease in the prefrontal-to-frontal directed alpha connectivity. In contrast, there were no changes in N400 component elicited by incongruent words in the dexmedetomidine group or in anterior-posterior alpha connectivity.

Table 8. The changes detected in different measures from one experimental state to another. The subjective experiences from interviews are marked under the state after which the interview was done. Abbreviations: ↑, the measure increased; ↓, the measure decreased; ↔, the measure did not change; *, based on a trend, not a statistical test, since the formal analysis of the differences was not part of the analysis plan (for proportions of reports, a difference of 10 percentage points in a minimum of 3 participants was considered suggestive of a trend); -, not measured; dexmed., dexmedetomidine.

	baseline → SED	**SED → LOR1**	**baseline → LOR1**	**LOR1 → ROR1**	**LOR1 → LOR2**	**baseline → LOC**	**LOR1 → LOC**	**LOR2 → LOC**
N400 COMPONENT FOR INCONGRUENT WORDS	-	-	↔ with dexmed.	-	↔ with dexmed.*	↔ with dexmed.	↔ with dexmed.*	↔ with dexmed.*
N400 COMPONENT FOR CONGRUENT WORDS	-	-	↑ with dexmed.	-	↔ with dexmed.*	↑ with dexmed.	↔ with dexmed.*	↔ with dexmed.*
N400 EFFECT	-	-	↓*	-	↔ with dexmed.*	↓*	↔ with dexmed.*	↔ with dexmed.*
PREFRONTAL-FRONTAL ALPHA COHERENCE	↑	↑	↑	↓	-	↑	↑	-
PREFRONTAL-FRONTAL ALPHA WPLI	↔	↑	↑	↓	-	↑	↔ with dexmed., ↑ with propofol	-
PREFRONTAL-TO-FRONTAL ALPHA DPLI	↔ with dexmed., ↓ with propofol	↓	↓	↑	-	↓	↔ with dexmed., ↓ with propofol	-
ANTERIOR-POSTERIOR ALPHA COHERENCE	↔	↔	↔	↔	-	↔	↑	-
ANTERIOR-POSTERIOR ALPHA WPLI	↔ with dexmed., ↓ with propofol	↔	↔	↔	-	↔	↔	-
ANTERIOR-TO-POSTERIOR ALPHA DPLI	↔	↔	↔	↔	-	↓	↓	-

(Table 8 continued)

	baseline → SED	SED → LOR1	baseline → LOR1	LOR1 → ROR1	LOR1 → LOR2	baseline → LOC	LOR1 → LOC	LOR2 → LOC
NO RECALL OF EXPERIENCES	-	-	-	-	↑ with dexmed.*	-	↔*	↓ with dexmed.*
RESPONSIVE-NESS REPORT	-	-	-	-	↔ with dexmed.*	-	↔ with dexmed., ↑ with propofol*	↔ with dexmed.*
WHITE REPORT	-	-	-	-	↔ with dexmed.*	-	↔*	↔ with dexmed.*
UNRESPON-SIVENESS REPORT	-	-	-	-	↓ with dexmed.*	-	↔ with dexmed., ↔ with propofol*	↑ with dexmed.*
DREAMING	-	-	-	-	↓ with dexmed.*	-	↔ with dexmed., ↑ with propofol*	↔ with dexmed.*
MEMORY INCORPORATION	-	-	-	-	↓ with dexmed.*	-	↓ with dexmed., ↔ with propofol*	↑ with dexmed.*
AWARENESS	-	-	-	-	↔ with dexmed.*	-	↔*	↓ with dexmed.*
RECOGNITION OF SENTENCES	-	-	↓*	-	↔*	↓*	↔*	↔*
RECOGNITION OF SOUNDS	-	-	-	-	↔	-	↔	↔

5.7 The impact of the analysis method on detecting N400 effect in awake state (Study IV)

Data from 79 participants and two paradigms were analyzed in Study IV. Therefore, the maximum number of detected N400 effects could have been 158. There was a substantial agreement between the three raters in the visual inspection of N400 effect (Fleiss's κ 0.68). All the three raters detected N400 effect in 105/158 cases and at least two raters detected N400 effect in 118 cases. When the agreement of all three raters was required, N400 effect was detected in at least one paradigm in 67 participants. With ANOVA, cluster-based non-parametric testing, and the Bayesian method, N400 effect was detected in at least one paradigm in 54, 47, and 70 participants, respectively. The variants of t-CWT method detected N400 effect in at

least one paradigm in 25, 17, and 47 participants with the split-half 50%/50%, split-half 80%/20%, and group-hold-out algorithms, respectively. The different variants of t-CWT showed relatively low concordance.

The overlap of the detection of N400 effect was evaluated between visual inspection, ANOVA, cluster-based non-parametric testing, and the Bayesian method. The t-CWT was excluded due to the discrepancies between its different variants. N400 effect was detected by at least one of the four methods in 86% (68/79) of participants in the active paradigm and in 86% (68/79) of participants in the passive paradigm. Visual inspection covered 82% and 72%, ANOVA 63% and 49%, the cluster-based method 57% and 37%, and Bayesian regression 88% and 88% of the participants with N400 effect detected by at least one of the four methods in the active (N=68) and passive (N=68) paradigms, respectively. The methods overlapped only partially and all the methods but ANOVA detected N400 effect in cases that were not detected by any other method. All the four methods detected N400 effect in 29 participants in the active and 20 participants in the passive paradigm. In addition, the three-method intersection of visual inspection, ANOVA, and Bayesian method covered 10 participants in the active and 10 participants in the passive paradigm, and the two-method intersection of visual inspection and Bayesian method was 8 participants in the active and 10 participants in the passive paradigm. The Bayesian method was the most liberal approach, and it was the only method to detect the N400 effect in 7 participants in the active and 17 participants in the passive paradigm. N400 effect was detected by visual inspection in almost all the participants who also showed N400 effect with ANOVA and the cluster-based method. The concordance of the N400 effect detection between the two paradigms was only partial (Figure 11). In four (5%) participants N400 effect was not identified by any of these four methods in either active or passive paradigm. The t-CWT 80%/20% detected N400 in two of these participants.

The performance of the different methods was evaluated with quantitative and qualitative analysis. The t-CWT results were not included due to the high variability between the different t-CWT approaches. The detection of N400 effect was associated with more negative amplitude, maximum, and median of the difference wave in 300–600 ms time window ($P<0.005$) in Cz electrode compared with the cases without detected effect. This applied to the four methods separately and in combination with the exception of the maximum of participant-wise average in the passive paradigm, which only differed statistically significantly with ANOVA and the cluster-method. Any other measures (standard deviation, kurtosis, and skewness between the trials or within the average ERP, or the maximum and average of GFP) did not differ significantly between the cases with and without a detected N400 effect ($P>0.005$). Thus, these comparisons provided no explanation for the differences between the four methods.

The qualitative analysis revealed that the cases where N400 effect was not detected by any of the four methods were characterized by inconsistent timing, inconsistent or local topography, inconsistent or short length, or inconsistent morphology of N400 ERP waveform. The Bayesian regression was the only method that detected several cases categorized as inconsistent with respect to some characteristic. The N400 effects that were typical in terms of timing, topography, length, or shape were primarily detected with visual inspection, ANOVA and the Bayesian method but the cluster-method only detected half of them or less.

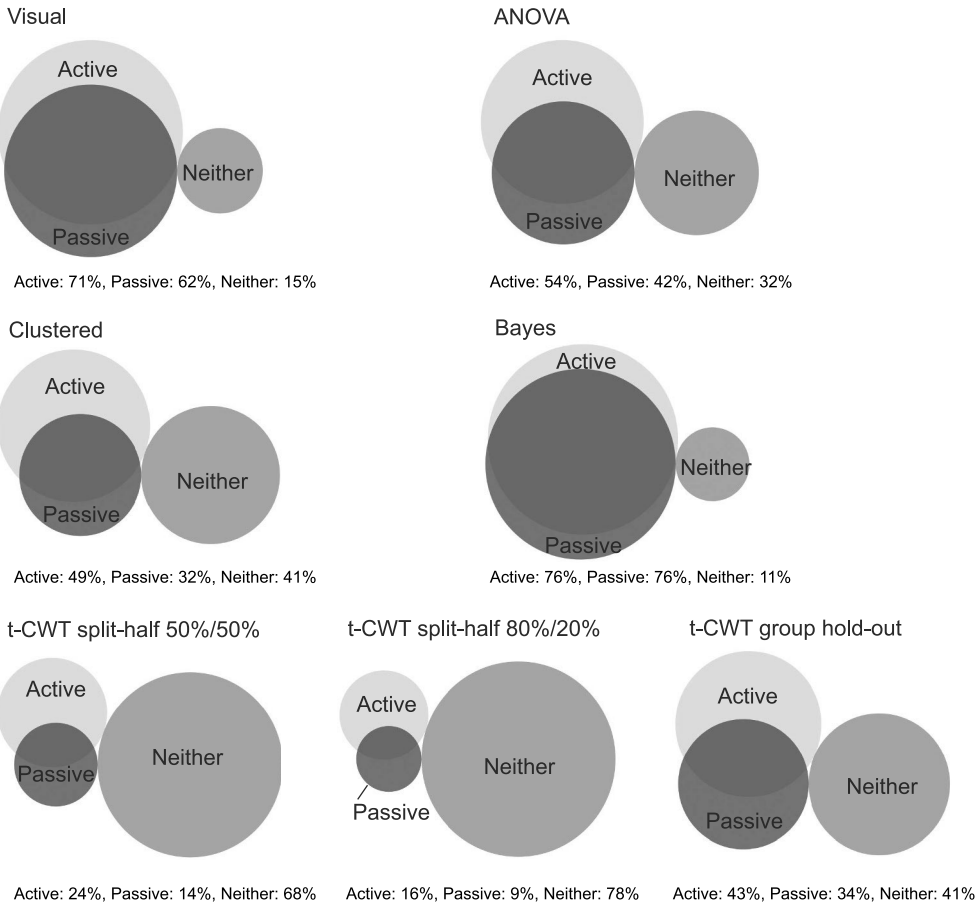

Figure 11. The numbers of participants with N400 effect detected in active paradigm (light grey), passive paradigm (dark grey), and neither (medium grey). The area of the circles is proportional to the number of participants. Total number of participants is 79. Out of the variants of t-CWT method, the three approaches using Hotelling's T2 test are shown.

6 Discussion

The current understanding of changes in brain function and in the states and contents of consciousness during sedation and general anesthesia is incomplete. In this study, the anesthetic-induced unresponsiveness was explored from the perspectives of the EEG-based features of brain activity with and without stimulation and the experiences of the participants. The awakening of the participants during constant anesthetic infusion enabled the examination of state-related effects apart from the effects of the drug concentration, and the recording of their experiences without memory confusions related to delayed interviews. Many previous studies examining anesthetic-induced alterations in the state of consciousness have assumed that the anesthetic effects on the brain directly reflect the neural correlates of consciousness but, in reality, the drugs have wide effects on the brain that are not necessarily related to the state of consciousness (Brown et al., 2010; Franks, 2008).

The altered state of consciousness caused by anesthetics can be characterized in terms of responsiveness, connectedness, and consciousness. More precise anesthesia monitors are needed to take into account the different aspects of the experiences occurring during general anesthesia, and for objective on-line monitoring of the patient's state of consciousness to minimize the possibility of intraoperative awareness. New tools for the monitoring of the state of consciousness could also be useful in other behaviorally unresponsive conditions, such as disorders of consciousness, and the information on the experience-related brain functions may help in constructing brain-computer interfaces.

The loss of the interplay between the anterior and posterior parts of the brain is often considered to have a major role in inducing unconsciousness during general anesthesia. The results of this study show that the loss of functional or directed alpha-band connectivity between anterior and posterior regions is not a correlate of anesthetic-induced unresponsiveness. Instead, unresponsiveness is accompanied by the increase of prefrontal-frontal functional connectivity and the reversion of prefrontal-frontal directed connectivity in the alpha band, and the changes return to a level preceding unresponsiveness upon rousal despite constant drug infusion. This highlights the possibilities of frontal EEG monitoring of general anesthesia. The results regarding the N400 ERP show that dexmedetomidine and propofol anesthesia

disrupt the understanding of complex linguistic stimuli. However, the processing of meaning is not necessarily completely lost, at least not during dexmedetomidine-induced unresponsiveness, but the anesthetic may interfere with the processing of individual words in relation to the preceding context. The detection rate of N400 effect was only 76% at the highest at single-participant level during wakefulness which shows that N400 cannot be reliably used to explore connectedness at individual-level even in the awake state. The increased low frequency background activity prevented the study of the individual-level N400 in anesthesia.

The roles of cortex and subcortical structures in the altered states of consciousness have been a topic of a long-lasting debate (Alkire et al., 2008a; Boly et al., 2012; Pujol et al., 2021; Raz et al., 2014; Scheinin et al., 2021). Also, the frontal and parietal brain structures have been in the core of many theories and experimental studies but the results have been contradictory (Boly et al., 2017; Mashour et al., 2012; Odegaard et al., 2017; Pal et al., 2018). The thalamus, anterior and posterior cingulate cortices, and bilateral angular gyri have been suggested as key structures in the changes between responsive and unresponsive, or connected and disconnected states under exposure to anesthetics (Franks, 2008; Kantonen et al., submitted; Långsjö et al., 2012; Scheinin et al., 2021). Compared with the hemodynamic signal measured with fMRI that may be only weakly coupled with neural activity in the resting state measurements, EEG is a direct measure of the neuronal activity (Drew, 2019). The EEG measures mostly cortical signals but also subcortical sources can be extracted from measurements to some extent (Seeber et al., 2019). Even source-localized EEG signal fails to detect some of the active areas detected with fMRI due to, for example, the cancellation of superimposed signals from multiple sources (Ahlfors et al., 2010). When the analysis is limited to the sensor space, the comparability of EEG measurements with brain imaging methods is low, yet the challenges related to the assumptions in the inverse problem and to constructing a network in a source space are avoided (Korhonen et al., 2021; Mahjoory et al., 2017; Michel and Brunet, 2019).

The present study is based on measuring the brain activity solely using EEG analyzed in sensor space, and thus cannot reveal the underlying sources of the N400 or connectivity in the brain. However, the results can be interpreted in the context of sensor space and previous source-based studies utilizing EEG and other methods. Sensor-based approach is important from the viewpoint of monitoring anesthesia in the clinical setting as it provides an easy-access, model-free representation of the measured signals. For the purpose of anesthesia monitoring, developing methods for the reliable differentiation of brain states is more urgent than fully understanding the complete brain processes underlying the differences. The pyramidal layer 5 neurons are the main source of EEG signal and they have been suggested to play a crucial role in modulating the state in general anesthesia via both thalamo-cortical and

cortico-cortical processing (Bachmann, 2021; Suzuki and Larkum, 2020), which further highlights EEG as an interesting method to monitor anesthesia.

In the current study, two different anesthetic agents acting through different molecular mechanisms were used to identify shared brain processes related to consciousness that are not drug-specific. The existence of one unitary mechanism of anesthetic-induced unconsciousness playing a role independent of the drug has been questioned (Bonhomme et al., 2019). However, the present results demonstrate multiple features shared between dexmedetomidine- and propofol-induced unresponsiveness. In addition to the disruption of contextual processing of sentence stimuli, indicated by the loss of the N400 effect, and shared trends in alpha connectivity, most of the participants reported subjective experiences originating from the unresponsive period. Memory incorporation of the research environment was frequent with both drugs in the reports obtained after the recovery of responsiveness, and the modality and complexity of the reported experiences did not differ between the two drugs.

In addition to the observed similarities between dexmedetomidine and propofol, several phenomena were typical only for one of the drugs. Despite the common behavioral end-points, the overall levels of anterior-posterior functional and directed connectivity values (wPLI and dPLI) differed between the two drugs in the anesthetized states. The N400 component persisted in all unresponsive experimental states induced by dexmedetomidine. Although the propofol group also showed negativity in the N400 time window, the high background noise did not allow drawing conclusions regarding the N400 component during propofol-induced anesthesia. The awakenings from unresponsiveness during constant infusion were more often successful in the dexmedetomidine than in the propofol group although there were many successful awakenings also with propofol. The participants receiving dexmedetomidine reported experiences from the unresponsive period more often than the participants receiving propofol whereas propofol was associated with more reports of wake-related experiences. The participants in the dexmedetomidine group had more dreaming and awareness content in the dream reports than propofol participants. The participants receiving propofol regained responsiveness before the 30-minute cut-off after the highest anesthetic concentration more often than dexmedetomidine participants.

6.1 The experimental states in relation to the Hierarchical Framework of Experiences

The key features characterizing anesthetic-induced states include responsiveness, connectedness, and consciousness, as described in the Hierarchical Framework of Experiences (Section 2.2.6). In the present study, the dexmedetomidine and propofol

administration was titrated to the same behavioral endpoint, unresponsiveness. However, the connectedness and consciousness may have varied between the participants even within the same experimental state. Responsiveness was measured by asking the participants to press handles in response to sentence stimuli. Responding to the sentence stimuli is a sum of several components: motor ability to respond, connectedness, comprehension, and ability and willingness to follow commands. Consequently, in baseline, the participants were responsive, connected, and conscious as they were able to coherently respond to the stimuli. Also the N400 effect indicated the semantic processing of complex linguistic stimuli in baseline.

During the sedative steps before LOR1, the participant was still able to respond to one or more sentences of the responsiveness test despite the presence of the anesthetic drug. Regardless of being, by definition, a responsive state, the highest sedative step already displayed changes in EEG connectivity that were further strengthened after loss of responsiveness: the prefrontal-frontal functional connectivity measured with coherence was already increased in the alpha band and, with propofol, the prefrontal-to-frontal alpha band directed connectivity was decreased.

The next increase in the drug target concentration caused LOR1 state that was, by definition, an unresponsive state. In LOR1, the N400 effect was lost but, at least with dexmedetomidine, the first and last words of the sentences elicited an N400 component which resembled the N400 component elicited by the incongruent words in the awake state. Thus, stimulus-related brain activity was preserved in LOR1 although the contextual processing of the words was disrupted. There were no signs of remembering the sentences presented during unresponsiveness after the experiment, but the participants responded faster to the emotional sounds heard during unresponsiveness than to unfamiliar sounds. The participants receiving dexmedetomidine recognized the familiar emotional stimuli more often than the participants receiving propofol. All but three of the participants had experiences originating from the unresponsive period, which indicates that the participants were, on average, conscious during LOR1. Most of the reports contained both dreaming and memory incorporation of the events related to the experimental situation, but all of the awareness-related experiences were associated with arousals during the experimental state. Based on the N400, memory test results, and experiences, it seems that the LOR1 state was often a conscious state and there were aspects of both connected and disconnected experiences.

In LOR2, the N400 component and effect were very similar to LOR1 in the dexmedetomidine group. Unresponsiveness-related experiences were observed in 75% of the interview reports. However, there were only two reports from LOR2 in the propofol group, and only one was an unresponsiveness report. Most of the reports included dream experiences but the memory incorporation seemed to be less

common than after LOR1. The effect of the preceding steps with escalating anesthetic dose was minimized in the LOR2 interviews and the state seemed to be quite similar to LOR1.

Finally, the drug concentration was increased to 1.5-fold to achieve the LOC state. The measured plasma concentration of dexmedetomidine was somewhat higher than the dose typically used in intensive care units for sedation and the concentration of propofol was slightly lower than in surgical general anesthesia (Nimmo et al., 2019; Weerink et al., 2017). The N400 component and effect were similar in LOR1, LOR2, and LOC states in the dexmedetomidine group, which could suggest that the LOC state might rather represent a deeper loss of responsiveness than the true loss of consciousness. Since almost all the participants had experiences during unresponsiveness, the dosing protocol of the present study may not have led to sufficiently deep anesthetized states to cover all the phases of losing consciousness described in Section 2.2.6. At the same time, there were participants who were unconscious based on their interview reports already in LOR1 and LOR2. Like in LOR1 and LOR2, the unresponsiveness reports were the most common report type in LOC and the reports contained mostly both dreaming and memory incorporation, although the reports from LOC were collected after a higher drug concentration and following a different awakening procedure than in the case of the LOR1 and LOR2 states. The memory test results did not differ between LOR1, LOR2, and LOC. It therefore remains unresolved whether the experimental LOC state was different from the LOR1 and LOR2 states and whether the higher drug concentration affected the rates of connectedness and consciousness.

The Hierarchical Framework of Experiences presented in Section 2.2.6 describes the loss of consciousness as a sequence of losing responsiveness, connectedness, and consciousness. However, the order of the states may be different, and a person may become unconscious without going through the intermediate phases of being unresponsive and conscious. Also, the timeframe of the different states is currently unknown and may vary. The effects of vigilance and natural sleep while under exposure to anesthetics most likely complicate the picture. As the general anesthesia is characterized by dynamically varying dominant network patterns (Li et al., 2019; Vlisides et al., 2019), it is possible that also the presence of consciousness and connectedness fluctuates during anesthesia. Individual characteristics may modify the effect of anesthetics on the state of consciousness due to, for example, differences in drug metabolism or dream frequency (Section 6.6).

Voluntary control may be an important aspect that is not included in the Framework, since the detection of responsiveness is also dependent on the willingness to respond. For example, the patients who are able to communicate with the help of brain imaging only represent a subset of those with a miscategorized disorder of consciousness (Naci et al., 2017), which highlights the need for different

tasks and the combination of stimulus-dependent and stimulus-free designs when studying the consciousness.

The results of the current study highlight the difficulty of defining the state of consciousness of an unresponsive person based on unified criteria. If observed responsiveness had been sufficient to define the state of consciousness, there would not have been between-subject variability in the types of subjective reports, recognition performance, stimulus-related EEG, or brain connectivity within the experimental states. Also, if the drug concentration directly correlated with the state of consciousness, the differences between the LOR and LOC states would have been more prominent. This is in line with Bayne and Howhy (2016) who suggested that different states are overlapping regions within a multidimensional space of consciousness.

6.2 Prefrontal-frontal alpha connectivity differentiates experimental states (Study I)

Connectivity between or within brain regions has previously shown potential in indexing impaired communication in different anesthetized and other altered states of consciousness (Hudetz and Mashour, 2016; Laureys and Schiff, 2012; Massimini et al., 2005). Especially the loss of anterior-posterior functional connectivity, which may reflect thalamo-cortical and/or cortico-cortical changes, has long been considered as a promising correlate of anesthetic-induced unresponsiveness or unconsciousness (Hudetz and Mashour, 2016). However, the roles of connectivity in subcortical brain structures (Mhuircheartaigh et al., 2010), posterior cortical areas (Koch et al., 2016), and anterior cortical areas (Guldenmund et al., 2016) have also been highlighted. The decrease of frontal-to-parietal EEG connectivity has been observed to correlate with anesthetic-induced decreases in the functional connectivity of the anterior default mode network and thalamo-cortical networks measured with fMRI (Jordan et al., 2013; Ranft et al., 2016). However, the comparisons of different studies are complicated by methodological differences related to measuring functional, directed, or effective connectivity with fMRI or EEG, limiting the analysis to the sensors, specific cortical or subcortical regions or networks of interest, and the differences in controlling and distinguishing drug- and state-related effects. Most of the previous studies on connectivity have been confounded by the simultaneous changes in the drug concentration and the state. This has typically been accompanied by the use of fixed group-level dosing or anesthetic doses similar to surgical anesthesia, whereas the present study was based on the individually titrated dosing with small increments until a minimally unresponsive state was achieved.

In Study I, the responsive and unresponsive states associated with a constant dexmedetomidine or propofol concentration could not be differentiated based on anterior-posterior coherence, wPLI, or dPLI in the alpha frequency band. In addition, the functional connectivity measured with coherence and wPLI did not show a consistent dose-related trend across the states with different anesthetic concentrations. This is in contrast to a wide range of fMRI, EEG, and MEG data with different anesthetic agents suggesting that the disruption of long-distance anterior-posterior feedback connectivity of the waking state could be a key mechanism of anesthetic-induced unresponsiveness (Blain-Moraes et al., 2014; Boly et al., 2012; Jordan et al., 2013; Ku et al., 2011; Lee et al., 2013b; Muthukumaraswamy et al., 2015; Ranft et al., 2016; Schröter et al., 2012; Untergehrer et al., 2014; Vlisides et al., 2017). The results of the Study I suggest that anterior-posterior functional connectivity measured in the alpha frequency band does not have a critical role in separating responsive and unresponsive states, but the anterior-posterior changes may reflect the concentration of the anesthetics instead of the state. These results are supported by a previous study where the emergence from surgical anesthesia did not correlate with the fronto-parietal functional connectivity in the alpha band measured with wPLI (Zierau et al., 2021) and by other studies where the fronto-parietal alpha connectivity failed to distinguish the anesthetized states (Li et al., 2019; Vlisides et al., 2019). The current results are also in line with a recent rodent study demonstrating that the anterior-posterior connectivity remains suppressed despite pharmacologically induced wakefulness, which suggests that the anterior-posterior connectivity is linked to the presence of the anesthetic in the brain and not to the behavioral state (Pal et al., 2020). The fronto-parietal EEG connectivity correlates with thalamo-cortical fMRI connectivity (Ranft et al., 2016) and, interestingly, the loss of responsiveness has induced changes in subcortical connections but thalamo-cortical connections have been preserved despite unresponsiveness in some studies (Mhuircheartaigh et al., 2010; Sanders et al., 2012).

However, the association of the anterior-posterior connectivity with the state of consciousness cannot be completely ruled out even in the alpha band since, in Study I, the net connectivity turned to posterior-to-anterior direction upon the concentration increase inducing the LOC state. The state of consciousness in the LOC state could not be confirmed from immediate reports (Section 6.5) but it likely did not represent unconsciousness in all of the participants. The anterior-posterior connectivity should be further studied contrasting unconsciousness with disconnected and connected consciousness.

Instead, the prefrontal-frontal functional and directed connectivity differentiated unresponsiveness from responsiveness during the continuous anesthetic infusion in Study I. The direction of the prefrontal-frontal connectivity reversed upon

unresponsiveness and returned to a level comparable with the preceding responsive states upon the recovery of responsiveness despite the constant infusion of dexmedetomidine or propofol. This indicates that the changes in the prefrontal-frontal connectivity were rather related to the state and not to the drug concentration. Also the states with different anesthetic concentrations could be separated based on the prefrontal-frontal connectivity and the connectivity values showed a solid association with the drug concentration. Thus, the ability of the prefrontal-frontal connectivity to reflect the state of the individual may also extend to higher doses and a threshold value for unconsciousness might exist. Since the state- and drug-related effects have been intertwined in the previous studies, it has been challenging to separate the correlates of responsiveness, consciousness, and the overall drug effect. In Study I, the differences between the LOR and LOR_{late} epochs showed that the relatively long unresponsive period during LOR1 state was not completely stable but the connectivity values shifted towards the values of the LOC state despite the pseudo-steady-state infusion.

The results of Study I highlight the anterior alpha connectivity as a correlate of responsiveness and are in line with other studies (Banks et al., 2020; Lee et al., 2017a; Pullon et al., 2022). Although the brain activity measured in terms of cerebral blood flow is affected already before the loss of responsiveness, for example, in the frontal cortical areas (Scheinin et al., 2021), the sensor-space renderings of connectivity that stem from cortico-cortical and/or thalamo-cortical connectivity can differentiate behaviorally different states. Thus, the EEG, especially when measured at the anterior sites, is a method suitable for measuring the anesthetized states. Different theories of consciousness deeply disagree as to the role of the prefrontal cortex in the neural correlates of consciousness. The posterior hot zone model, stemming from the Information Integration Theory, excludes the frontal cortex from the neural correlates of consciousness entirely, whereas in the Global Neuronal Workspace Theory, frontal areas are necessarily involved in the global neuronal workspace of consciousness (Dehaene and Changeux, 2011; Koch et al., 2016; Ihalainen et al., 2021; Mashour et al., 2020; Siclari et al., 2017). The present study supports the importance of the prefrontal cortex for consciousness (Mashour et al., 2022), or at least its role as an important site for measuring changes related to consciousness. However, the dynamic connectivity patterns reported during the maintenance phase of anesthesia suggest that the frontal alpha connectivity alone may be insufficient to reliably differentiate the anesthetized states (Li et al., 2019; Vlisides et al., 2019).

Study I is the first report of directed connectivity in dexmedetomidine anesthesia. The reversal of the anterior net connectivity to the frontal-to-prefrontal direction during unresponsiveness has also been shown in other studies with propofol (Chen et al., 2022; Lee et al., 2017a). Dexmedetomidine is not known for frontal alpha

hypersynchrony, unlike propofol (Ching et al., 2010; Guldenmund et al., 2016; Liu et al., 2017a; Supp et al., 2011; Vijayan et al., 2013). Although both dexmedetomidine and propofol induce increase in the power of the frontal alpha band, propofol induces several fold higher spectral power of the frontal alpha band than dexmedetomidine (Akeju et al., 2014a; Scheinin et al., 2018). Also, the phase-amplitude coupling of the alpha and delta bands is different with dexmedetomidine and propofol (Scheinin et al., 2018). Nevertheless, the observed changes in connectivity were relatively similar in both treatment groups. The results are further supported by a previous study with ketamine that does not induce spectral power in the alpha frequency band but shows suppression of prefrontal-to-frontal dPLI in the alpha band (Vlisides et al., 2017). When combined with the previous studies, the results of Study I show the potential of measuring connectivity between anterior channels as an agent-independent marker of unresponsiveness.

The results of Study I align with the previous studies which have shown that connectivity is confined to the structurally connected brain areas (Demertzi et al., 2019; Ma et al., 2019; Schröter et al., 2012; Uhrig et al., 2018) or the communication between different parts of the brain is simplified during anesthetic-induced unresponsiveness (Golkowski et al., 2019; Vlisides et al., 2019). The results are also consistent with the study where the phase relationships between anterior channels became more stereotyped during unresponsiveness (Lee et al., 2017a). This is also supported by an fMRI study showing the topological reconfiguration of functional connectivity towards locally segregated networks during anesthetic-induced unresponsiveness (Schröter et al., 2012). The results of Study I are well in line with the study of Banks and co-workers (2020) where the authors found that N2 and N3 sleep and propofol-induced unresponsiveness induce a shift of the dominant functional connections in alpha band from the temporal cortex to the prefrontal cortex. In their study, the connectivity centered in the local areas in unresponsive states. Sleep and anesthesia showed similar changes of connectivity in the prefrontal alpha band but only propofol increased the alpha power. Combined with the results of Study I where prefrontal-frontal alpha connectivity differentiated states also with dexmedetomidine, the two studies suggest that the increased local anterior alpha connectivity might be a correlate of unresponsiveness irrespective of the way the altered state has been induced.

Dexmedetomidine and propofol are known to increase the local coherence within the anterior area (Akeju et al., 2014a, 2016a; Purdon et al., 2013). In Study I, two different methods for estimating functional connectivity were applied. Although prefrontal-frontal coherence displayed a higher prediction probability than wPLI for the differentiation of the states with increasing drug concentrations (0.83 vs. 0.76), coherence could not separate the LOR and ROR states at a statistically significant level (P=0.065). It seems that calculating the more complex phase synchronization

indices that ignore the zero-lag false positives provides advantages over the relatively simple coherence. All the connectivity measures of this study (coherence, wPLI, and dPLI) distinguished the states of increasing dexmedetomidine concentration better than the anterior alpha power, which suggests that connectivity can provide treatment-independent information more effectively than the mere power in the alpha band. This is in line with previous studies where the connectivity and spectral content have provided complementary information (Banks et al., 2020; Sattin et al., 2021; Vlisides et al., 2017).

In the present study, the connectivity analyses were focused on the alpha frequency band. The frontal alpha power has been suggested as a promising marker of anesthetic-induced unconsciousness during propofol anesthesia (Purdon et al., 2013; Scheinin et al., 2018) but it cannot distinguish responsive and unresponsive sedated patients at the single-patient level (Banks et al., 2020; Gaskell et al., 2017). The prefrontal-frontal alpha connectivity is a more robust measure than many other EEG-based measures yet it also undergoes dynamic changes during the maintenance of general anesthesia in adults (Puglia et al., 2022; Vlisides et al., 2019). Although the alpha band has been found to be the most prominent frequency band in terms of connectivity in many studies, also other views have been published highlighting, for example, the low frequencies (Bourdillon et al., 2020). In Study I, the focus on the alpha band was chosen based on the previous studies on anesthetic-related changes in connectivity (Banks et al., 2020; Blain-Moraes et al., 2014; Chennu et al., 2016; Kim et al., 2016; Lee et al., 2013a; Supp et al., 2011; Vlisides et al., 2017) and the studies where both dexmedetomidine and propofol have induced increases in the alpha band despite their different molecular mechanisms (Akeju et al., 2014a; Scheinin et al., 2018). Most of the overall wPLI changes between 0 and 30 Hz occurred in the alpha frequency range of 8–14 Hz in Study I. The EEG-based connectivity at the lower frequencies (<30 Hz) and especially in the alpha band has previously been shown to correlate with the fMRI resting-state connectivity (Deligianni et al., 2014; Scheeringa et al., 2012). Also, the EEG connectivity in the alpha band correlates with brain glucose metabolism detected with PET (Chennu et al., 2017). Many of the changes in EEG connectivity and spectral power co-occur in the same frequency band, as seen in Study I and previous reports (Lee et al., 2017a; Vlisides et al., 2017) yet Study I demonstrated that connectivity can still provide added value. While the alpha band was targeted in the Study I, studies in the other frequency bands and using other neural recording modalities or analytic techniques could yield different results. Future studies should explore the association of the state of consciousness with within-anterior and anterior-posterior connectivity also in frequency bands other than alpha.

The mechanisms underlying the observed changes in connectivity are not yet completely clear. The anterior hypersynchrony has been suggested to block long-

range anterior-posterior cortical communication (Supp et al., 2011; Vlisides et al., 2019). The simultaneous anterior simplification of oscillatory communication and the loss of global network efficiency at the time scale of tens of seconds may contribute to the loss of responsiveness (Pullon et al., 2022). The frontal cortical and medial thalamic within-network connectivity have been suggested to play a part in the loss of between-network connection (Golkowski et al., 2019). Also, the loss of information content within the frontal area co-occurs with the reduction of thalamo-cortical connectivity during sevoflurane administration (Ranft et al., 2016). The loss of connectivity between the frontal and parietal cortices, and the disconnection of the fronto-parietal network from the primary sensory cortices have been of interest as potential mechanisms of the loss of responsiveness: there is a loss of connectivity within the frontal-parietal network but the loss of stimulus processing is rather caused by the disruption of communication between sensory and fronto-parietal networks (Naci et al., 2018). In the present study, the anterior-posterior alpha dPLI decreased along with increasing dosing, indicating that the posterior-to-anterior flow of information becomes dominant during propofol anesthesia, but this was unrelated to responsiveness.

To summarize, the results of the Study I show that measuring alpha band connectivity in the anterior EEG channels has potential for the monitoring of anesthetized states. The EEG-derived functional and directed connectivity within the anterior channels differentiated the experimental states defined by responsiveness and drug concentration in both dexmedetomidine and propofol groups. This observation may be clinically useful since the frontal electrodes can be easily accessed in the operating theater. The findings are further corroborated by the previous reports showing that the frontal alpha connectivity can also differentiate states of consciousness in conditions that are not associated with increases in the spectral power of the alpha band, such as ketamine anesthesia and natural sleep.

6.3 Semantic processing during anesthetic-induced unresponsiveness and N400 as its indicator (Studies II and IV)

In Studies II and IV, semantic processing was measured with N400 ERP as a response to spoken sentences. The N400 was studied during anesthetic-induced unresponsiveness, and the performance of different methods for the analysis of N400 at single-subject level were explored. Semantic processing is an essential cognitive ability in the normal, awake state and its importance is well acknowledged in disorders of consciousness where the neural correlates of speech comprehension are associated with a positive prognosis in uncommunicative patients (Coleman et al., 2009; Rohaut et al., 2015; Sokoliuk et al., 2021a; Steppacher et al., 2013). If the

understanding of meaning is preserved in a behaviorally unresponsive person, it is possible that also other kinds of information are processed beyond the primary sensory processing, or the individual is in a state that does not completely differ from normal wakefulness. Also, the information on the processing of semantic information may help in constructing better brain-computer interfaces for decoding covert speech production in unresponsive individuals (Moon et al., 2022).

The N400 component is typically induced by all words of a sentence but its amplitude decreases gradually towards the end of the sentence when the context narrows word by word (Kutas and Hillyard, 1984). In the awake state, the semantically or associatively unexpected stimuli, such as the sentence endings that do not match the context, elicit higher N400 component than the expected stimuli. The N400 effect is observed between the ERP components in response to congruent and incongruent stimuli. In Study II, the N400 effect was absent in all unresponsive states (LOR1, LOR2, LOC) in the dexmedetomidine group, which suggests that the normal understanding of meaning is lost at dexmedetomidine doses minimally sufficient to induce unresponsiveness. However, the N400 component elicited by incongruent sentence endings was of the same magnitude as in wakefulness and a component of a similar amplitude was also observed in response to the congruent last words and to the first words of sentences. Thus, stimulus-dependent processing in a late time window was detected during dexmedetomidine-induced unresponsiveness resembling the processing of incongruent words in the awake state. In wakefulness, the amplitude of N400 component is related to the effort of retrieving the representation of a semantic stimulus. The loss of N400 effect during dexmedetomidine administration was caused by the increased amplitude of N400 component elicited by congruent words. One potential explanation for this could be that dexmedetomidine hampers the contextual connections of the natural language to a point where all words cause maximal exertion for retrieving the representation of a word. This might be related to the loss of memory for the sentence beginnings or to inability to integrate the words into the sentences.

Also in the propofol group, negative voltages were detected in the N400 time window in LOR1 and LOR2 states in response to different types of stimuli. However, when the voltages were compared with the respective time window before the stimulus, no statistically significant N400 component was detected in most of the comparisons. In addition, the detected components were not consistent across different stimulus types, and the averaged ERPs showed no distinctive waveform. Thus, the conclusions regarding N400 in propofol-induced unresponsiveness are limited. Interestingly, N400 effect was detected in LOR2 where the analysis encompassed only three participants. Although the same three individuals did not show a similar effect when analyzed in LOR1, the presence of a true N400 effect in LOR2 cannot be excluded. The awakening after LOR1 had a prominent effect on the

state of most of the propofol participants: although ten individuals woke up into ROR1, only four of them achieved the unresponsive state again without an increase in the drug dose. Thus, the awakening seemed to affect the state of propofol participants more fundamentally than that of dexmedetomidine participants, and it is possible that the three persons included in the LOR2 N400 analysis were in a lighter unresponsive state than in their respective LOR1 and therefore had preserved semantic processing.

It is known that cortical auditory processing is preserved, although attenuated, during sedation (Davis et al., 2007; Dueck et al., 2005; Heinke et al., 2004b; Plourde et al., 2006). Propofol has previously been found to attenuate the auditory brain responses more than dexmedetomidine (Banks et al., 2018; Frölich et al., 2017). The processing of word stimuli is preserved in propofol sedation (Adapa et al., 2014; Davis et al., 2007; Ní Mhuircheartaigh et al., 2013; Plourde et al., 2006) and also after the loss of responsiveness (Davis et al., 2007; Ní Mhuircheartaigh et al., 2013), but differentiation of ambiguous and unambiguous sentences is lost already at light sedation characterized by slowed conversational response (Davis et al., 2007). Propofol-induced unresponsiveness has also been shown to degrade the connections between the sensory and higher-order networks when listening to verbal stimuli (Liu et al., 2012; Naci et al., 2018). Despite these converging results with propofol, little is known about semantic processing under exposure to dexmedetomidine. Study II is the first study to examine semantic processing using the N400 event-related potential in anesthetic-induced unresponsiveness, which is interesting since N400 is a more sensitive method for studying semantic relations than fMRI (Geukes et al., 2013). Previously, N400 has only been measured in combination with anesthetic drugs in an alert and active state during ketamine administration that caused the degradation of the N400 repetition effect (Grunwald et al., 1999). The dexmedetomidine results of Study II are in line with the previous information about propofol-induced unresponsive state suggesting preserved processing of words but loss of functional differentiation of meaning.

During wakefulness, language processing can be detected as a sequential activation in broad temporo-frontal network (Heinke et al., 2004b). The major brain areas that have been associated with the generation of N400 are the (left) superior and middle temporal areas, anterior temporal cortex and inferior frontal cortex (Lau et al., 2008; Van Petten and Luka, 2006; Zhu et al., 2019). The previous fMRI results suggest that the activation of the superior and middle temporal gyri in response to sentence stimuli is preserved under exposure to propofol (Davis et al., 2007; Heinke et al., 2004b). Instead, the activation of the inferior frontal gyrus in response to speech is degraded by propofol even at doses lower than those needed to induce unresponsiveness (Adapa et al., 2014; Davis et al., 2007; Heinke et al., 2004b; Liu et al., 2012). As these are the main brain structures related to N400, the results of

Study II align with the previous anesthesia literature also in terms of the brain areas responsible for semantic processing. However, temporal activation elicited by semantic stimuli has been shown to disappear in deep general anesthesia (Heinke et al., 2004b).

Although the results of Study II seem to converge well with the previous anesthesia studies, it is possible that the ERP measured in the time window 300–600 ms post-stimulus is not associated with the same processes during wakefulness and during anesthesia. Typically, studies on ERP components are interpreted in the context of observations from the paradigm that is known to produce a certain component. Because the N400 has not been previously studied during drug-induced unresponsiveness, the interpretation of the current findings largely relies on the knowledge from awake subjects reported during the past 40 years, and on other unresponsive states, such as sleep or disorders of consciousness where N400 effect has been detected (Beukema et al., 2016; Daltrozzo et al., 2012b; Ibáñez et al., 2006; Kotchoubey et al., 2005; Rohaut et al., 2015). At this point, there are no convincing alternative explanations for the indisputable event-related component observed 300–600 ms post-stimulus in dexmedetomidine-induced unresponsiveness in Study II. The latency and the centroparietal topography of the ERP component detected during unresponsiveness matches the N400 component in awake state. Thus, interpreting the ERP component observed during sedation as N400 is the simplest option. However, the nature of the processing associated with the N400 during anesthesia cannot be fully validated using the data from the current study, and future studies should examine the N400 at different depths of sedation. The N400 observed during drug-induced unresponsiveness may not be fully analogous with the N400 observed in wakefulness.

If the detected ERP component is accepted as the N400 component, another question remains: whether N400 reflects processes necessary or relevant for consciousness. The association of N400 with both automatic and controlled processing has been suggested with contradicting results from the experiments where the stimuli have been masked or degraded, and where the perception of the stimuli has been distracted with a competing task. Taken together, the previous studies suggest that both the automatic and integrative processes participate in the generation of N400 (Nieuwland et al., 2020; Rabovsky et al., 2018) or at least the automatic processing responsible for N400 is strengthened by top-down controlled processes (Kiefer and Martens, 2010). Higher-order processes have a greater role in the N400 induced by sentence stimuli compared with less complicated stimulus types (Daltrozzo et al., 2012a; Hagoort et al., 2004; Mongelli et al., 2019). Accordingly, the N400 effect is strengthened by directed attention (Erlbeck et al., 2014; Holcomb, 1988) and active task (Cruse et al., 2014; Erlbeck et al., 2014). In Studies II and IV, both the active responding and the passive listening conditions were measured at

wakefulness to examine the effect of responding on the N400. As expected, the N400 effect was detected in fewer individuals in the passive than in the active task in Study IV. In the passive condition, the variation between different analysis methods was also higher and the size of N400 effect was smaller than in the active condition. The preservation of directed attention was promoted during the anesthesia experiment (Study II) by instructing the participants to always respond to the stimuli, yet bottom-up, stimulus-driven attention may be more likely than top-down attention during unresponsiveness. Spoken stimuli naturally attract the attention and they therefore constitute the ideal type of stimulation for studying the unresponsive states (Naci et al., 2017).

When evaluating the applicability of N400 as an index for consciousness, the technical performance of the measurement has a critical role. This was studied at the level of individual participants in the Study IV. The choice of analysis method had a substantial effect on the detection rate of the N400 effect that varied between 16–76% and 9–76% in the active and passive task paradigm, respectively. The N400 effect could not be detected with any of the five methods in 8/79 participants in the active and 10/79 participants in the passive paradigm although they understood the sentences as indicated by the correct responses in the active baseline. This poses a critical problem of measuring N400 at the level of single individuals, which is a shared limitation of all cognitive ERPs (Connolly and D'Arcy, 2000). Different ERP amplitudes and waveforms across individuals may be caused, for example, by anatomical differences (Luck et al., 2011) or by differences in cognitive factors, like the overall vigilance, motivation, and attention. As the findings of Study IV converge with the results of the previous studies and N400 effect cannot be detected in all healthy individuals (Cruse et al., 2014; Daltrozzo et al., 2009; Hinterberger et al., 2005; Kotchoubey, 2005; Rohaut et al., 2015; Sculthorpe-Petley et al., 2015), the presence of N400 can show the preservation of semantic processing at the single-subject level but the lack of N400 is not informative. Nevertheless, the clinical utility of complex cognitive ERPs cannot be abandoned as they provide an easily accessible method for studying multiple cognitive functions in unresponsive patients (Bekinschtein et al., 2009; Connolly and D'Arcy, 2000; Rohaut et al., 2015; Steppacher et al., 2013). In addition, N400 has shown promise in machine learning based classification paradigms and brain-computer interfaces (Dijkstra et al., 2019, 2020; Sculthorpe-Petley et al., 2015).

The studies on the N400 highlight the signal-to-noise ratio of an ERP as a limiting factor because the signal strength greatly varies across individuals (Dijkstra et al., 2020). The variance between trials within a participant is wider in the case of a late ERP component compared with early automatic ERP components (Sculthorpe-Petley et al., 2015). The EEG recorded in unresponsive conditions typically differs from the EEG in wakefulness. Spectral analysis of the anesthesia experiment

indicated that dexmedetomidine and propofol increase the delta (1–4 Hz) and slow delta (0.1–1 Hz) power also in the centroparietal area compared to the awake baseline (Scheinin et al., 2018). Especially propofol also induces an increase in the power of alpha oscillations (8–14 Hz), which likely contributes to the high variation of averaged ERP signal and the lack of consistent N400 waveform in the propofol group, limiting the ability to draw conclusions on the N400 during propofol-induced unresponsiveness. While comparing the time window of the N400 component (300–600 ms) with the corresponding pre-stimulus baseline (from –600 to –300 ms) can control for any drug-induced increase in the power of non-synchronized oscillations, it is difficult to dissect the roles of non-specific drug-induced delta and its synchronization. Although the precise roles of increased neural activation and phase synchronization in ERP formation have not been resolved (Fell et al., 2004; Telenczuk et al., 2010; Xu et al., 2016), the N400 indeed arises at least partly from the synchronization of neuronal activity in the delta frequency band (Fell et al., 2004).

During anesthesia, all three types of stimuli (first words, and congruent and incongruent last words) elicited an N400 component that resembled the N400 component associated with incongruent last words in the awake state in Study II. The dexmedetomidine-induced strong delta cannot be ruled out as the underlying cause of the increased amplitude of the N400 component in the dexmedetomidine group. However, such an increase in the amplitude of the N400 component has not been reported during natural sleep or disorders of consciousness, even though the N400 has been observed in these conditions and they are also associated with an increase in the delta power. The N400 effect has been observed during sleep although mostly with a diminished amplitude, or in a partial or delayed form (Brualla et al., 1998; Daltrozzo et al., 2012b; Ibáñez et al., 2006; Perrin et al., 2002), and in patients with disorders of consciousness (Balconi and Arangio, 2015; Beukema et al., 2016; Daltrozzo et al., 2009; Hinterberger et al., 2005; Kotchoubey, 2005; Kotchoubey et al., 2005; Schoenle and Witzke, 2004). In the disorders of consciousness, the presence of N400 is a positive prognostic marker of the recovery to the communicative state (Rohaut et al., 2015; Steppacher et al., 2013). In the present study, the increase in the amplitude of N400 only occurred in the cases of the first and congruent last words of the sentences whereas the amplitude of the N400 component elicited by incongruent last words showed no difference between the baseline and LOR. Therefore, the increase in the amplitude of the N400 component does not seem to be a completely unspecific phenomenon caused by, for example, the changes in spectral power induced by dexmedetomidine. Dexmedetomidine and propofol both induce a similar increase in the power of the delta frequency band in the central and posterior channels (Scheinin et al., 2018). Therefore, if the N400 arose solely from stimulus-locked phase resetting of the background delta activity,

differences in the N400 components between the drugs would suggest a difference in stimulus-locked phase resetting. However, the current data do not allow such a comparison due to the inconclusive N400 results in the propofol group.

In general, Study IV highlights an important issue often ignored in studies of ERPs or any other brain-related phenomena: the choice of the analysis method has a huge impact on the results, especially if the phenomenon needs to be studied separately in each individual. Large differences between analysis methods have previously been demonstrated in the case of MMN (Gabriel et al., 2016). Different methods utilize the different dimensions of the data to varying extents and there are several analysis options even with as simple measurements as ERPs. Among the methods of Study IV, visual inspection only employed average ERPs over trials, ANOVA utilized amplitude averages over sample points, and the cluster-based nonparametric mapping, t-CWT, and Bayesian regression took into account more aspects of the data, such as the interactions between neighboring channels, variation between independent trials, or background EEG.

The focus of Study IV was in methods readily available for use and applying these methods as implemented in published packages. Even within each method, the choices made affected the results: requiring the agreement of two out of three reviewers in the visual inspection or changing the channel selection of ANOVA would likely have slightly changed the results. However, the aim was to use the conventional or recommended parameters that are typically applied in conjunction with each method to enable comparisons with previous single-subject studies. This way, the results achieved with the different methods in Study IV may not be as comparable as possible but they rather represent the true differences between studies encountered in the literature.

When the quantitative and qualitative properties of the data were analyzed to explore the differences of the analysis methods used in the Study IV, the results revealed few associations. The quantitative properties did not explain the differences between the analysis methods and the amplitude of the N400 effect was the only quantitative property that was associated with the detection of the effect. The results of the qualitative comparison reflect the properties of the different methods: for example, the visual inspection and cluster-method were powerful in detecting early effects and sensitive to problems in the quality of the signal. The Bayesian regression detected also weak and short effects and was tolerant of noise.

There is no firm yardstick or specific criteria for what constitutes an N400 or any ERP component in general. Thus, there is no watertight definition of N400 and a specific ERP component is operationalized by the method used in empirical studies. Thus, it is impossible to know whether the N400 effect should be detected in each individual in Study IV despite the correct responding – a problem that does not exist in simulated EEG. Several publications utilizing simulated data and comparing

different analysis methods have been previously published (Groppe et al., 2011; Real et al., 2014), although these studies have not examined N400 component. The aim of Study IV was to use naturalistic EEG from a large sample of healthy individuals and analyze it with easily accessible and commonly used analysis methods. Thus, adding a simulated dataset with several parameter modifications was beyond the scope of Study IV, and would deserve a separate study. Finding the best analysis method with the optimal sensitivity and specificity is not straightforward and was not achieved in this study. One method alone is likely insufficient to make informed clinical decisions on the presence or absence of an ERP component.

Taken together, the results regarding the N400 in the Study II reveal interesting information on the semantic processing in the unresponsive state, yet the Study IV shows the difficulties related to the use of complex cognitive ERPs in unresponsive patients.

6.4 The memory traces related to sentences and emotional stimuli (Studies II–III)

Memory is an important factor affecting the measurement of the anesthetized state. Amnesia is one of the targets of general anesthesia and intraoperative awareness is measured with self-reports of postoperative recall. Different anesthetics affect distinct phases of memory formation and retrieval. Dexmedetomidine has been shown to cause a dose-dependent decrease in memory encoding while the retrieval is relatively well preserved (Hayama et al., 2012; Pryor et al., 2010). Instead, the amnestic effects of propofol sedation are more strongly associated with problems in retrieval (Pryor et al., 2010; Veselis et al., 1992, 2004). At low sedative doses of dexmedetomidine, long-term memory for emotionally negatively arousing stimuli is preserved better than for neutral stimuli, that is, the preferential memory for emotional stimuli seen in wakefulness is preserved despite dexmedetomidine (Hayama et al., 2012). The response of the amygdala to emotional stimuli during dexmedetomidine sedation resembles the activation in the placebo group (Hayama et al., 2012). Propofol also leaves the response of the amygdala to emotionally arousing stimuli unaffected but it may degrade the memory for emotional stimuli more than the memory for neutral ones (Pryor et al., 2015).

The recognition memory for the sentences was disrupted by dexmedetomidine and propofol in Study II. The time from response cue to response did not indicate any difference between novel and familiar sentence stimuli, further suggesting that the sentences heard during unresponsiveness were not remembered. This is in line with a previous study that demonstrated that the speech-specific neural activity can occur in propofol anesthesia without subsequent memory traces (Davis et al., 2007). A conservative response bias was observed, meaning that a high degree of familiarity

was needed for familiar-responses in Study II. The sentences included in the responsiveness test were recognized above chance level but less frequently than the sentences presented in the awake experiment. This suggests that responsive sedation impaired but did not preclude explicit memory for the semantic stimuli with either of the two drugs. However, the precise timing of the memory trace and the effect of repetition cannot be distinguished in the Study II, since the sentences of the responsiveness test were heard multiple times in responsive and unresponsive sedation. The findings are in line with a previous study showing enhanced memory for repeated stimuli heard during anesthesia (Block et al., 1991). However, another study found no differences between repeated and non-repeated stimuli (Bonebakker et al., 1996).

The results of the recognition tests of sentences and emotional sounds in the Studies II and III are particularly interesting when contrasted with each other. In the interviews of Study III, none of the participants reported having heard the emotional sounds during the unresponsiveness. The participants had not been informed about the emotional sounds before the experiment. In contrast to the sentence recognition results, the participants in the dexmedetomidine group indicated the previously heard emotional stimuli as familiar more often than novel sounds and their performance in the task was better than that of the participants in the propofol group. This could reflect explicit memory for the emotional stimuli in the dexmedetomidine group. The result is in line with the previous studies where the preferential memory trace for emotional stimuli is preserved in dexmedetomidine but not in propofol sedation (Hayama et al., 2012; Pryor et al., 2015). The reaction times in response to the previously heard emotional stimuli were shorter than in response to the novel stimuli without any treatment- or state-specific effects. As posttraumatic effects are possible without explicit recall of intraoperative awareness, the amnestic effects of anesthetics on emotional stimuli are of special interest (Wang et al., 2012; Whitlock et al., 2015).

The yes/no recognition task to test familiarity (know response) was used, but recollection (remember response) could not be excluded with the task instructions of Studies II and III. Familiarity and recollection both contribute to the yes/no recognition test (Bayley et al., 2008; Khoe et al., 2000). The methods used in the current study do not allow the differentiation of the two types of recognition memory and thus cannot inform the controversy over the differential effects of dexmedetomidine on the familiarity and recollection processes (Hayama et al., 2012; Veselis et al., 2009).

Implicit learning of verbal stimuli presented during general anesthesia has been previously reported (Deeprose et al., 2004; Iselin-Chaves et al., 2005; Linassi et al., 2021; Lubke et al., 1999). In Study II, the reaction times confirmed the impairment of the memory for sentences. Instead, the responses to the familiar emotional stimuli

of Study III were faster than to novel stimuli in both dexmedetomidine and propofol groups, which can be related to implicit learning. The current study design was not optimal for the testing of implicit sentence or sound recognition since the participants were not instructed to respond as quickly as possible, and the reaction times therefore need to be interpreted with caution. Also, the recognition test was performed shortly after the recovery of responsiveness, and the residual anesthetic concentrations may have affected the results (Andrade, 1995; Hall et al., 2000; Veselis et al., 1997).

Different types of memory are also related to the immediate processing of semantic stimuli during unresponsive states. In awake participants, N400 ERP has been suggested to reflect the process of retrieving the representation of a semantic stimulus from semantic memory in a process that is facilitated by the context (Lau et al., 2008). N400 has been associated with the capacity of working memory for speech (Daltrozzo et al., 2012b) and with the implicit learning (Rabovsky et al., 2018) and thus the loss of N400 effect in the Study II may be related to the known effects of dexmedetomidine on memory encoding. The N400 component elicited by incongruent words during unresponsiveness was at a level comparable to the awake state and the loss of N400 effect was caused by the increased negativity of the N400 component in response to the congruent stimuli in the dexmedetomidine group. Assuming that the ERP component represents the same phenomenon under exposure to anesthetics as in the awake state, it is possible that the words are not integrated into the context, or the semantic activity generated by the preceding words (the context) had already faded away when the final word of the sentence was presented. A similar mechanism of the fast decay of the memory trace may be present in some patients with memory deficits (Revonsuo et al., 1998). The impairment of memory could cause all the words to evoke maximal effort related to semantic processing.

The memory effects of anesthetics are an integral part of the reporting of subjective experiences from the unresponsive period. The interviews need to be performed as soon as possible after anesthesia similarly to dream research, but the residual anesthetics may also affect the reported experiences. The memory effects related to the reported experiences are further discussed in the next section (Section 6.5).

6.5 Experiences reported after unresponsiveness (Study III)

In Study III, disconnected experiences were common during the anesthetic-induced unresponsiveness. The reports associated with experiences from the unresponsive period constituted 90% and 74% of the successful interviews among participants receiving dexmedetomidine and propofol, respectively. Dreaming was present in most of the reports, and it was more common in the dexmedetomidine group (86%

in the dexmedetomidine and 77% in the propofol group). These proportions are much higher than in studies with immediate interviews after general anesthesia related to surgery (Brandner et al., 1997; Chen et al., 2021; Errando et al., 2008; Kim et al., 2011; Leslie et al., 2007, 2009; Yoshida et al., 2021) and slightly higher than in other studies with experimental sedation (Noreika et al., 2011; Radek et al., 2021; Valli et al., submitted). The report frequencies in Study III resemble the incidence of reports of experiences after natural sleep (Nielsen, 2000; Valli et al., submitted). In this study, a thorough interview protocol was used, the participants were carefully instructed about the interview questions in advance, and the interviews were also performed during the drug infusion in addition to the post-anesthetic interview, which could contribute to the differences with other studies.

Most of the unresponsiveness reports included experiences from more than one class of content types: dreaming, memory incorporation, and awareness. Importantly, the awareness content was always associated with dreaming or memory incorporation, or both. This highlights the multifaceted nature of the anesthetized state: connected and disconnected experiences occur and can be remembered from the same unresponsive period. Thus, the recall of dreaming after anesthesia does not exclude the possibility of having also had connected experiences during anesthesia. The awareness reports were always related to periods where brief arousals had been detected during an otherwise unresponsive state. Thus, the awareness reports likely originated from arousals that could be detected based on behavioral signs. However, this is not always the case in general anesthesia consisting of multiple drugs including neuromuscular blocking agents. Such occasions may cause undetected intraoperative awareness with harmful psychological symptoms (Ghoneim et al., 2009; Whitlock et al., 2015). The isolated forearm technique has shown that postoperative reports of intraoperative awareness likely underestimate the true frequency of connected experiences during general anesthesia and that the connectedness is often associated with pain (Lennertz et al., 2023; Sanders et al., 2017). Awareness reports are rare even when an individual has been responsive during sedation (Radek et al., 2021). Therefore, EEG-based indices of the depth of anesthesia are needed to evaluate the presence of connected experiences already during general anesthesia.

Sanders and co-workers (2012) have suggested that norepinephrine signaling has an important role in controlling the connectedness during anesthesia. Natural sleep and alpha-2-agonists like dexmedetomidine suppress norepinephrine signaling, whereas GABAergic anesthetics like propofol do not. Consequently, GABAergic anesthesia could be expected to demonstrate more frequent awareness experiences. However, the awareness reports in Study III were equally likely in the dexmedetomidine and propofol groups. The N400 component elicited by semantic stimuli and the preservation of memory traces for emotional sounds were also only

detected during dexmedetomidine-induced unresponsiveness. Thus, propofol does not seem to be associated with a higher likelihood of connected consciousness during unresponsiveness based on Studies II–III.

In this study, the memory incorporation of the study environment was categorized as a separate content type distinct from dreaming and awareness. This fine-grained analysis allowed separately inspecting the different types of experiences and prevented the risk of over-interpreting the experiences that might have been classified as dreaming or awareness in other studies. However, the inclusion of the third category also complicated drawing conclusions on the anesthetized state as there were only few reports of pure dreaming or pure memory incorporation. It is also possible that some of the reports considered as memory incorporation were actually awareness experiences, which would lead to underestimation of the frequency of awareness in this study. Memory incorporation occurred in 72% and 88% of the reports in the dexmedetomidine and propofol groups, respectively, which is on the same scale as the frequency of dreaming. The high frequency of the reports with memory incorporation may also be related to the thorough interview and the experimental situation itself that likely was an unusual event for the healthy, young participants. Memory incorporation or dreaming related to surgery or anesthesia have been commonly reported in other anesthesia studies (Kim et al., 2011; Leslie et al., 2005; Noreika et al., 2011). The rates of memory incorporation in the Study III and the study by Valli and co-workers (submitted) are much higher than in another study with smaller anesthetic doses (Radek et al., 2021).

Dream reports from natural sleep differ between measurements in the laboratory and collection at home (Sikka et al., 2018; Waterman et al., 1993). In this study, the experiments were performed at the Intensive Care Unit of the Turku University Hospital and the environment was very similar to typical clinical general anesthesia, surgery, and post-anesthesia recovery including cannulas, the measuring equipment, and several researchers in the room. The environment was thus far from a home-like environment or an every-day situation. The environmental characteristics and the residual anesthetic effects during interviews may have affected the recalled experiences. It is therefore quite surprising how similar the reported experiences were with early-night NREM dreams (Kim et al., 2011; Leslie and Skrzypek, 2007).

Since studying the original first-person experiences is not possible, the reports of experiences were analyzed in this study. Successful interviews were obtained from 60% of the participants (28/47) after LOR1 and 91% (20/22) after LOR2. All the participants who reached the LOC state were interviewed after recovery. However, the state of consciousness remained unknown in 43% (20/47) of the participants in LOR1, 14% (3/22) in LOR2 and 2% (1/45) in LOC due to a white report, non-rousability from LOR1 or LOR2, or the lack of a successful interview.

Thus, a substantial number of experimental states could not be assigned to the categories of connected, disconnected, and unconscious.

The unresponsiveness reports were common in all three interviews, namely 89.3%, 75.0%, and 84.4% of the participants reported experiences from the unresponsive time after LOR1, LOR2, and LOC states respectively. This suggests that the experiences can occur and are likely during anesthetic-induced unresponsiveness and do not only originate from the post-anesthetic emergence period. However, this study cannot prove the existence of experiences during general anesthesia, because the LOR-concentration was lower than in surgical general anesthesia and the ROR3 reports were delayed. Although the unresponsiveness reports were more common with dexmedetomidine and the responsiveness reports were more frequent with propofol, the reports from all three interviews and with both drugs were rather similar in terms of their content.

The awakening of the participants during constant target-controlled infusion allowed mapping the experiences to the preceding period of drug infusion without the confounding effect of a lengthy emergence period. As the ROR2 interview was performed when possible, the paradigm employed in the present study can be considered as the serial awakening paradigm. The study of dreaming during natural sleep has demonstrated that it is critical to minimize the temporal lag between the arousal and the reporting of the dream experiences (Aspy et al., 2015; Putois et al., 2020), and previous anesthesia studies have shown the degradation of experiences when the interview is delayed (Leslie and Skrzypek, 2007). In delayed interviews, many experiences or their details may be lost. Even if the experiences can be recalled, motivational factors may affect the reporting and cause a reporting bias evidenced by dream research: only the most salient or exciting experiences may be reported (Zadra and Robert, 2012). Interrupting events and residual anesthetic may cause the corruption of memory for experiences or the generation of new memories even within a couple of minutes between the arousal and dream report (Aspy et al., 2015; Valli et al., submitted). The ROR2 interview allowed the accurate timing of the experiences occurring between ROR1 and ROR2 interviews. Therefore, the results clearly show that experiences do occur during constant drug infusion that is sufficient to induce unresponsiveness. However, the participants were not roused immediately after the higher concentration step (LOC state). The lag between the LOC state and ROR3 interview varied widely: some of the participants regained responsiveness within a couple of minutes after stopping the infusion and the lag was very short, while others were roused after the 30 minutes allowed for spontaneous recovery. Another source of uncertainty related to ROR3 interviews stems from the participants who could not be roused for the interview after LOR1 and thus they reported experiences from the whole duration of the experiment during which they had been unresponsive at two different drug concentrations. Thus, all the experiences

in the ROR3 reports cannot be considered to originate from the LOC state, but they can also originate from the recovery period or even from the previous experimental states with lower drug concentration.

The thorough interview and the detailed content analysis of the reports allowed studying different types of experiences also beyond hallucination-like and narrative dreaming (Windt et al., 2016). The memory incorporation and awareness experiences were mostly static but also scenery and dynamic experiences constituted marked proportions of the dream experiences. Most of the dream content was visual and one third of the dreams also contained auditory perceptions. In contrast, the memory incorporations and awareness experiences included mostly auditory perceptions and the number of different types of perceptions within an experience was typically smallest in the awareness experiences. In addition to visual and auditory percepts, the kinesthetic and cognitive experiences were prominent types of content in dreaming, memory incorporation, and awareness experiences. In this study, relatively few dream experiences could be classified as positive (21%) or negative (15%), which is in line with dreams from natural sleep when the external raters evaluate the valence of the dream (Sikka et al., 2014). Overall, the experiences reported in Study III were in line with the previous studies of experiences during anesthesia as most of the reports were simple and negative emotions were only present in a minority of the reports (Kim et al., 2011; Leslie and Skrzypek, 2007; Noreika et al., 2011).

The participants in the propofol group regained responsiveness within 30 minutes after ceasing the LOC infusion more often than the participants in the dexmedetomidine group who often had to be roused after 30 minutes. When interviewed in ROR3, the dexmedetomidine participants gave more unresponsiveness reports than the propofol participants. However, the time from the end of the infusion to the beginning of the ROR3 interview was not associated with the occurrence of dreaming or memory incorporation in either group. In a previous study, propofol sedation resulted in a rapid emergence and was associated with a five-fold higher incidence of dreaming and more vivid dreams than those in a midazolam group, where the emergence was slower (Kim et al., 2011). The difference in the rate of dreaming was suggested to be partly associated with the earlier and clearer communication with the interviewer in the propofol group (Kim et al., 2011). In the case of natural sleep, the forced awakening may result in a higher frequency of dream recall (Stickgold et al., 2001) and the interview reports obtained after abrupt awakening include less cognition-related content when compared with reports obtained after gradual awakening (Goodenough et al., 1965). In this study, the reported frequencies of the different content types did not differ between the interviews from ROR1, ROR2, and ROR3 states. Therefore, the reports from different states were combined for the content analysis.

In this study, the experiences could not be combined with the connectivity and N400 data due to the small number of connected and unconscious experiences in each of the measured unresponsive states. However, future studies should aim at combining experiences and connectivity measurements. A higher functional connectivity shortly after awakening has previously been associated with an increased dream report rate in natural sleep, which has been suggested to be related to the short-term memory in the dream-wake transition (Vallat et al., 2020). Also the combination of ERPs and experiences during unresponsiveness are worth a study as enhanced stimulus-related responses during sleep have been observed in high versus low recallers (Eichenlaub et al., 2014). Thus far, the occurrence of experiences during unresponsiveness has been mostly associated with relatively simple spectral measures (Casey et al., 2022; Chellappa et al., 2011; Eer et al., 2009; Leslie et al., 2009; Matus et al., 2021; Siclari et al., 2017, 2018) and distinguishing those with recalled experiences from those without has been unsuccessful in many studies (Aamodt et al., 2021; Leslie et al., 2007; Wong et al., 2020).

The interview questions and the analysis protocol may have prominent impact on the results on subjective experiences. In the Study III, two raters aimed to classify the reports to different content categories offline based on the transcripts of the semi-structured interviews. In the study of Casey and co-workers (2022), the participants were given a more prominent role in the classification of their own reports as the participants were, for example, asked to determine whether they had been awake, dreaming, or unconscious during anesthesia. It is known that the self-ratings and external ratings of dream experiences from natural sleep differ at least when the valence of the experience is evaluated (Sikka et al., 2014, 2021). It would therefore be interesting to know whether there is a similar disagreement between self-ratings and external raters in the classification of the experiences occurring during anesthetic-induced unresponsiveness.

6.6 EEG-based measuring of the anesthetized states

In this thesis, anesthetic-induced states were explored based on two EEG-based measures, connectivity and N400. As discussed in the previous sections, responsiveness was the most reliable discriminator of the experimental states. Because the numbers of connected or unconscious cases were also insufficient for subgroup analyses, the conclusions are limited to the EEG-based correlates of unresponsiveness.

As many efforts in the field are aimed to disentangle the problem of measuring consciousness, studying the neural correlates of responsiveness might seem uninteresting. However, responsiveness is a critical threshold as historically, and still

today, anesthetized states are studied using responsiveness as a surrogate of consciousness. The unresponsive state is the most objectively defined state in the continuum of states from the fully conscious and connected state to complete unconsciousness, and the monitoring of general anesthesia and disorders of consciousness largely relies on observing the behavior. Responsiveness determined with the isolated forearm technique is the current gold standard method for defining intraoperative connected consciousness (Sanders et al., 2017; Lennertz et al., 2023). During general anesthesia, muscle relaxants interfere with detecting the responsiveness and the anesthetized individual may not be able to respond despite attempts to do so (Ghoneim et al., 2009; Kerssens et al., 2003). An index of responsiveness without the physical responding might be very helpful also in different paralyzed conditions, such as the locked-in syndrome, yet the physical inability to respond may also affect the neural correlates. However, mere responsiveness is an insufficient measure of unconsciousness and an imperfect surrogate of disconnection.

The identification of the neural correlates of the state of consciousness could impact the patient care in many specialties of medicine. Finding the neural correlates of responsiveness may help in finding the correlates of consciousness in the future. As shown in the Study I, the prefrontal-frontal connectivity measures changed from responsiveness to unresponsiveness and the values further changed along with the deepening anesthesia from LOR to LOC state. This may indicate that the prefrontal-frontal connectivity measures could be also used to differentiate conscious and unconscious individuals, although it could not be shown in the current study.

It can be questioned whether it is possible and necessary to separate all the different phases of losing consciousness (Section 2.2.6) in the medical practice. In the case of general anesthesia, the most relevant distinction might be between the disconnected and connected states, and in the case of the disorders of consciousness, between the unconscious and conscious states. Since the line between the fundamentally different states might differ between the different causes of alterations in the state of consciousness, it is important to know the neural correlates of different states as thoroughly as possible.

When searching for the optimal method to measure the anesthetized states, it is important to consider the roles of the paradigm and task. The use of stimuli and active task allow the testing of the stimulus-related processing and the ability to follow commands. The stimuli help to detect specific types of sensory or cognitive processing, and the manipulation of the complexity of stimuli allows fine-tuning the targeted type of processing. Stimuli and tasks allow combining the connected contents of consciousness with the state of consciousness. However, the preservation of a specific brain activity in response to stimulation does not necessarily prove the preservation of consciousness (Naccache, 2018). When used during anesthetic

infusion, the stimuli and task may also enable controlling overt responsiveness. However, the salience of the stimuli affects responsiveness (Purdon et al., 2013). On one hand, a stimulus-related task might help in detecting covert consciousness especially if the task is related to following the stimuli. On the other hand, measuring the resting state in the absence of stimulation is more straightforward and depends less on the setting, vigilance, or willingness to perform the task or the confounding factors related to active responding. In addition, the EEG activity related to performing a task, such as a mental imagery task, may show extremely large individual differences (Curley et al., 2018). The detection of covert consciousness using task-related activation and brain imaging or EEG have yielded highly interesting findings (Cruse et al., 2011; Huang et al., 2018a; Owen et al., 2006) but passive paradigms with stimulation have been successful when evaluating the prognosis in disorders of consciousness (Naci et al., 2014, 2017; Rohaut et al., 2015; Sokoliuk et al., 2021a). The current study utilized both connectivity measured in the resting state and the N400 that is a stimulus-related measure.

In the clinical setting, the depth-of-anesthesia monitors need to perform in a dynamical manner. Out of the measures used in this study, the connectivity analysis can be implemented on a much finer temporal scale (e.g., 10 seconds) than implemented in the Study I. Although the 2-min epochs were optimal for the current research questions, shorter epochs could be a better choice for clinical applications. The calculation of alpha connectivity in shorter time windows can be implemented using the conventional method of initially bandpass filtering the EEG signals and then computing the phase coupling across all the time points in the filtered signals, instead of the multitaper analysis implemented in the present study. This applies to coherence as well as wPLI/dPLI. Thus, all the connectivity measures used in Study I are equally capable of allowing a fine-grained temporal resolution in the clinical setting. The analysis of event-related potentials requires the averaging over several stimuli, and especially presenting stimuli to elicit cognitive ERPs is relatively time-consuming, which lengthens the time needed for measuring complex and late ERPs. Time-efficient stimulus paradigms have been suggested for N400 and other ERPs for clinical use (Ghosh Hajra et al., 2018; Sculthorpe-Petley et al., 2015), although the decreased signal-to-noise ratio in the altered states of consciousness certainly presents a challenge.

Inter-individual differences play an important role in the search for means to measure consciousness. When vulnerable patients are studied, the observation of one exception, a "black swan," may be sufficient to overturn the possibilities of a potential measure (Gaskell et al., 2017; Mashour and Avidan, 2017). However, if the underlying reasons for the exception can be characterized, the measure might still be applicable. The most used measures for anesthesia monitoring, such as BIS or Narcotrend, are not perfect (Lewis et al., 2012; Mashour et al., 2012; Russell, 2006)

but their problems have been accepted in the absence of better indices. To reduce the subjectivity of evaluating the patient's state, the use of measurements, such as the EEG-derived indices is widely recommended (National Institute for Clinical Excellence NICE Diagnostics Guidance, 2012). Study IV demonstrated the individual differences in a potential neural correlate of semantic processing, N400, in wakefulness. The individual differences detected during wakefulness may also be reflected to the anesthetized state (Chennu et al., 2016; Liu et al., 2019). The reasons of the variability may be related to individual neurobiology (Ní Mhuircheartaigh et al., 2013) or background demographics (Obert et al., 2021) but they also often remain unresolved (Veselis et al., 2004).

It seems unlikely that a single, simple measure could be used to reflect the state of the patient perfectly but the multivariate measures combining different types of information are more likely to succeed (Engemann et al., 2018; Imperatori et al., 2021). The combination of the connectivity measures, N400, and spectral measures might provide complementary predictive power over any single measure.

6.7 Methodological considerations

6.7.1 Strengths of the study

In this study, healthy participants were studied during either dexmedetomidine or propofol administration in a highly controlled experimental setting. This allowed examining the isolated effects of a single general anesthetic at a time without the confounding caused by other drugs, surgery, pain, or background conditions, such as variation in age and morbidity. Young patients have an increased risk for intraoperative awareness and thus represent a relevant study population (Lennertz et al., 2023; Pandit et al., 2014b). The two drugs of interest act through different molecular mechanisms and have previously been shown to display both similarities and differences in the brain structures they affect and in their effects on the signaling in the brain.

In the present study, the brain functioning of the participants was studied with several different methods within the same experiment. The resting-state measures, stimulus-related measures, and semi-structured interviews enabled the holistic assessment of the state of the participants. The titration of the anesthetic drug individually based on a behavioral end-point, and the rousing of the participants during constant anesthetic concentration, enabled studying the participants' state independent from the drug-induced effects.

EEG-based indices of the state of consciousness and the depth of anesthesia are feasible methods to be implemented in the operating room, especially when they can be measured in the frontal channels that are easily accessible and match the routinely

used monitoring electrode bands. EEG has been reported to show greater sensitivity in the detection of covert consciousness than fMRI in disorders of consciousness when volitional responses and mental imagery are studied (Curley et al., 2018).

The present study also aimed to control the effects of methodological choices. The connectivity study (Study I) took advantage of two methods to describe the functional connectivity and one method to assess the directed connectivity. The N400 study (Study II) was accompanied by a single-subject study evaluating the effects of the analysis methods on the detection of a complex cognitive ERP (Study IV).

In unresponsive states, only the best performing stimulus paradigms should be used and the stimuli should be presented with intervals long enough for detecting processing that may have slowed down (Rokos et al., 2021). In this study, the N400 paradigm was designed to induce as large N400 effect as possible by including an active task and carefully constructed sentence stimuli. To maximize N400, the stimuli were not repeated during the experiment. The optimization of the experimental design seems to have been successful as the cluster-based method showed better performance than in previous N400 studies with individual-level analyses (Cruse et al., 2014; Sculthorpe-Petley et al., 2015).

The experiences were collected after emergence from anesthesia and also during the constant infusion in the Study III. This approach enabled tracking the timing of the experiences: The experiences reported in ROR2 interview very likely occurred after the ROR1 interview, that is, in LOR2. The meticulous four-phase categorization of the content of the reports allowed distinguishing the disconnected and connected experiences and memories originating from the responsive period, and demonstrated the similarity of the experiences reported after unresponsiveness induced by different anesthetics. In Study III, the reports were rated by two independent observers and the agreement between them was good, which is an advantage over many of the previous studies of experiences during anesthesia.

6.7.2 Limitations of the study

There are several factors that limit the interpretation and application of the results of the current study. Although the number of participants in the anesthesia experiment was sufficient for assessing the overall effects across different anesthetics, the non-rousability of many of the propofol participants reduced the sample size in LOR2 and ROR2 states. The subjective experiences reported in ROR1, considered to represent LOR1 in the analyses, could also originate from the sedative steps preceding LOR1, which hinders the interpretation of the subjective experiences related to LOR1. Instead, the ROR2 reports can be localized more precisely in time. The definition of the presumed LOC state was only based on the responsiveness and

drug concentration. In addition, the final ROR3 interviews were not performed immediately after ceasing the anesthetic administration but after a maximum of 30 minutes of waiting for spontaneous recovery of responsiveness. Therefore, the true nature of the presumed LOC state in terms of experiences remains unclear. Although the interview reports in ROR3 were acquired differently from the reports in ROR1 and ROR2, the experiences in ROR3 did not differ from ROR1 and ROR2, which suggests that the experiences were not markedly affected by the way of awakening from the unresponsive state. After all, experiences can never be collected with interview reports instantly, but the interviews are always more or less delayed.

In the present study, the stimulus blocks were rather long. Therefore, the study is based on the assumption that the state of the participants is relatively stable during one experimental state or at one concentration step. However, both the brain functioning (Li et al., 2019; Vlisides et al., 2019) and the behavioral state (Kantonen et al., submitted) can change dynamically during a constant anesthetic concentration and the transitions from one state to another may be sudden and have neural correlates distinct from the surrounding states (Lee et al., 2017b; Pullon et al., 2022).

The key EEG results of the present study are related to the LOR1 state. It is probable that the depth of the participants' state deepened during the relatively long LOR1 state because of the cumulative drug effects despite the pseudo-steady-state drug infusion. This could indeed be seen both in the connectivity differences between LOR and LOR_{late} epochs in Study I, and in the previously reported EEG spectra of the same epochs (Scheinin et al., 2018). The LOR1 and ROR1 states could only be compared in the connectivity study (Study I) where the prefrontal-frontal connectivity differed between the LOR and ROR epochs. However, the ROR epoch originated from the time after the ROR1 interview when the participant was already allowed to fall asleep. Thus, the ROR epoch most likely originates from deeper – maybe already unresponsive – state, which may diminish the differences observed between the unresponsive and responsive conditions. Therefore, the changes detected between LOR1 and ROR1 states are rather under- than overestimated.

It would have been interesting to control the effect of the awakening attempt among the participants who did not wake up to ROR1 and ROR2 states. However, if the participant could not be roused to a ROR1/2 state after a LOR1/2 state, the drug dose was directly increased to 1.5-fold to induce the presumed LOC state. Therefore, a comparable 2 min epoch of stable EEG was not available after the awakening attempt from those participants who did not achieve the ROR state.

The connectivity and N400 results are based on group-level analysis and therefore represent average experimental states. The data were insufficient for single-subject analyses. Also, the stratification of the material based on reported experiences was not feasible because of the insufficient numbers of participants in the state-wise subgroups. Because of the insufficient material and the lack of

consensus to which extent the N400 ERP component is related to the state of consciousness, the N400 could not be utilized to distinguish the disconnected and connected individuals.

The study population was very homogeneous including only young, healthy males. Only males were studied due to the PET studies included in the experiment series. For clinical applications, all the measures should be tested in realistic populations including both women and men, patients of different ages, different types of surgeries, and combinations with other drugs related to general anesthesia. If the results are compared with patients with disorders of consciousness, it needs to be acknowledged that the brain lesions underlying these conditions are highly variable and the patients are mainly older people. For example, the age and sex affect N400: women and younger adults display larger N400 effect compared with men and the elderly, and the processing strategies of speech comprehension differ between the young and the old (Daltrozzo et al., 2007; Broderick et al., 2021).

As no source localization was applied in the EEG-based Studies I, II and IV, the results can provide little information on the underlying anatomical sources in the brain (Palva and Palva, 2012). The field of source localization of EEG has considerably developed in the recent years (Asadzadeh et al., 2020), although the methodological choices – which are numerous over the analysis pathway – affect the results of modeling (Mahjoory et al., 2017; Michel and Brunet, 2019; Piastra et al., 2021). The methodological uncertainties related to source localization have also been described in the cases of connectivity and ERP analyses (Cho et al., 2015; Conte and Richards, 2021). As tens of different source localization methods with different assumptions are available (Asadzadeh et al., 2020), the choice of the method can be expected to markedly affect the result. Also, the study in the awake state (Study IV) showed the notable effects of the methodological choices in single-subject ERP analyses.

To maximize the comparability with the previous studies utilizing wPLI and dPLI, the w/dPLI connectivity analyses of the current study employed the most commonly used reference channels, namely one or two mastoids (Blain-Moraes et al., 2014; Lee et al., 2013a; Li et al., 2019; Vlisides et al., 2019; Zierau et al., 2021). Since wPLI and dPLI are designed to be robust to the volume conduction effect by accounting for only nonzero phase lead/lag relationships (Vinck et al., 2011; Stam and van Straaten, 2012), there was no need for additional correction for volume conduction by re-referencing. If surface Laplacian transform had been used to suppress the volume conduction effect in EEG signals, the application of wPLI/dPLI on the transformed signals would have been expected to underestimate the true connectivity level because of the inherent ignoring of the zero-phase-lag connectivity. A confirmatory analysis with Laplacian transform was performed (data not shown) and, as expected, the wPLI and dPLI demonstrated lower values as

compared to the values in the Study I. However, both the spectral and spatial distribution of w/dPLI were highly similar between the two different reference montages and, for example, the difference between the LOR and ROR states seemed to be even larger with Laplacian referencing than with mastoid average reference. Thus, the conclusions regarding the wPLI and dPLI were robust irrespective of the reference used. Since coherence is sensitive to the volume conduction effect, surface Laplacian transformed EEG was used in the coherence analysis (Winter et al., 2007). Nevertheless, spurious connections may remain even with methods that are immune to zero phase-lag connections at least in source-localized data (Palva et al., 2018).

The N400 analyses were also performed using mastoid averages since the mastoid average or linked mastoids are the most conventional, utilized, and recommended reference for analyzing the N400 component (Duncan et al., 2009). The number of previous studies using, for example, surface Laplacian method in N400 analysis is very limited. The topography of the N400 elicited by visual stimuli has been shown to differ between Laplacian and linked mastoid reference (Curran et al., 1993). However, also with the Laplacian reference, the N400 effect is most prominent at the vertex (Cz) and not, for example, at the temporal electrodes (Curran et al., 1993). One reason for the limited use of Laplacian reference in N400 studies might be the critical comments made, for example, by Johnson and Hamm (2000), although there does not seem to be empirical evidence for the insensitivity of Laplacian reference for deep generators (Kayser and Tenke, 2015). In addition to the potential effect of the reference montage, the preprocessing steps, such as artifact removal and filtering have an essential role in the differences between studies.

The differences between the analysis methods examined in the Study IV were multiple and each method used different a priori information. The differences between the methods could have been mitigated, for example, by using a limited set of channels or a more constrained time window in the cluster-based analysis to make it more similar to the other methods. For example, the time window of the t-CWT analysis could have been broadened and the analysis could have been focused on the negative extrema to make t-CWT analysis more similar to the cluster-based analysis. However, such choices would have lost the unique features that constitute the advantages of the different methods. Also, only the built-in features of readily-available packages were used in this study and, for example, the t-CWT method may not have reached its full potential. For example, the randomization tests used in some previous studies for the correction of the results (Bostanov and Kotchoubey, 2006; Real et al., 2014) are not included in the t-CWT 2.01 package and were thus not implemented in the present study. Only three out of five t-CWT variants allowed direct comparison with each other and with all the other methods without those additional corrections. Therefore, there still remains a need for a more thorough methodological comparison between the t-CWT and clustered permutation tests as

also previously suggested (Kotchoubey, 2015). Also, different parameter values within each of the five methods were not tested, which represents a potential target for comparative ERP studies in the future.

Other limitations related to the experimental design include analyzing connectivity only in the alpha band (Study I), fixed stimulus and block order in the N400 studies (Studies II and IV), not specifically instructing the participants to respond as quickly as possible in the yes/no recognition task (Study II), and the risk of classifying some awareness-related experiences as memory incorporation (Study III).

6.8 Future directions

Almost all of the unresponsive participants in this study had experiences originating from the unresponsive time, which clearly indicates that responsiveness cannot be used as a surrogate of consciousness. Future studies on consciousness, responsiveness, and anesthetics should invest in using accurate concepts, such as consciousness, connectedness, and responsiveness to avoid conveying imprecise information. The careful definition of the concepts will also help in creating improved experimental designs where the effects of the state and drug can be separated using, for example, serial awakenings.

The field of anesthesiology seems to have abandoned amnesia as the main target of general anesthesia (Sanders et al., 2016). It remains to be considered whether general anesthesia should lead to unconsciousness or whether disconnected consciousness would suffice. However, defining the boundaries of disconnectedness and connectedness is a highly challenging question. Would a horrifying nightmare that is thematically related to the operating room and includes detailed and distorted memory incorporation from the awake state represent a desired disconnected state? Can hallucinatory experiences always be differentiated from awareness when they were mostly intertwined in the interview reports of this thesis?

Before this study, the EEG-based connectivity under dexmedetomidine anesthesia has been sparsely explored. Future studies should further explore effective connectivity and aim to find the network-level indices and source-localized pathways of connectivity affected by anesthetics acting with different molecular mechanisms, and especially by the non-GABAergic anesthetic agents that have been less studied thus far. Combining the fMRI-related and EEG-related results on connectivity and formulating a cohesive picture is one of the future challenges that could increase the understanding of the brain functioning under anesthesia and in losing and regaining consciousness.

The N400 has previously been shown to have predictive potential in the treatment of patients with disorders of consciousness. Interestingly, the N400 effect

was lost already in minimally unresponsive state induced by dexmedetomidine, which contrasts with N2 and REM sleep where the effect has been reported. This suggests that the unresponsive state of natural sleep is different from the anesthetic-induced unresponsiveness in terms of the semantic processing of words. Comparing both connectivity and N400 within the same participants during anesthesia and during sleep would be extremely interesting. In the future, the N400 ERP component needs to be studied during responsive sedation and with other anesthetics accompanied by a placebo group to allow conclusions on the course of the anesthetic-induced degradation of semantic processing. Although there is one published study on N400 during responsive ketamine sedation (Grunwald et al., 1999), the effects of other sedative drugs also need to be studied since ERPs may be studied in patients with disorders of consciousness also during sedation (Tzovara et al., 2015).

A perfect anesthesia monitor or indicator of consciousness would be characterized by as simple measuring equipment as possible, real-time feedback, and clear threshold values for the interpretation. In addition, the method should work either independently of the anesthetic agent or have tailored programs for each group of anesthetics. The knowledge of the other unresponsive states, such as sleep and disorders of consciousness, also has a critical role in the construction of a cohesive picture of the correlates of consciousness. The successful indices for assessing the state of consciousness are likely to be excessively complex multivariate measures (Engemann et al., 2018) that take advantage of a wide range of different measurements with customized weights. The results of this thesis may contribute towards the development of such indices by elucidating the characteristics of anesthetic-induced unresponsiveness and its EEG-related correlates.

7 Conclusions

In this thesis, two experiments and two anesthetics with individually titrated dosing were used to explore the EEG-based correlates of different behavioral endpoints and to characterize the cognitive abilities and experiences during anesthetic administration. The thesis shows that the brain functioning during anesthetic-induced unresponsiveness differs from wakefulness but the brain still reacts to complex cognitive stimuli, and subjective experiences are widely reported after unresponsive periods. The two drugs acting through different molecular mechanisms produced similar changes in the anterior EEG leads in different experimental states, suggesting that the findings reflect generalizable markers of state.

With all of the approaches used – connectivity, N400, and subjective experiences – the methodological considerations were emphasized: the three different methods for assessing connectivity were compared with each other and with spectral power, and five different analysis methods were contrasted for the analysis of N400. The subjective experiences were evaluated by two raters in four phases in order to find phenomenal categories that best match the experiences.

In the hierarchy of the states from awake consciousness to unconsciousness induced by general anesthesia, unresponsiveness and disconnection from the environment are major intermediate phases, and the recognition of these phases is important for developing better anesthesia monitors. The study increases the knowledge on the characteristics of light experimental general anesthesia and the methods to measure it.

The following conclusions can be drawn:

1. The within-anterior connectivity in the alpha frequency band differentiates the responsive and unresponsive states during both dexmedetomidine and propofol administration. Instead, the anterior-posterior alpha connectivity does not correlate with responsiveness and may rather be related to the drug concentration than the state.
2. The differentiation of congruent and incongruent semantic content, measured with the N400 effect, disappears in the dexmedetomidine and propofol sedation that induces unresponsiveness. However, the N400 component persists during unresponsiveness in the dexmedetomidine

group, suggesting preserved but limited processing of spoken language, possibly caused by failure to utilize contextual information.

3. Subjective experiences are often present during anesthetic-induced unresponsiveness. The experiences are relatively simple, mostly disconnected, and often related to the study environment.
4. The recognition memory for semantic stimuli is lost during unresponsiveness. However, signs of implicit learning of emotional stimuli can be detected with both dexmedetomidine and propofol, and the explicit learning of emotional stimuli may also be preserved during dexmedetomidine-induced unresponsiveness.
5. The choice of the analysis method has considerable impact on the detection of N400, a complex cognitive ERP, at single-subject level. The contribution of the analysis method should be considered when comparing the different studies and interpreting ERP measurements in vulnerable patient populations.

Abbreviations

ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists physical status classification
AUC	Area under the ROC curve
BAEP	Brainstem auditory evoked potentials
BIS	Bispectral index
BOLD	Blood oxygen level dependent
c	Response bias
CI	Confidence interval
d'	Discriminability measure
dPLI	Directed phase lag index
DMN	Default mode network
ECI	Explainable consciousness indicator
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electro-oculogram
ERP	Event-related potential
FIR	Finite impulse response
fMRI	Functional magnetic resonance imaging
GABA	Gamma aminobutyric acid
$GABA_A$	Gamma aminobutyric acid receptor A
GEE	Generalized estimating equations
GFP	Global field power
ICA	Independent component analysis
LLAEP	Long-latency auditory evoked potentials
LOC	Loss of consciousness
LOR	Loss of responsiveness
LP	Late positive event-related potential component
MCS	Minimally conscious state
MEG	Magnetoencephalogram
MLAEP	Middle-latency auditory evoked potentials

MMN	Mismatch negativity event-related potential component
mN400	Magnetoencephalographic N400
N1	N1 event-related potential component; NREM sleep stage 1
N2	NREM sleep stage 2
N3	NREM sleep stage 3
N400	N400 event-related potential component
NMDA	N-methyl D-aspartate
NREM	Non-rapid eye movement
P3a	P3a event-related potential component
P3b	P3b event-related potential component
PCI	Perturbational complexity index
PET	Positron emission tomography
P_K	Prediction probability
PLI	Phase lag index
REM	Rapid eye movement
ROC	Receiver operator characteristics
ROR	Return of responsiveness
SE	Standard error
SED	Sedative state
SEDA	Subjective experiences during anesthesia microlevel scale
SD	Standard deviation
t-CWT	Studentized continuous wavelet transform
TMS	Transcranial magnetic stimulation
UWS	Unresponsive wakefulness syndrome
VS	Vegetative state
wPLI	Weighted phase lag index

List of References

Aamodt A, Nilsen AS, Thürer B, Moghadam FH, Kauppi N, Juel BE, Storm JF. 2021. EEG signal diversity varies with sleep stage and aspects of dream experience. Front. Psychol. 12: 655884.

Abel JH, Badgeley MA, Meschede-Krasa B, Schamberg G, Garwood IC, Lecamwasam K, Chakravarty S, Zhou DW, Keating M, Purdon PL, Brown EN. 2021. Machine learning of EEG spectra classifies unconsciousness during GABAergic anesthesia. PLoS One 16: e0246165.

Adapa RM, Davis MH, Stamatakis EA, Absalom AR, Menon DK. 2014. Neural correlates of successful semantic processing during propofol sedation. Hum. Brain Mapp. 35: 2935–49.

Ahlfors SP, Han J, Lin FH, Witzel T, Belliveau JW, Hämäläinen MS, Halgren E. 2010. Cancellation of EEG and MEG signals generated by extended and distributed sources. Hum. Brain Mapp. 31: 140–149.

Aho AJ, Kamata K, Jäntti V, Kulkas A, Hagihira S, Huhtala H, Yli-Hankala A. 2015. Comparison of Bispectral Index and Entropy values with electroencephalogram during surgical anaesthesia with sevoflurane. Br. J. Anaesth. 115: 258–266.

Ahonen J, Haavisto A, Helenius P, Kalliomäki M, Koponen T, Münte S, Puolakka P, Rautakorpi P, Yli-Hankala A. 2017. Suomen anestesiologiyhdistyksen anestesiavalvontaa koskevat suositukset. Finnanest 50: 53–57.

Akeju O, Pavone KJ, Westover MB, Vazquez R, Prerau MJ, Harrell PG, Hartnack KE, Rhee J, Sampson AL, Habeeb K, Gao L, Lei G, Pierce ET, Walsh JL, Brown EN, Purdon PL. 2014a. A comparison of propofol- and dexmedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis. Anesthesiology 121: 978–989.

Akeju O, Loggia ML, Catana C, Pavone KJ, Vazquez R, Rhee J, Contreras Ramirez V, Chonde DB, Izquierdo-Garcia D, Arabasz G, Hsu S, Habeeb K, Hooker JM, Napadow V, Brown EN, Purdon PL. 2014b. Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. Elife 3: e04499.

Akeju O, Kim S-E, Vazquez R, Rhee J, Pavone KJ, Hobbs LE, Purdon PL, Brown EN. 2016a. Spatiotemporal dynamics of dexmedetomidine-induced electroencephalogram oscillations. PLoS One 11: e0163431.

Akeju O, Song AH, Hamilos AE, Pavone KJ, Flores FJ, Brown EN, Purdon PL. 2016b. Electroencephalogram signatures of ketamine anesthesia-induced unconsciousness. Clin. Neurophysiol. 127: 2414–2422.

Akeju O, Brown EN. 2017. Neural oscillations demonstrate that general anesthesia and sedative states are neurophysiologically distinct from sleep. Curr. Opin. Neurobiol. 44: 178–185.

Alkire MT, Haier RJ, Fallon JH. 2000. Toward a unified theory of narcosis: Brain imaging evidence for a thalamocortical switch as the neurophysiologic basis of anesthetic-induced unconsciousness. Conscious. Cogn. 9: 370–386.

Alkire MT, Hudetz AG, Tononi G. 2008a. Consciousness and anesthesia. Science 322: 876–880.

Alkire MT, Gruver R, Miller J, McReynolds JR, Hahn EL, Cahill L. 2008b. Neuroimaging analysis of an anesthetic gas that blocks human emotional memory. Proc. Natl. Acad. Sci. U. S. A. 105: 1722–1727.

Ameen MS, Heib DPJ, Blume C, Schabus M. 2022. The brain selectively tunes to unfamiliar voices during sleep. J. Neurosci. 42: 1791–1803.

American Society of Anesthesiologists. 2019. Continuum of depth of sedation: Definition of general anesthesia and levels of sedation/analgesia. https://www.asahq.org/standards-and-guidelines/continuum-of-depth-of-sedation-definition-of-general-anesthesia-and-levels-of-sedationanalgesia (Accessed August 24, 2022).

An S, Oh SJ, Jun SB, Sung JE. 2022. Aging-related dissociation of spatial and temporal N400 in sentence-level semantic processing: Evidence from source analyses. Front. Aging Neurosci. 14: 877235.

Anderson JE, Holcomb PJ. 1995. Auditory and visual semantic priming using different stimulus onset asynchronies: an event-related brain potential study. Psychophysiology 32: 177–90.

Andrade J. 1995. Learning during anaesthesia: a review. Br. J. Psychol. 86 (Pt 4): 479–506.

André-Obadia N, Zyss J, Gavaret M, Lefaucheur J-P, Azabou E, Boulogne S, Guérit J-M, McGonigal A, Merle P, Mutschler V, Naccache L, Sabourdy C, Trébuchon A, Tyvaert L, Vercueil L, Rohaut B, Delval A. 2018. Recommendations for the use of electroencephalography and evoked potentials in comatose patients. Neurophysiol. Clin. 48: 143–169.

Angelakis E, Liouta E, Andreadis N, Korfias S, Ktonas P, Stranjalis G, Sakas DE. 2014. Transcranial direct current stimulation effects in disorders of consciousness. Arch. Phys. Med. Rehabil. 95: 283–289.

Aru J, Bachmann T, Singer W, Melloni L. 2012. Distilling the neural correlates of consciousness. Neurosci. Biobehav. Rev. 36: 737–746.

Aru J, Suzuki M, Rutiku R, Larkum ME, Bachmann T. 2019. Coupling the state and contents of consciousness. Front. Syst. Neurosci. 13: 43.

Aru J, Suzuki M, Larkum ME. 2020. Cellular mechanisms of conscious processing. Trends Cogn. Sci. 24: 814–825.

Asadzadeh S, Yousefi Rezaii T, Beheshti S, Delpak A, Meshgini S. 2020. A systematic review of EEG source localization techniques and their applications on diagnosis of brain abnormalities. J. Neurosci. Methods 339: 108740.

Aspy DJ, Delfabbro P, Proeve M. 2015. Is dream recall underestimated by retrospective measures and enhanced by keeping a logbook? A review. Conscious. Cogn. 33: 364–374.

Baars BJ. 2005. Global workspace theory of consciousness: toward a cognitive neuroscience of human experience. Prog. Brain Res. 150: 45–53.

Bachmann T. 2012. How to begin to overcome the ambiguity present in differentiation between contents and levels of consciousness? Front. Psychol. 3: 82.

Bachmann T, Hudetz AG. 2014. It is time to combine the two main traditions in the research on the neural correlates of consciousness: C = L × D. Front. Psychol. 5: 940.

Bachmann T. 2021. Representational “touch” and modulatory ’retouch’-two necessary neurobiological processes in thalamocortical interaction for conscious experience. Neurosci. Conscious. 2021: niab045.

Bai Y, Lin Y, Ziemann U. 2021. Managing disorders of consciousness: the role of electroencephalography. J. Neurol. 268: 4033–4065.

Balconi M, Arangio R, Guarnerio C. 2013. Disorders of consciousness and N400 ERP measures in response to a semantic task. J. Neuropsychiatry Clin. Neurosci. 25: 237–243.

Balconi M, Arangio R. 2015. The relationship between coma near coma, disability ratings, and event-related potentials in patients with disorders of consciousness: a semantic association task. Appl. Psychophysiol. Biofeedback 40: 327–337.

Balkin TJ, Braun AR, Wesensten NJ, Jeffries K, Varga M, Baldwin P, Belenky G, Herscovitch P. 2002. The process of awakening: A PET study of regional brain activity patterns mediating the re-establishment of alertness and consciousness. Brain 125: 2308–2319.

Ballesteros JJ, Briscoe JB, Ishizawa Y. 2020. Neural signatures of α2-adrenergic agonist-induced unconsciousness and awakening by antagonist. Elife 9: 1–18.

Banks MI, Moran NS, Krause BM, Grady SM, Uhlrich DJ, Manning KA. 2018. Altered stimulus representation in rat auditory cortex is not causal for loss of consciousness under general anaesthesia. Br. J. Anaesth. 121: 605–615.

Banks MI, Krause BM, Endemann CM, Campbell DI, Kovach CK, Dyken ME, Kawasaki H, Nourski K V. 2020. Cortical functional connectivity indexes arousal state during sleep and anesthesia. Neuroimage 211: 116627.

Bassett DS, Bullmore ET. 2017. Small-world brain networks revisited. Neuroscientist 23: 499–516.

Basti A, Nili H, Hauk O, Marzetti L, Henson RN. 2020. Multi-dimensional connectivity: a conceptual and mathematical review. Neuroimage 221: 117179.

Bastos AM, Schoffelen J-M. 2015. A tutorial review of functional connectivity analysis methods and their interpretational pitfalls. Front. Syst. Neurosci. 9: 175.

Bastos AM, Donoghue JA, Brincat SL, Mahnke M, Yanar J, Correa J, Waite AS, Lundqvist M, Roy J, Brown EN, Miller EK. 2021. Neural effects of propofol-induced unconsciousness and its reversal using thalamic stimulation. Elife 10: e60824.

Bayley PJ, Wixted JT, Hopkins RO, Squire LR. 2008. Yes/no recognition, forced-choice recognition, and the human hippocampus. J. Cogn. Neurosci. 20: 505–512.

Bayne T, Hohwy J. 2016. Modes of consciousness. In: Sinnott-Armstrong W, editor. Finding consciousness: The neuroscience, ethics and law of severe brain damage, 1e. Sheridan, Wyoming, USA: Oxford University Press, p 57–80.

Bayne T, Hohwy J, Owen AM. 2016. Are there levels of consciousness? Trends Cogn. Sci. 20: 405–413.

Bekinschtein TA, Dehaene S, Rohaut B, Tadel F, Cohen L, Naccache L. 2009. Neural signature of the conscious processing of auditory regularities. Proc. Natl. Acad. Sci. U. S. A. 106: 1672–1677.

Bentin S, Kutas M, Hillyard SA. 1995. Semantic processing and memory for attended and unattended words in dichotic listening: behavioral and electrophysiological evidence. J. Exp. Psychol. Hum. Percept. Perform. 21: 54–67.

Berry RB, Brooks R, Gamaldo CE, Harding SM, Lloyd RM, Marcus C V, Vaughn B V, Medicine for the AA of S. 2015. The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications, v2.2. Darien, Illinois, USA: American Academy of Sleep Medicine.

Besche-Richard C, Iakimova G, Hardy-Baylé MC, Passerieux C. 2014. Behavioral and brain measures (N400) of semantic priming in patients with schizophrenia: Test-retest effect in a longitudinal study. Psychiatry Clin. Neurosci. 68: 365–373.

Beukema S, Gonzalez-Lara LE, Finoia P, Kamau E, Allanson J, Chennu S, Gibson RM, Pickard JD, Owen AM, Cruse D. 2016. A hierarchy of event-related potential markers of auditory processing in disorders of consciousness. NeuroImage. Clin. 12: 359–371.

Bharioke A, Munz M, Brignall A, Kosche G, Eizinger MF, Ledergerber N, Hillier D, Gross-Scherf B, Conzelmann K-K, Macé E, Roska B. 2022. General anesthesia globally synchronizes activity selectively in layer 5 cortical pyramidal neurons. Neuron 110: 2024-2040.e10.

Blagrove M, Pace-Schott EF. 2010. Trait and neurobiological correlates of individual differences in dream recall and dream content. Int. Rev. Neurobiol. 92: 155–80.

Blain-Moraes S, Lee U, Ku S, Noh G, Mashour GA. 2014. Electroencephalographic effects of ketamine on power, cross-frequency coupling, and connectivity in the alpha bandwidth. Front. Syst. Neurosci. 8: 1–9.

Blain-Moraes S, Tarnal V, Vanini G, Alexander A, Rosen D, Shortal B, Janke E, Mashour GA. 2015. Neurophysiological correlates of sevoflurane-induced unconsciousness. Anesthesiology 122: 307–316.

Block RI, Ghoneim MM, Ping STS, Ali MA. 1991. Human learning during general anaesthesia and surgery. Br. J. Anaesth. 66: 170–178.

Blume C, del Giudice R, Lechinger J, Wislowska M, Heib DPJ, Hoedlmoser K, Schabus M. 2017. Preferential processing of emotionally and self-relevant stimuli persists in unconscious N2 sleep. Brain Lang. 167: 72–82.

Bocskai T, Loibl C, Vamos Z, Woth G, Molnar T, Bogar L, Lujber L. 2018. Cost-effectiveness of anesthesia maintained with sevoflurane or propofol with and without additional monitoring: a prospective, randomized controlled trial. BMC Anesthesiol. 18: 100.

Boehler CN, Schoenfeld MA, Heinze HJ, Hopf JM. 2008. Rapid recurrent processing gates awareness in primary visual cortex. Proc. Natl. Acad. Sci. U. S. A. 105: 8742–8747.

Bokil H, Andrews P, Kulkarni JE, Mehta S, Mitra PP. 2010. Chronux: A platform for analyzing neural signals. J. Neurosci. Methods 192: 146–151.

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

Boly M, Moran R, Murphy M, Boveroux P, Bruno M-A, Noirhomme Q, Ledoux D, Bonhomme V, Brichant J-F, Tononi G, Laureys S, Friston K. 2012. Connectivity changes underlying spectral EEG changes during propofol-induced loss of consciousness. J. Neurosci. 32: 7082–7090.

Boly M, Massimini M, Tsuchiya N, Postle BR, Koch C, Tononi G. 2017. Are the neural correlates of consciousness in the front or in the back of the cerebral cortex? Clinical and neuroimaging evidence. J. Neurosci. 37: 9603–9613.

Bonebakker AE, Bonke B, Klein J, Wolters G, Stijnen T, Passchier J, Merikle PM. 1996. Information processing during general anesthesia: evidence for unconscious memory. Mem. Cognit. 24: 766–776.

Bonhomme V, Staquet C, Montupil J, Defresne A, Kirsch M, Martial C, Vanhaudenhuyse A, Chatelle C, Larroque SK, Raimondo F, Demertzi A, Bodart O, Laureys S, Gosseries O. 2019. General anesthesia: A probe to explore consciousness. Front. Syst. Neurosci. 13: 36.

Bornkessel-Schlesewsky I, Schlesewsky M. 2019. Toward a neurobiologically plausible model of language-related, negative event-related potentials. Front. Psychol. 10: 298.

Bostanov V. 2004. BCI Competition 2003--Data sets Ib and IIb: feature extraction from event-related brain potentials with the continuous wavelet transform and the t-value scalogram. IEEE Trans. Biomed. Eng. 51: 1057–1061.

Bostanov V, Kotchoubey B. 2006. The t-CWT: A new ERP detection and quantification method based on the continuous wavelet transform and Student's t-statistics. Clin. Neurophysiol. 117: 2627–2644.

Bostanov V. 2015. Multivariate assessment of event-related potentials with the t-CWT method. BMC Neurosci. 16: 73.

Boudewyn MA, Gordon PC, Long D, Polse L, Swaab TY. 2012. Does discourse congruence influence spoken language comprehension before lexical association? Evidence from event-related potentials. Lang. Cogn. Process. 27: 698–733.

Bourdillon P, Hermann B, Guénot M, Bastuji H, Isnard J, King J-R, Sitt J, Naccache L. 2020. Brain-scale cortico-cortical functional connectivity in the delta-theta band is a robust signature of conscious states: an intracranial and scalp EEG study. Sci. Rep. 10: 14037.

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

Bradley MM, Lang PJ. 2007. The International Affective Digitized Sounds (2nd edition; IADS-2): Affective ratings of sounds and instruction manual. Technical Report B-3. Gainesville, FL, USA.

Brandner B, Blagrove M, McCallum G, Bromley LM. 1997. Dreams, images and emotions associated with propofol anaesthesia. Anaesthesia 52: 750–755.

Brice DD, Hetherington RR, Utting JE. 1970. A simple study of awareness and dreaming during anaesthesia. Br. J. Anaesth. 42: 535–542.

Broderick MP, Anderson AJ, Di Liberto GM, Crosse MJ, Lalor EC. 2018. Electrophysiological correlates of semantic dissimilarity reflect the comprehension of natural, narrative speech. Curr. Biol. 28: 803-809.e3.

Broderick MP, Di Liberto GM, Anderson AJ, Rofes A, Lalor EC. 2021. Dissociable electrophysiological measures of natural language processing reveal differences in speech comprehension strategy in healthy ageing. Sci. Rep. 11: 4963.

Brouwer H, Crocker MW, Venhuizen NJ, Hoeks JCJ. 2017. A neurocomputational model of the N400 and the P600 in language processing. Cogn. Sci. 41: 1318–1352.

Brown C, Hagoort P. 1993. The processing nature of the N400: evidence from masked priming. J. Cogn. Neurosci. 5: 34–44.

Brown EN, Lydic R, Schiff ND. 2010. General anesthesia, sleep, and coma. N. Engl. J. Med. 363: 2638–2650.

Brown EN, Pavone KJ, Naranjo M. 2018. Multimodal general anesthesia: Theory and practice. Anesth. Analg. 127: 1246–1258.

Brown R, Lau H, LeDoux JE. 2019. Understanding the higher-order approach to consciousness. Trends Cogn. Sci. 23: 754–768.

Browning H, Veit W. 2020. The measurement problem of consciousness. Philos. Top. 48: 85–108.

Brualla J, Romero MF, Serrano M, Valdizán JR. 1998. Auditory event-related potentials to semantic priming during sleep. Electroencephalogr. Clin. Neurophysiol. 108: 283–290.

Bruno M-A, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S. 2011. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J. Neurol. 258: 1373–1384.

Bruno M-A, Laureys S, Demertzi A. 2013. Coma and disorders of consciousness. Handb. Clin. Neurol. 118: 205–213.

Buzsáki G, Draguhn A. 2004. Neuronal oscillations in cortical networks. Science 304: 1926–9.

Buzsáki G, Anastassiou CA, Koch C. 2012. The origin of extracellular fields and currents--EEG, ECoG, LFP and spikes. Nat. Rev. Neurosci. 13: 407–420.

Campbell JM, Huang Z, Zhang J, Wu X, Qin P, Northoff G, Mashour GA, Hudetz AG. 2020. Pharmacologically informed machine learning approach for identifying pathological states of unconsciousness via resting-state fMRI. Neuroimage 206: 116316.

Cao J, Zhao Y, Shan X, Wei H liang, Guo Y, Chen L, Erkoyuncu JA, Sarrigiannis PG. 2022. Brain functional and effective connectivity based on electroencephalography recordings: A review. Hum. Brain Mapp. 43: 860–879.

Carlesimo GA, Lombardi MG, Caltagirone C, Barban F. 2015. Recollection and familiarity in the human thalamus. Neurosci. Biobehav. Rev. 54: 18–28.

Carr M, Solomonova E. 2019. Dream recall and content in different sleep stages. In: Valli K, Hoss RJ, editors. Dreams: Understanding biology, psychology, and culture, Vol. 1. Santa Barbara, CA, USA: Greenwood Press/ABC-CLIO, p 188–195.

Casali AG, Gosseries O, Rosanova M, Boly M, Sarasso S, Casali KR, Casarotto S, Bruno M-A, Laureys S, Tononi G, Massimini M. 2013. A theoretically based index of consciousness independent of sensory processing and behavior. Sci. Transl. Med. 5: 198ra105.

Casarotto S, Comanducci A, Rosanova M, Sarasso S, Fecchio M, Napolitani M, Pigorini A, G Casali A, Trimarchi PD, Boly M, Gosseries O, Bodart O, Curto F, Landi C, Mariotti M, Devalle G, Laureys S, Tononi G, Massimini M. 2016. Stratification of unresponsive patients by an independently validated index of brain complexity. Ann. Neurol. 80: 718–729.

Cascella M, Fusco R, Caliendo D, Granata V, Carbone D, Muzio MR, Laurelli G, Greggi S, Falcone F, Forte CA, Cuomo A. 2017. Anesthetic dreaming, anesthesia awareness and patient satisfaction after deep sedation with propofol target controlled infusion: A prospective cohort study of patients undergoing day case breast surgery. Oncotarget 8: 79248–79256.

Cascella M. 2020. The challenge of accidental awareness during general anesthesia. In: Cascella M, editor. General Anesthesia Research. Neuromethods, 1e. New York, NY, USA: Humana Press Inc., p 1–33.

Casey CP, Tanabe S, Farahbakhsh Z, Parker M, Bo A, White M, Ballweg T, Mcintosh A, Filbey W, Saalmann Y, Pearce RA, Sanders RD. 2022. Distinct EEG signatures differentiate unconsciousness and disconnection during anaesthesia and sleep. Br. J. Anaesth. 128: 1006–1018.

Chalmers DJ. 1995. Facing up to the problem of consciousness. J. Conscious. Stud. 2: 200–219.

Chalmers DJ. 2000. What is a neural correlate of consciousness? In: Metzinger T, editor. Neural correlates of consciousness: Empirical and conceptual questions. Massachusetts, USA: MIT Press Ltd, p 17–39.

Chalmers DJ. 2013. How can we construct a science of consciousness? Ann. N. Y. Acad. Sci. 1303: 25–35.

Chan MTV, Cheng BCP, Lee TMC, Gin T. 2013. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J. Neurosurg. Anesthesiol. 25: 33–42.

Chellappa SL, Frey S, Knoblauch V, Cajochen C. 2011. Cortical activation patterns herald successful dream recall after NREM and REM sleep. Biol. Psychol. 87: 251–256.

Chen L, Zhang J, He W, Liu W. 2021. Comparative effects of dexmedetomidine and midazolam on dreaming of patients undergoing flexible bronchoscopy during general anesthesia. Med. Sci. Monit. 27: e929000.

Chen Y, Li S, Wu F, Zou L, Zhang J. 2022. Altered functional and directed connectivity in propofol-induced loss of consciousness: A source-space resting-state EEG study. Clin. Neurophysiol. 142: 209–219.

Chennu S, Bekinschtein TA. 2012. Arousal modulates auditory attention and awareness: insights from sleep, sedation, and disorders of consciousness. Front. Psychol. 3: 65.

Chennu S, O'Connor S, Adapa R, Menon DK, Bekinschtein TA. 2016. Brain connectivity dissociates responsiveness from drug exposure during propofol-induced transitions of consciousness. PLoS Comput. Biol. 12: 1–17.

Chennu S, Annen J, Wannez S, Thibaut A, Chatelle C, Cassol H, Martens G, Schnakers C, Gosseries O, Menon D, Laureys S. 2017. Brain networks predict metabolism, diagnosis and prognosis at the bedside in disorders of consciousness. Brain 140: 2120–2132.

Chhabra A, Subramaniam R, Srivastava A, Prabhakar H, Kalaivani M, Paranjape S. 2016. Spectral entropy monitoring for adults and children undergoing general anaesthesia. Cochrane database Syst. Rev. 3: CD010135.

Ching S, Cimenser A, Purdon PL, Brown EN, Kopell NJ. 2010. Thalamocortical model for a propofol-induced alpha-rhythm associated with loss of consciousness. Proc. Natl. Acad. Sci. U. S. A. 107: 22665–22670.

Cho JH, Vorwerk J, Wolters CH, Knösche TR. 2015. Influence of the head model on EEG and MEG source connectivity analyses. Neuroimage 110: 60–77.

Chow HM, Horovitz SG, Carr WS, Picchioni D, Coddington N, Fukunaga M, Xu Y, Balkin TJ, Duyn JH, Braun AR. 2013. Rhythmic alternating patterns of brain activity distinguish rapid eye movement sleep from other states of consciousness. Proc. Natl. Acad. Sci. U. S. A. 110: 10300–10305.

Chwilla DJ, Brown CM, Hagoort P. 1995. The N400 as a function of the level of processing. Psychophysiology 32: 274–285.

Cicogna PC, Natale V, Occhionero M, Bosinelli M. 1998. A comparison of mental activity during sleep onset and morning awakening. Sleep 21: 462–470.

Cofré R, Herzog R, Mediano PAM, Piccinini J, Rosas FE, Perl YS, Tagliazucchi E. 2020. Whole-brain models to explore altered states of consciousness from the bottom up. Brain Sci. 10: 1–29.

Cohen MX. 2017. Where does EEG come from and what does it mean? Trends Neurosci. 40: 208–218.

Coleman MR, Rodd JM, Davis MH, Johnsrude IS, Menon DK, Pickard JD, Owen AM. 2007. Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. Brain 130: 2494–2507.

Coleman MR, Davis MH, Rodd JM, Robson T, Ali A, Owen AM, Pickard JD. 2009. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. Brain 132: 2541–2552.

Connolly JF, D'Arcy RC. 2000. Innovations in neuropsychological assessment using event-related brain potentials. Int. J. Psychophysiol. 37: 31–47.

Conte S, Richards JE. 2021. The influence of the head model conductor on the source localization of auditory evoked potentials. Brain Topogr. 34: 793–812.

Cook DA, Beckman TJ. 2006. Current concepts in validity and reliability for psychometric instruments: theory and application. Am. J. Med. 119: 166.e7-166.e16.

Cook TM, Pandit JJ. 2015. Pitfalls of comparing incidences of awareness from NAP5 and from Brice studies. Br. J. Anaesth. 115: 471–472.

Coulson S, Brang D. 2010. Sentence context affects the brain response to masked words. Brain Lang. 113: 149–155.

Crone JS, Soddu A, Höller Y, Vanhaudenhuyse A, Schurz M, Bergmann J, Schmid E, Trinka E, Laureys S, Kronbichler M. 2014. Altered network properties of the fronto-parietal network and the thalamus in impaired consciousness. NeuroImage Clin. 4: 240–248.

Cruse D, Chennu S, Chatelle C, Bekinschtein TA, Fernández-Espejo D, Pickard JD, Laureys S, Owen AM. 2011. Bedside detection of awareness in the vegetative state: a cohort study. Lancet 378: 2088–2094.

Cruse D, Beukema S, Chennu S, Malins JG, Owen AM, McRae K. 2014. The reliability of the N400 in single subjects: implications for patients with disorders of consciousness. NeuroImage. Clin. 4: 788–799.

Curley WH, Forgacs PB, Voss HU, Conte MM, Schiff ND. 2018. Characterization of EEG signals revealing covert cognition in the injured brain. Brain 141: 1404–1421.

Curran T, Tucker DM, Kutas M, Posner MI. 1993. Topography of the N400: brain electrical activity reflecting semantic expectancy. Electroencephalogr. Clin. Neurophysiol. Evoked Potentials 88: 188–209.

D'Arcy RCN, Connolly JF, Service E, Hawco CS, Houlihan ME. 2004. Separating phonological and semantic processing in auditory sentence processing: a high-resolution event-related brain potential study. Hum. Brain Mapp. 22: 40–51.

Daltrozzo J, Wioland N, Kotchoubey B. 2007. Sex differences in two event-related potentials components related to semantic priming. Arch. Sex. Behav. 36: 555–68.

Daltrozzo J, Wioland N, Mutschler V, Lutun P, Calon B, Meyer A, Pottecher T, Lang S, Jaeger A, Kotchoubey B. 2009. Cortical information processing in coma. Cogn. Behav. Neurol. 22: 53–62.

Daltrozzo J, Wioland N, Kotchoubey B. 2012a. The N400 and Late Positive Complex (LPC) effects reflect controlled rather than automatic mechanisms of sentence processing. Brain Sci. 2: 267–297.

Daltrozzo J, Claude L, Tillmann B, Bastuji H, Perrin F. 2012b. Working memory is partially preserved during sleep. PLoS One 7: e50997.

Darracq M, Funk CM, Polyakov D, Riedner B, Gosseries O, Nieminen JO, Bonhomme V, Brichant J-F, Boly M, Laureys S, Tononi G, Sanders RD. 2018. Evoked alpha power is reduced in disconnected consciousness during sleep and anesthesia. Sci. Rep. 8: 16664.

Davis MH, Coleman MR, Absalom AR, Rodd JM, Johnsrude IS, Matta BF, Owen AM, Menon DK. 2007. Dissociating speech perception and comprehension at reduced levels of awareness. Proc. Natl. Acad. Sci. U. S. A. 104: 16032–16037.

De Lucia M, Tzovara A. 2016. Reply: Replicability and impact of statistics in the detection of neural responses of consciousness. Brain 139: e32.

Deacon D, Hewitt S, Yang C, Nagata M. 2000. Event-related potential indices of semantic priming using masked and unmasked words: evidence that the N400 does not reflect a post-lexical process. Brain Res. Cogn. Brain Res. 9: 137–146.

Debruille JB. 2007. The N400 potential could index a semantic inhibition. Brain Res. Rev. 56: 472–477.

Deeprose C, Andrade J, Varma S, Edwards N. 2004. Unconscious learning during surgery with propofol anaesthesia. Br. J. Anaesth. 92: 171–177.

Deeprose C, Andrade J, Harrison D, Edwards N. 2005. Unconscious auditory priming during surgery with propofol and nitrous oxide anaesthesia: a replication. Br. J. Anaesth. 94: 57–62.

Dehaene S, Changeux J-P. 2011. Experimental and theoretical approaches to conscious processing. Neuron 70: 200–227.

Deligianni F, Centeno M, Carmichael DW, Clayden JD. 2014. Relating resting-state fMRI and EEG whole-brain connectomes across frequency bands. Front. Neurosci. 8: 258.

Delogu F, Brouwer H, Crocker MW. 2019. Event-related potentials index lexical retrieval (N400) and integration (P600) during language comprehension. Brain Cogn. 135: 103569.

Demertzi A, Tagliazucchi E, Dehaene S, Deco G, Barttfeld P, Raimondo F, Martial C, Fernández-Espejo D, Rohaut B, Voss HU, Schiff ND, Owen AM, Laureys S, Naccache L, Sitt JD. 2019. Human consciousness is supported by dynamic complex patterns of brain signal coordination. Sci. Adv. 5: eaat7603.

Deshpande G, Kerssens C, Sebel PS, Hu X. 2010. Altered local coherence in the default mode network due to sevoflurane anesthesia. Brain Res. 1318: 110–121.

Dien J, Santuzzi AM. 2005. Application of repeated measures ANOVA to high-density ERP datasets: A review and tutorial. In: Handy TC, editor. Event-related potentials: A methods handbook, 1e. Cambridge, MA, USA: MIT Press, p 57–81.

Dijkstra K, Farquhar J, Desain P. 2019. Electrophysiological responses of relatedness to consecutive word stimuli in relation to an actively recollected target word. Sci. Rep. 9: 14514.

Dijkstra K V., Farquhar JDR, Desain PWM. 2020. The N400 for brain computer interfacing: complexities and opportunities. J. Neural Eng. 17: 022001.

Drew PJ. 2019. Vascular and neural basis of the BOLD signal. Curr. Opin. Neurobiol. 58: 61–69.

Dueck MH, Petzke F, Gerbershagen HJ, Paul M, Hesselmann V, Girnus R, Krug B, Sorger B, Goebel R, Lehrke R, Sturm V, Boerner U. 2005. Propofol attenuates responses of the auditory cortex to acoustic stimulation in a dose-dependent manner: a FMRI study. Acta Anaesthesiol. Scand. 49: 784–791.

Duncan CC, Barry RJ, Connolly JF, Fischer C, Michie PT, Näätänen R, Polich J, Reinvang I, Van Petten C. 2009. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. Clin. Neurophysiol. 120: 1883–1908.

Eagleman SL, Drover DR. 2018. Calculations of consciousness: electroencephalography analyses to determine anesthetic depth. Curr. Opin. Anaesthesiol. 31: 431–438.

Eagleman SL, Drover CM, Li X, MacIver MB, Drover DR. 2021. Offline comparison of processed electroencephalogram monitors for anaesthetic-induced electroencephalogram changes in older adults. Br. J. Anaesth. 126: 975–984.

Edlow BL, Claassen J, Schiff ND, Greer DM. 2021. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. Nat. Rev. Neurol. 17: 135–156.

Eer AS, Padmanabhan U, Leslie K. 2009. Propofol dose and incidence of dreaming during sedation. Eur. J. Anaesthesiol. 26: 833–836.

Eichenlaub J-B, Bertrand O, Morlet D, Ruby P. 2014. Brain reactivity differentiates subjects with high and low dream recall frequencies during both sleep and wakefulness. Cereb. Cortex 24: 1206–1215.

Ekstrom A. 2010. How and when the fMRI BOLD signal relates to underlying neural activity: the danger in dissociation. Brain Res. Rev. 62: 233–244.

Elger CE, Grunwald T, Lehnertz K, Kutas M, Helmstaedter C, Brockhaus A, Van Roost D, Heinze HJ. 1997. Human temporal lobe potentials in verbal learning and memory processes. Neuropsychologia 35: 657–667.

Engemann DA, Raimondo F, King J-R, Rohaut B, Louppe G, Faugeras F, Annen J, Cassol H, Gosseries O, Fernandez-Slezak D, Laureys S, Naccache L, Dehaene S, Sitt JD. 2018. Robust EEG-based cross-site and cross-protocol classification of states of consciousness. Brain 141: 3179–3192.

Erlbeck H, Kübler A, Kotchoubey B, Veser S. 2014. Task instructions modulate the attentional mode affecting the auditory MMN and the semantic N400. Front. Hum. Neurosci. 8: 654.

Erlbeck H, Real RGL, Kotchoubey B, Mattia D, Bargak J, Kübler A. 2017. Basic discriminative and semantic processing in patients in the vegetative and minimally conscious state. Int. J. Psychophysiol. 113: 8–16.

Errando CL, Sigl JC, Robles M, Calabuig E, García J, Arocas F, Higueras R, Del Rosario E, López D, Peiró CM, Soriano JL, Chaves S, Gil F, García-Aguado R. 2008. Awareness with recall during general anaesthesia: a prospective observational evaluation of 4001 patients. Br. J. Anaesth. 101: 178–185.

Federmeier KD, Kutas M. 2005. Aging in context: age-related changes in context use during language comprehension. Psychophysiology 42: 133–141.

Federmeier KD, Laszlo S. 2009. Time for meaning: Electrophysiology provides insights into the dynamics of representation and processing in semantic memory. In: Ross BH, editor. Psychology of learning and motivation - Advances in research and theory. Cambridge, MA, USA: Academic Press, p 1–44.

Fell J, Dietl T, Grunwald T, Kurthen M, Klaver P, Trautner P, Schaller C, Elger CE, Fernández G. 2004. Neural bases of cognitive ERPs: more than phase reset. J. Cogn. Neurosci. 16: 1595–1604.

Flouda L, Pandazi A, Papageorgiou C, Perrea D, Krepi E, Kostopanagiotou G. 2013. Comparative effects of sevoflurane and propofol based general anaesthesia for elective surgery on memory. Arch. Med. Sci. 9: 105–111.

Ford JM, Woodward SH, Sullivan E V, Isaacks BG, Tinklenberg JR, Yesavage JA, Roth WT. 1996. N400 evidence of abnormal responses to speech in Alzheimer's disease. Electroencephalogr. Clin. Neurophysiol. 99: 235–246.

Fosse R, Stickgold R, Hobson JA. 2004. Thinking and hallucinating: reciprocal changes in sleep. Psychophysiology 41: 298–305.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102: 9673–9678.

Franks NP. 2008. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. Nat. Rev. Neurosci. 9: 370–386.

Friederici AD. 2012. The cortical language circuit: from auditory perception to sentence comprehension. Trends Cogn. Sci. 16: 262–268.

Fries P. 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn. Sci. 9: 474–480.

Fries P. 2015. Rhythms for cognition: communication through coherence. Neuron 88: 220–235.

Friston K. 2010. The free-energy principle: a unified brain theory? Nat. Rev. Neurosci. 11: 127–138.

Friston KJ. 2011. Functional and effective connectivity: a review. Brain Connect. 1: 13–36.

Frölich MA, Banks C, Ness TJ. 2017. The effect of sedation on cortical activation: a randomized study comparing the effects of sedation with midazolam, propofol, and dexmedetomidine on auditory processing. Anesth. Analg. 124: 1603–1610.

Fuller PM, Fuller P, Sherman D, Pedersen NP, Saper CB, Lu J. 2011. Reassessment of the structural basis of the ascending arousal system. J. Comp. Neurol. 519: 933–956.

Gabriel D, Muzard E, Henriques J, Mignot C, Pazart L, André-Obadia N, Ortega J-P, Moulin T. 2016. Replicability and impact of statistics in the detection of neural responses of consciousness. Brain 139: e30.

Ganis G, Kutas M, Sereno MI. 1996. The search for “common sense”: an electrophysiological study of the comprehension of words and pictures in reading. J. Cogn. Neurosci. 8: 89–106.

Ganis G, Kutas M. 2003. An electrophysiological study of scene effects on object identification. Brain Res. Cogn. Brain Res. 16: 123–144.

Gaskell AL, Hight DF, Winders J, Tran G, Defresne A, Bonhomme V, Raz A, Sleigh JW, Sanders RD. 2017. Frontal alpha-delta EEG does not preclude volitional response during anaesthesia: prospective cohort study of the isolated forearm technique. Br. J. Anaesth. 119: 664–673.

Gazzaniga MS, Heatherton TF. 2006. Psychological science: Mind, brain, and behavior, 2e. New York, USA: W. W. Norton & Company.

Geukes S, Huster RJ, Wollbrink A, Junghöfer M, Zwitserlood P, Dobel C. 2013. A large N400 but no BOLD effect--comparing source activations of semantic priming in simultaneous EEG-fMRI. PLoS One 8: e84029.

Ghoneim MM, Block RI, Dhanaraj VJ, Todd MM, Choi WW, Brown CK. 2000. Auditory evoked responses and learning and awareness during general anesthesia. Acta Anaesthesiol. Scand. 44: 133–143.

Ghoneim MM, Block RI, Haffarnan M, Mathews MJ. 2009. Awareness during anesthesia: risk factors, causes and sequelae: a review of reported cases in the literature. Anesth. Analg. 108: 527–535.

Ghosh Hajra S, Liu CC, Song X, Fickling SD, Cheung TPL, D’Arcy RCN. 2018. Multimodal characterization of the semantic N400 response within a rapid evaluation brain vital sign framework. J. Transl. Med. 16: 151.

Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, Barbano R, Hammond FM, Laureys S, Ling GSF, Nakase-Richardson R, Seel RT, Yablon S, Getchius TSD, Gronseth GS, Armstrong MJ. 2018. Practice guideline update recommendations summary: disorders of consciousness. Neurology 91: 450–460.

Goldenholz DM, Ahlfors SP, Hämäläinen MS, Sharon D, Ishitobi M, Vaina LM, Stufflebeam SM. 2009. Mapping the signal-to-noise-ratios of cortical sources in magnetoencephalography and electroencephalography. Hum. Brain Mapp. 30: 1077–1086.

Golkowski D, Larroque SK, Vanhaudenhuyse A, Plenevaux A, Boly M, Di Perri C, Ranft A, Schneider G, Laureys S, Jordan D, Bonhomme V, Ilg R. 2019. Changes in whole brain dynamics and connectivity patterns during sevoflurane- and propofol-induced unconsciousness identified by functional magnetic resonance imaging. Anesthesiology 130: 898–911.

Goodenough DR, Lewis HB, Shapiro A, Jaret L, Sleser I. 1965. Dream reporting following abrupt and gradual awakenings from different types of sleep. J. Pers. Soc. Psychol. 2: 170–179.

Grigor J, Van Toller S, Behan J, Richardson A. 1999. The effect of odour priming on long latency visual evoked potentials of matching and mismatching objects. Chem. Senses 24: 137–144.

Groppe DM, Urbach TP, Kutas M. 2011. Mass univariate analysis of event-related brain potentials/fields II: Simulation studies. Psychophysiology 48: 1726–1737.

Gruenewald M, Harju J, Preckel B, Molnár Z, Yli-Hankala A, Rosskopf F, Koers L, Orban A, Bein B, AoA Study Group. 2021. Comparison of adequacy of anaesthesia monitoring with standard clinical practice monitoring during routine general anaesthesia: An international, multicentre, single-blinded randomised controlled trial. Eur. J. Anaesthesiol. 38: 73–81.

Grunwald T, Beck H, Lehnertz K, Blümcke I, Pezer N, Kurthen M, Fernández G, Van Roost D, Heinze HJ, Kutas M, Elger CE. 1999. Evidence relating human verbal memory to hippocampal N-methyl-D-aspartate receptors. Proc. Natl. Acad. Sci. U. S. A. 96: 12085–12089.

Guldenmund P, Gantner IS, Baquero K, Das T, Demertzi A, Boveroux P, Bonhomme V, Vanhaudenhuyse A, Bruno M-A, Gosseries O, Noirhomme Q, Kirsch M, Boly M, Owen AM, Laureys S, Gómez F, Soddu A. 2016. Propofol-induced frontal cortex disconnection: A study of resting-state networks, total brain connectivity, and mean BOLD signal oscillation frequencies. Brain Connect. 6: 225–237.

Guldenmund P, Vanhaudenhuyse A, Sanders RD, Sleigh J, Bruno MA, Demertzi A, Bahri MA, Jaquet O, Sanfilippo J, Baquero K, Boly M, Brichant JF, Laureys S, Bonhomme V. 2017. Brain functional

connectivity differentiates dexmedetomidine from propofol and natural sleep. Br. J. Anaesth. 119: 674–684.

Gyulaházi J, Redl P, Karányi Z, Varga K, Fülesdi B. 2016. Dreaming under anesthesia: is it a real possiblity? Investigation of the effect of preoperative imagination on the quality of postoperative dream recalls. BMC Anesthesiol. 16: 53.

Haenggi M, Ypparila H, Takala J, Korhonen I, Luginbühl M, Petersen-Felix S, Jakob SM. 2004. Measuring depth of sedation with auditory evoked potentials during controlled infusion of propofol and remifentanil in healthy volunteers. Anesth. Analg. 99: 1728–1736.

Hagoort P, Hald L, Bastiaansen M, Petersson KM. 2004. Integration of word meaning and world knowledge in language comprehension. Science 304: 438–441.

Haider B, Häusser M, Carandini M. 2013. Inhibition dominates sensory responses in the awake cortex. Nature 493: 97–102.

Hald LA, Steenbeek-Planting EG, Hagoort P. 2007. The interaction of discourse context and world knowledge in online sentence comprehension. Evidence from the N400. Brain Res. 1146: 210–218.

Halgren E, Dhond RP, Christensen N, Van Petten C, Marinkovic K, Lewine JD, Dale AM. 2002. N400-like magnetoencephalography responses modulated by semantic context, word frequency, and lexical class in sentences. Neuroimage 17: 1101–1116.

Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. 2000. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth. Analg. 90: 699–705.

Hamp T, Mairweck M, Schiefer J, Krammel M, Pablik E, Wolzt M, Plöchl W. 2016. Feasibility of a "reversed" isolated forearm technique by regional antagonization of rocuronium-induced neuromuscular block: a pilot study. Br. J. Anaesth. 116: 797–803.

Hari R, Salmelin R. 2012. Magnetoencephalography: From SQUIDs to neuroscience. Neuroimage 20th anniversary special edition. Neuroimage 61: 386–396.

Hashmi JA, Loggia ML, Khan S, Gao L, Kim J, Napadow V, Brown EN, Akeju O. 2017. Dexmedetomidine disrupts the local and global efficiencies of large-scale brain networks. Anesthesiology 126: 419–430.

Hautus MJ. 1995. Corrections for extreme proportions and their biasing effects on estimated values ofd′. Behav. Res. Methods, Instruments, Comput. 27: 46–51.

Hayama HR, Drumheller KM, Mastromonaco M, Reist C, Cahill LF, Alkire MT. 2012. Event-related functional magnetic resonance imaging of a low dose of dexmedetomidine that impairs long-term memory. Anesthesiology 117: 981–995.

He B, Astolfi L, Valdes-Sosa PA, Marinazzo D, Palva S, Benar CG, Michel CM, Koenig T. 2019. Electrophysiological brain connectivity: theory and implementation. IEEE Trans. Biomed. Eng. 66: 2115–2137.

Heinke W, Kenntner R, Gunter TC, Sammler D, Olthoff D, Koelsch S. 2004a. Sequential effects of increasing propofol sedation on frontal and temporal cortices as indexed by auditory event-related potentials. Anesthesiology 100: 617–625.

Heinke W, Fiebach CJ, Schwarzbauer C, Meyer M, Olthoff D, Alter K. 2004b. Sequential effects of propofol on functional brain activation induced by auditory language processing: an event-related functional magnetic resonance imaging study. Br. J. Anaesth. 92: 641–650.

Hermann B, Sangaré A, Munoz-Musat E, Salah A Ben, Perez P, Valente M, Faugeras F, Axelrod V, Demeret S, Marois C, Pyatigorskaya N, Habert M-O, Kas A, Sitt JD, Rohaut B, Naccache L. 2021. Importance, limits and caveats of the use of "disorders of consciousness" to theorize consciousness. Neurosci. Conscious. 2021: niab048.

Hight DF, Gaskell AL, Kreuzer M, Voss LJ, García PS, Sleigh JW. 2019. Transient electroencephalographic alpha power loss during maintenance of general anaesthesia. Br. J. Anaesth. 122: 635–642.

Hillyard SA, Kutas M. 1983. Electrophysiology of cognitive processing. Annu. Rev. Psychol. 34: 33–61.

Hinterberger T, Wilhelm B, Mellinger J, Kotchoubey B, Birbaumer N. 2005. A device for the detection of cognitive brain functions in completely paralyzed or unresponsive patients. IEEE Trans. Biomed. Eng. 52: 211–220.

Hirota K. 2006. Special cases: ketamine, nitrous oxide and xenon. Best Pract. Res. Clin. Anaesthesiol. 20: 69–79.

Hobson JA, Hong CC-H, Friston KJ. 2014. Virtual reality and consciousness inference in dreaming. Front. Psychol. 5: 1133.

Hodapp A, Rabovsky M. 2021. The N400 ERP component reflects an error-based implicit learning signal during language comprehension. Eur. J. Neurosci. 54: 7125–7140.

Hoelscher TJ, Klinger E, Barta SG. 1981. Incorporation of concern- and nonconcern-related verbal stimuli into dream content. J. Abnorm. Psychol. 90: 88–91.

Hohlfeld A, Martín-Loeches M, Sommer W. 2015. Is semantic processing during sentence reading autonomous or controlled? Evidence from the N400 component in a dual task paradigm. Adv. Cogn. Psychol. 11: 42–55.

Hohwy J. 2009. The neural correlates of consciousness: new experimental approaches needed? Conscious. Cogn. 18: 428–438.

Holcomb PJ. 1988. Automatic and attentional processing: an event-related brain potential analysis of semantic priming. Brain Lang. 35: 66–85.

Holcomb PJ, Neville HJ. 1990. Auditory and visual semantic priming in lexical decision: a comparison using event-related brain potentials. Lang. Cogn. Process. 5: 281–312.

Holcomb PJ, Neville HJ. 1991. Natural speech processing: an analysis using event-related brain potentials. Psychobiology 19: 286–300.

Holcomb PJ. 1993. Semantic priming and stimulus degradation: implications for the role of the N400 in language processing. Psychophysiology 30: 47–61.

Huang Y-Y, Chu Y-C, Chang K-Y, Wang Y-C, Chan K-H, Tsou M-Y. 2007. Performance of AEP Monitor/2-derived composite index as an indicator for depth of sedation with midazolam and alfentanil during gastrointestinal endoscopy. Eur. J. Anaesthesiol. 24: 252–257.

Huang Z, Vlisides PE, Tarnal VC, Janke EL, Keefe KM, Collins MM, McKinney AM, Picton P, Harris RE, Mashour GA, Hudetz AG. 2018a. Brain imaging reveals covert consciousness during behavioral unresponsiveness induced by propofol. Sci. Rep. 8: 13195.

Huang Z, Liu X, Mashour GA, Hudetz AG. 2018b. Timescales of intrinsic BOLD signal dynamics and functional connectivity in pharmacologic and neuropathologic states of unconsciousness. J. Neurosci. 38: 2304–2317.

Huang Z, Tarnal V, Vlisides PE, Janke EL, McKinney AM, Picton P, Mashour GA, Hudetz AG. 2021. Asymmetric neural dynamics characterize loss and recovery of consciousness. Neuroimage 236: 118042.

Hudetz AG, Mashour GA. 2016. Disconnecting consciousness: is there a common anesthetic end point? Anesth. Analg. 123: 1228–1240.

Hulsen T, de Vlieg J, Alkema W. 2008. BioVenn - a web application for the comparison and visualization of biological lists using area-proportional Venn diagrams. BMC Genomics 9: 488.

Hutchison RM, Womelsdorf T, Allen EA, Bandettini PA, Calhoun VD, Corbetta M, Della Penna S, Duyn JH, Glover GH, Gonzalez-Castillo J, Handwerker DA, Keilholz S, Kiviniemi V, Leopold DA, de Pasquale F, Sporns O, Walter M, Chang C. 2013. Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage 80: 360–78.

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

Ibáñez A, López V, Cornejo C. 2006. ERPs and contextual semantic discrimination: degrees of congruence in wakefulness and sleep. Brain Lang. 98: 264–275.

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

Imperatori LS, Cataldi J, Betta M, Ricciardi E, Ince RAA, Siclari F, Bernardi G. 2021. Cross-participant prediction of vigilance stages through the combined use of wPLI and wSMI EEG functional connectivity metrics. Sleep 44: zsaa247.

Iselin-Chaves IA, Willems SJ, Jermann FC, Forster A, Adam SR, Van der Linden M. 2005. Investigation of implicit memory during isoflurane anesthesia for elective surgery using the process dissociation procedure. Anesthesiology 103: 925–933.

Jackson F, Foti D, Kotov R, Perlman G, Mathalon DH, Proudfit GH. 2014. An incongruent reality: the N400 in relation to psychosis and recovery. Schizophr. Res. 160: 208–215.

Johnson BW, Hamm JP. 2000. High-density mapping in an N400 paradigm: evidence for bilateral temporal lobe generators. Clin. Neurophysiol. 111: 532–545.

Jordan D, Ilg R, Riedl V, Schorer A, Grimberg S, Neufang S, Omerovic A, Berger S, Untergehrer G, Preibisch C, Schulz E, Schuster T, Schröter M, Spoormaker V, Zimmer C, Hemmer B, Wohlschläger A, Kochs EF, Schneider G. 2013. Simultaneous electroencephalographic and functional magnetic resonance imaging indicate impaired cortical top-down processing in association with anesthetic-induced unconsciousness. Anesthesiology 119: 1031–1042.

Joshi GP. 2021. General anesthetic techniques for enhanced recovery after surgery: Current controversies. Best Pract. Res. Clin. Anaesthesiol. 35: 531–541.

Juottonen K, Revonsuo A, Lang H. 1996. Dissimilar age influences on two ERP waveforms (LPC and N400) reflecting semantic context effect. Brain Res. Cogn. Brain Res. 4: 99–107.

Kaiser HA, Hirschi T, Sleigh C, Reineke D, Hartwich V, Stucki M, Rummel C, Sleigh J, Hight D. 2020. Comorbidity-dependent changes in alpha and broadband electroencephalogram power during general anaesthesia for cardiac surgery. Br. J. Anaesth. 125: 456–465.

Kantonen O, Laaksonen L, Alkire M, Scheinin A, Långsjö J, Kallionpää RE, Kaisti K, Radek L, Johansson J, Laitio T, Maksimow A, Scheinin J, Nyman M, Scheinin M, Solin O, Vahlberg T, Revonsuo A, Valli K, Scheinin H. Decreased thalamic activity is a correlate for the absence of connected consciousness during anesthesia. Submitted.

Kaplan PW, Genoud D, Ho TW, Jallon P. 1999. Etiology, neurologic correlations, and prognosis in alpha coma. Clin. Neurophysiol. 110: 205–213.

Kaskinoro K, Maksimow A, Långsjö J, Aantaa R, Jääskeläinen S, Kaisti K, Särkelä M, Scheinin H. 2011. Wide inter-individual variability of bispectral index and spectral entropy at loss of consciousness during increasing concentrations of dexmedetomidine, propofol, and sevoflurane. Br. J. Anaesth. 107: 573–580.

Kayser J, Tenke CE. 2015. Issues and considerations for using the scalp surface Laplacian in EEG/ERP research: A tutorial review. Int. J. Psychophysiol. 97: 189–209.

Kelly SD, Kravitz C, Hopkins M. 2004. Neural correlates of bimodal speech and gesture comprehension. Brain Lang. 89: 253–260.

Kerssens C, Klein J, Bonke B. 2003. Awareness: Monitoring versus remembering what happened. Anesthesiology 99: 570–575.

Kerssens C, Hamann S, Peltier S, Hu XP, Byas-Smith MG, Sebel PS. 2005. Attenuated brain response to auditory word stimulation with sevoflurane: a functional magnetic resonance imaging study in humans. Anesthesiology 103: 11–19.

Kerssens C, Gaither JR, Sebel PS. 2009. Preserved memory function during bispectral index-guided anesthesia with sevoflurane for major orthopedic surgery. Anesthesiology 111: 518–524.

Khoe W, Kroll NEA, Yonelinas AP, Dobbins IG, Knight RT. 2000. The contribution of recollection and familiarity to yes-no and forced-choice recognition tests in healthy subjects and amnesics. Neuropsychologia 38: 1333–1341.

Kiang M, Patriciu I, Roy C, Christensen BK, Zipursky RB. 2013. Test-retest reliability and stability of N400 effects in a word-pair semantic priming paradigm. Clin. Neurophysiol. 124: 667–674.

Kiefer M. 2002. The N400 is modulated by unconsciously perceived masked words: further evidence for an automatic spreading activation account of N400 priming effects. Brain Res. Cogn. Brain Res. 13: 27–39.

Kiefer M, Brendel D. 2006. Attentional modulation of unconscious "automatic" processes: evidence from event-related potentials in a masked priming paradigm. J. Cogn. Neurosci. 18: 184–198.

Kiefer M, Martens U. 2010. Attentional sensitization of unconscious cognition: task sets modulate subsequent masked semantic priming. J. Exp. Psychol. Gen. 139: 464–489.

Kim D-K, Joo Y, Sung T-Y, Kim S-Y, Shin H-Y. 2011. Dreaming in sedation during spinal anesthesia: a comparison of propofol and midazolam infusion. Anesth. Analg. 112: 1076–1081.

Kim M, Mashour GA, Moraes S-B, Vanini G, Tarnal V, Janke E, Hudetz AG, Lee U. 2016. Functional and topological conditions for explosive synchronization develop in human brain networks with the onset of anesthetic-induced unconsciousness. Front. Comput. Neurosci. 10: 1.

Kim H, Moon J-Y, Mashour GA, Lee U. 2018. Mechanisms of hysteresis in human brain networks during transitions of consciousness and unconsciousness: Theoretical principles and empirical evidence. PLoS Comput. Biol. 14: e1006424.

King J-R, Sitt JD, Faugeras F, Rohaut B, El Karoui I, Cohen L, Naccache L, Dehaene S. 2013. Information sharing in the brain indexes consciousness in noncommunicative patients. Curr. Biol. 23: 1914–1919.

Kirwan B. 2016. Cognitive neuroscience. In: Miller HL, editor. The SAGE Encyclopedia of Theory in Psychology, 1e. Thousand Oaks, California, USA: SAGE Publications, Inc., p 152–155.

Koch C, Massimini M, Boly M, Tononi G. 2016. Neural correlates of consciousness: progress and problems. Nat. Rev. Neurosci. 17: 307–321.

Koelsch S, Heinke W, Sammler D, Olthoff D. 2006. Auditory processing during deep propofol sedation and recovery from unconsciousness. Clin. Neurophysiol. 117: 1746–1759.

Koivisto M, Revonsuo A. 2001. Cognitive representations underlying the N400 priming effect. Brain Res. Cogn. Brain Res. 12: 487–490.

Kondziella D, Friberg CK, Frokjaer VG, Fabricius M, Møller K. 2016. Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatry 87: 485–492.

Kondziella D, Bender A, Diserens K, van Erp W, Estraneo A, Formisano R, Laureys S, Naccache L, Ozturk S, Rohaut B, Sitt JD, Stender J, Tiainen M, Rossetti AO, Gosseries O, Chatelle C, EAN Panel on Coma D of C. 2020. European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. Eur. J. Neurol. 27: 741–756.

Konkoly KR, Appel K, Chabani E, Mangiaruga A, Gott J, Mallett R, Caughran B, Witkowski S, Whitmore NW, Mazurek CY, Berent JB, Weber FD, Türker B, Leu-Semenescu S, Maranci J-B, Pipa G, Arnulf I, Oudiette D, Dresler M, Paller KA. 2021. Real-time dialogue between experimenters and dreamers during REM sleep. Curr. Biol. 31: 1417-1427.e6.

Korhonen O, Zanin M, Papo D. 2021. Principles and open questions in functional brain network reconstruction. Hum. Brain Mapp. 42: 3680–3711.

Kotchoubey B. 2005. Apallic syndrome is not apallic: is vegetative state vegetative? Neuropsychol. Rehabil. 15: 333–356.

Kotchoubey B, Lang S, Mezger G, Schmalohr D, Schneck M, Semmler A, Bostanov V, Birbaumer N. 2005. Information processing in severe disorders of consciousness: vegetative state and minimally conscious state. Clin. Neurophysiol. 116: 2441–2453.

Kotchoubey B. 2015. Event-Related Potentials in Disorders of Consciousness. In: Rossetti AO, Laureys S, editors. Clinical Neurophysiology in Disorders of Consciousness. Vienna: Springer Vienna, p 107–123.

Kreuer S, Wilhelm W, Grundmann U, Larsen R, Bruhn J. 2004. Narcotrend index versus bispectral index as electroencephalogram measures of anesthetic drug effect during propofol anesthesia. Anesth. Analg. 98: 692–697.

Kriegeskorte N, Simmons WK, Bellgowan PSF, Baker CI. 2009. Circular analysis in systems neuroscience: the dangers of double dipping. Nat. Neurosci. 12: 535–540.

Krom AJ, Marmelshtein A, Gelbard-Sagiv H, Tankus A, Hayat H, Hayat D, Matot I, Strauss I, Fahoum F, Soehle M, Boström J, Mormann F, Fried I, Nir Y. 2020. Anesthesia-induced loss of consciousness disrupts auditory responses beyond primary cortex. Proc. Natl. Acad. Sci. U. S. A. 117: 11770–11780.

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

Kumar A, Bhattacharya A, Makhija N. 2000. Evoked potential monitoring in anaesthesia and analgesia. Anaesthesia 55: 225–241.

Kuperberg GR, Holcomb PJ, Sitnikova T, Greve D, Dale AM, Caplan D. 2003. Distinct patterns of neural modulation during the processing of conceptual and syntactic anomalies. J. Cogn. Neurosci. 15: 272–293.

Kuperberg GR, Brothers T, Wlotko EW. 2020. A tale of two positivities and the N400: distinct neural signatures are evoked by confirmed and violated predictions at different levels of representation. J. Cogn. Neurosci. 32: 12–35.

Kutas M, Hillyard SA. 1980. Reading senseless sentences: brain potentials reflect semantic incongruity. Science 207: 203–205.

Kutas M, Hillyard SA. 1983. Event-related brain potentials to grammatical errors and semantic anomalies. Mem. Cognit. 11: 539–550.

Kutas M, Hillyard SA. 1984. Brain potentials during reading reflect word expectancy and semantic association. Nature 307: 161–163.

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

Kutas M. 1993. In the company of other words: Electrophysiological evidence for single-word and sentence context effects. Lang. Cogn. Process. 8: 533–572.

Kuznetsova A, Brockhoff PB, Christensen RHB. 2017. lmerTest package: tests in linear mixed effects models. J. Stat. Softw. 82: 1–26.

Laine M, Virtanen P. 1999. Wordmill, lexical search program.

Lamme VA, Roelfsema PR. 2000. The distinct modes of vision offered by feedforward and recurrent processing. Trends Neurosci. 23: 571–579.

Lamme VAF. 2006. Towards a true neural stance on consciousness. Trends Cogn. Sci. 10: 494–501.

Lamme VAF. 2010. How neuroscience will change our view on consciousness. Cogn. Neurosci. 1: 204–220.

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

Lau EF, Phillips C, Poeppel D. 2008. A cortical network for semantics: (de)constructing the N400. Nat. Rev. Neurosci. 9: 920–933.

Lau E, Almeida D, Hines PC, Poeppel D. 2009. A lexical basis for N400 context effects: evidence from MEG. Brain Lang. 111: 161–172.

Lau H, Rosenthal D. 2011. Empirical support for higher-order theories of conscious awareness. Trends Cogn. Sci. 15: 365–373.

Lau EF, Holcomb PJ, Kuperberg GR. 2013. Dissociating N400 effects of prediction from association in single-word contexts. J. Cogn. Neurosci. 25: 484–502.

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

Laureys S, Schiff ND. 2012. Coma and consciousness: paradigms (re)framed by neuroimaging. Neuroimage 61: 478–491.

Lee U, Kim S, Noh G-J, Choi B-M, Hwang E, Mashour GA. 2009. The directionality and functional organization of frontoparietal connectivity during consciousness and anesthesia in humans. Conscious. Cogn. 18: 1069–1078.

Lee H, Mashour GA, Noh G-J, Kim S, Lee U. 2013a. Reconfiguration of network hub structure after propofol-induced unconsciousness. Anesthesiology 119: 1347–1359.

Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA. 2013b. Disruption of frontal-parietal communication by ketamine, propofol, and sevoflurane. Anesthesiology 118: 1264–1275.

Lee H, Noh G-J, Joo P, Choi B-M, Silverstein BH, Kim M, Wang J, Jung W-S, Kim S. 2017a. Diversity of functional connectivity patterns is reduced in propofol-induced unconsciousness. Hum. Brain Mapp. 38: 4980–4995.

Lee M, Sanders RD, Yeom S-K, Won D-O, Seo K-S, Kim HJ, Tononi G, Lee S-W. 2017b. Network properties in transitions of consciousness during propofol-induced sedation. Sci. Rep. 7: 16791.

Lee U, Mashour GA. 2018. Role of network science in the study of anesthetic state transitions. Anesthesiology 129: 1029–1044.

Lee M, Baird B, Gosseries O, Nieminen JO, Boly M, Postle BR, Tononi G, Lee S-W. 2019. Connectivity differences between consciousness and unconsciousness in non-rapid eye movement sleep: a TMS-EEG study. Sci. Rep. 9: 5175.

Lee M, Sanz LRD, Barra A, Wolff A, Nieminen JO, Boly M, Rosanova M, Casarotto S, Bodart O, Annen J, Thibaut A, Panda R, Bonhomme V, Massimini M, Tononi G, Laureys S, Gosseries O, Lee S-W. 2022. Quantifying arousal and awareness in altered states of consciousness using interpretable deep learning. Nat. Commun. 13: 1064.

Legendre G, Andrillon T, Koroma M, Kouider S. 2019. Sleepers track informative speech in a multitalker environment. Nat. Hum. Behav. 3: 274–283.

Lehembre R, Marie-Aurélie B, Vanhaudenhuyse A, Chatelle C, Cologan V, Leclercq Y, Soddu A, Macq B, Laureys S, Noirhomme Q. 2012. Resting-state EEG study of comatose patients: a connectivity and frequency analysis to find differences between vegetative and minimally conscious states. Funct. Neurol. 27: 41–47.

Lehmann D, Skrandies W. 1980. Reference-free identification of components of checkerboard-evoked multichannel potential fields. Electroencephalogr. Clin. Neurophysiol. 48: 609–621.

Lennertz R, Pryor KO, Raz A, Parker M, Bonhomme V, Schuller P, Schneider G, Moore M, Coburn M, Root JC, Emerson JM, Hohmann AL, Azaria H, Golomb N, Defresne A, Montupil J, Pilge S, Obert DP, van Waart H, Seretny M, Rossaint R, Kowark A, Blair A, Krause B, Proekt A, Kelz M, Sleigh J, Gaskell A, Sanders RD. 2023. Connected consciousness after tracheal intubation in young adults: an international multicentre cohort study. Br. J. Anaesth. 130: e217–e224.

Leslie K, Myles PS, Forbes A, Chan MT V, Swallow SK, Short TG. 2005. Dreaming during anaesthesia in patients at high risk of awareness. Anaesthesia 60: 239–244.

Leslie K. 2007. Awareness in a community-based anesthesia practice. Anesthesiology 107: 671–672.

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

Leslie K, Skrzypek H. 2007. Dreaming during anaesthesia in adult patients. Best Pract. Res. Clin. Anaesthesiol. 21: 403–414.

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

Lewis LD, Weiner VS, Mukamel EA, Donoghue JA, Eskandar EN, Madsen JR, Anderson WS, Hochberg LR, Cash SS, Brown EN, Purdon PL. 2012. Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness. Proc. Natl. Acad. Sci. U. S. A. 109: E3377–E3386.

Lewis SR, Pritchard MW, Fawcett LJ, Punjasawadwong Y. 2019. Bispectral index for improving intraoperative awareness and early postoperative recovery in adults. Cochrane database Syst. Rev. 9: CD003843.

Li D, Vlisides PE, Kelz MB, Avidan MS, Mashour GA, ReCCognition Study Group. 2019. Dynamic cortical connectivity during general anesthesia in healthy volunteers. Anesthesiology 130: 870–884.

Liao X, Vasilakos A V., He Y. 2017. Small-world human brain networks: Perspectives and challenges. Neurosci. Biobehav. Rev. 77: 286–300.

Linassi F, Zanatta P, Tellaroli P, Ori C, Carron M. 2018. Isolated forearm technique: a meta-analysis of connected consciousness during different general anaesthesia regimens. Br. J. Anaesth. 121: 198–209.

Linassi F, Obert DP, Maran E, Tellaroli P, Kreuzer M, Sanders RD, Carron M. 2021. Implicit memory and anesthesia: a systematic review and meta-analysis. Life (Basel, Switzerland) 11: 850.

Lioi G, Bell SL, Smith DC, Simpson DM. 2019. Measuring depth of anaesthesia using changes in directional connectivity: a comparison with auditory middle latency response and estimated bispectral index during propofol anaesthesia. Anaesthesia 74: 321–332.

Liu X, Lauer KK, Ward BD, Rao SM, Li S, Hudetz AG. 2012. Propofol disrupts functional interactions between sensory and high-order processing of auditory verbal memory. Hum. Brain Mapp. 33: 2487–2498.

Liu X, Lauer KK, Douglas Ward B, Roberts C, Liu S, Gollapudy S, Rohloff R, Gross W, Chen G, Xu Z, Binder JR, Li S-J, Hudetz AG. 2017a. Propofol attenuates low-frequency fluctuations of resting-state fMRI BOLD signal in the anterior frontal cortex upon loss of consciousness. Neuroimage 147: 295–301.

Liu X, Lauer KK, Ward BD, Roberts CJ, Liu S, Gollapudy S, Rohloff R, Gross W, Xu Z, Chen G, Binder JR, Li S-J, Hudetz AG. 2017b. Fine-grained parcellation of brain connectivity improves differentiation of states of consciousness during graded propofol sedation. Brain Connect. 7: 373–381.

Liu H, Jian M, Liu S, Li A, Li S, Fang J, Liang F, Liu B, Han R. 2019. Preserved individual differences in functional connectivity patterns under dexmedetomidine-induced sedation. Neurosci. Lett. 707: 134289.

Llinás R, Ribary U, Contreras D, Pedroarena C. 1998. The neuronal basis for consciousness. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 353: 1841–1849.

López Zunini R, Muller-Gass A, Campbell K. 2014. The effects of total sleep deprivation on semantic priming: event-related potential evidence for automatic and controlled processing strategies. Brain Cogn. 84: 14–25.

Lubke GH, Kerssens C, Phaf H, Sebel PS. 1999. Dependence of explicit and implicit memory on hypnotic state in trauma patients. Anesthesiology 90: 670–680.

Luck SJ, Vogel EK, Shapiro KL. 1996. Word meanings can be accessed but not reported during the attentional blink. Nature 383: 616–618.

Luck SJ, Mathalon DH, O'Donnell BF, Hämäläinen MS, Spencer KM, Javitt DC, Uhlhaas PJ. 2011. A roadmap for the development and validation of event-related potential biomarkers in schizophrenia research. Biol. Psychiatry 70: 28–34.

Luck SJ. 2014. An introduction to the event-related potential technique, 2e. Cambridge, MA, USA: MIT Press.

Lurie DJ, Kessler D, Bassett DS, Betzel RF, Breakspear M, Kheilholz S, Kucyi A, Liégeois R, Lindquist MA, McIntosh AR, Poldrack RA, Shine JM, Thompson WH, Bielczyk NZ, Douw L, Kraft D, Miller RL, Muthuraman M, Pasquini L, Razi A, Vidaurre D, Xie H, Calhoun VD. 2020. Questions and controversies in the study of time-varying functional connectivity in resting fMRI. Netw. Neurosci. (Cambridge, Mass.) 4: 30–69.

Ma L, Liu W, Hudson AE. 2019. Propofol anesthesia increases long-range frontoparietal corticocortical interaction in the oculomotor circuit in macaque monkeys. Anesthesiology 130: 560–571.

Mah RL, Connolly JF. 2018. A framework for the extended monitoring of levels of cognitive function in unresponsive patients. PLoS One 13: e0200793.

Mahjoory K, Nikulin V V., Botrel L, Linkenkaer-Hansen K, Fato MM, Haufe S. 2017. Consistency of EEG source localization and connectivity estimates. Neuroimage 152: 590–601.

Makov S, Sharon O, Ding N, Ben-Shachar M, Nir Y, Zion Golumbic E. 2017. Sleep disrupts high-level speech parsing despite significant basic auditory processing. J. Neurosci. 37: 7772–7781.

Maksimow A, Särkelä M, Långsjö JW, Salmi E, Kaisti KK, Yli-Hankala A, Hinkka-Yli-Salomäki S, Scheinin H, Jääskeläinen SK. 2006. Increase in high frequency EEG activity explains the poor performance of EEG spectral entropy monitor during S-ketamine anesthesia. Clin. Neurophysiol. 117: 1660–1668.

Maksimow A, Silfverhuth M, Långsjö J, Kaskinoro K, Georgiadis S, Jääskeläinen S, Scheinin H. 2014. Directional connectivity between frontal and posterior brain regions is altered with increasing concentrations of propofol. PLoS One 9: e113616.

Malekmohammadi M, Price CM, Hudson AE, DiCesare JAT, Pouratian N. 2019. Propofol-induced loss of consciousness is associated with a decrease in thalamocortical connectivity in humans. Brain 142: 2288–2302.

Maquet P, Degueldre C, Delfiore G, Aerts J, Péters JM, Luxen A, Franck G. 1997. Functional neuroanatomy of human slow wave sleep. J. Neurosci. 17: 2807–12.

Maris E, Oostenveld R. 2007. Nonparametric statistical testing of EEG- and MEG-data. J. Neurosci. Methods 164: 177–190.

Maris E. 2012. Statistical testing in electrophysiological studies. Psychophysiology 49: 549–565.

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

Martín-Loeches M, Ouyang G, Rausch P, Stürmer B, Palazova M, Schacht A, Sommer W. 2017. Test–retest reliability of the N400 component in a sentence-reading paradigm. Lang. Cogn. Neurosci. 32: 1261–1272.

Martin JM, Andriano DW, Mota NB, Mota-Rolim SA, Araújo JF, Solms M, Ribeiro S. 2020. Structural differences between REM and non-REM dream reports assessed by graph analysis. PLoS One 15: e0228903.

Mashour GA, Wang LYJ, Turner CR, Vandervest JC, Shanks A, Tremper KK. 2009. A retrospective study of intraoperative awareness with methodological implications. Anesth. Analg. 108: 521–526.

Mashour GA, Shanks A, Tremper KK, Kheterpal S, Turner CR, Ramachandran SK, Picton P, Schueller C, Morris M, Vandervest JC, Lin N, Avidan MS. 2012. Prevention of intraoperative awareness with explicit recall in an unselected surgical population: a randomized comparative effectiveness trial. Anesthesiology 117: 717–725.

Mashour GA, Alkire MT. 2013. Consciousness, anesthesia, and the thalamocortical system. Anesthesiology 118: 13–15.

Mashour GA, Kent C, Picton P, Ramachandran SK, Tremper KK, Turner CR, Shanks A, Avidan MS. 2013. Assessment of intraoperative awareness with explicit recall: a comparison of 2 methods. Anesth. Analg. 116: 889–891.

Mashour GA. 2014. Top-down mechanisms of anesthetic-induced unconsciousness. Front. Syst. Neurosci. 8: 115.

Mashour GA, Hudetz AG. 2017. Bottom-up and top-down mechanisms of general anesthetics modulate different dimensions of consciousness. Front. Neural Circuits 11: 44.

Mashour GA, Avidan MS. 2017. Black swans: challenging the relationship of anaesthetic-induced unconsciousness and electroencephalographic oscillations in the frontal cortex. Br. J. Anaesth. 119: 563–565.

Mashour GA. 2019a. Role of cortical feedback signalling in consciousness and anaesthetic-induced unconsciousness. Br. J. Anaesth. 123: 404–405.

Mashour GA. 2019b. General anesthesia and the cortex: communication breakdown? Anesthesiology 130: 526–527.
Mashour GA, Roelfsema P, Changeux J-P, Dehaene S. 2020. Conscious processing and the global neuronal workspace hypothesis. Neuron 105: 776–798.
Mashour GA, Pal D, Brown EN. 2022. Prefrontal cortex as a key node in arousal circuitry. Trends Neurosci. 45: 722–732.
Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. 2005. Breakdown of cortical effective connectivity during sleep. Science 309: 2228–2232.
Masui K, Upton RN, Doufas AG, Coetzee JF, Kazama T, Mortier EP, Struys MMRF. 2010. The performance of compartmental and physiologically based recirculatory pharmacokinetic models for propofol: a comparison using bolus, continuous, and target-controlled infusion data. Anesth. Analg. 111: 368–379.
Matus H, Kvolik S, Rakipovic A, Borzan V. 2021. Bispectral index monitoring and observer rating scale correlate with dreaming during propofol anesthesia for gastrointestinal endoscopies. Medicina (Kaunas). 58: 62.
McCarthy G, Nobre AC. 1993. Modulation of semantic processing by spatial selective attention. Electroencephalogr. Clin. Neurophysiol. 88: 210–9.
McCarthy G, Nobre AC, Bentin S, Spencer DD. 1995. Language-related field potentials in the anterior-medial temporal lobe: I. Intracranial distribution and neural generators. J. Neurosci. 15: 1080–1089.
McCarthy MM, Brown EN, Kopell N. 2008. Potential network mechanisms mediating electroencephalographic beta rhythm changes during propofol-induced paradoxical excitation. J. Neurosci. 28: 13488–13504.
McCormick DA, McGinley MJ, Salkoff DB. 2015. Brain state dependent activity in the cortex and thalamus. Curr. Opin. Neurobiol. 31: 133–140.
Messina AG, Wang M, Ward MJ, Wilker CC, Smith BB, Vezina DP, Pace NL. 2016. Anaesthetic interventions for prevention of awareness during surgery. Cochrane database Syst. Rev. 10: CD007272.
Mhuircheartaigh RN, Rosenorn-Lanng D, Wise R, Jbabdi S, Rogers R, Tracey I. 2010. Cortical and subcortical connectivity changes during decreasing levels of consciousness in humans: a functional magnetic resonance imaging study using propofol. J. Neurosci. 30: 9095–9102.
Michel CM, Brunet D. 2019. EEG source imaging: a practical review of the analysis steps. Front. Neurol. 10: 325.
Michel M. 2023. Calibration in consciousness science. Erkenntnis 88: 829–850.
Miller J, Patterson T, Ulrich R. 1998. Jackknife-based method for measuring LRP onset latency differences. Psychophysiology 35: 99–115.
Mitchell PF, Andrews S, Ward PB. 1993. An event-related potential study of semantic congruity and repetition in a sentence-reading task: effects of context change. Psychophysiology 30: 496–509.
Mongelli V, Meijs EL, van Gaal S, Hagoort P. 2019. No language unification without neural feedback: how awareness affects sentence processing. Neuroimage 202: 116063.
Monti MM, Coleman MR, Owen AM. 2009. Neuroimaging and the vegetative state: resolving the behavioral assessment dilemma? Ann. N. Y. Acad. Sci. 1157: 81–89.
Monti MM, Lutkenhoff ES, Rubinov M, Boveroux P, Vanhaudenhuyse A, Gosseries O, Bruno M-A, Noirhomme Q, Boly M, Laureys S. 2013. Dynamic change of global and local information processing in propofol-induced loss and recovery of consciousness. PLoS Comput. Biol. 9: e1003271.
Moody OA, Zhang ER, Vincent KF, Kato R, Melonakos ED, Nehs CJ, Solt K. 2021. The neural circuits underlying general anesthesia and sleep. Anesth. Analg. 132: 1254–1264.
Moon J-Y, Lee U, Blain-Moraes S, Mashour GA. 2015. General relationship of global topology, local dynamics, and directionality in large-scale brain networks. PLoS Comput. Biol. 11: e1004225.

Moon J, Orlandi S, Chau T. 2022. A comparison and classification of oscillatory characteristics in speech perception and covert speech. Brain Res. 1781: 147778.

Moses DA, Metzger SL, Liu JR, Anumanchipalli GK, Makin JG, Sun PF, Chartier J, Dougherty ME, Liu PM, Abrams GM, Tu-Chan A, Ganguly K, Chang EF. 2021. Neuroprosthesis for decoding speech in a paralyzed person with anarthria. N. Engl. J. Med. 385: 217–227.

Mukamel EA, Pirondini E, Babadi B, Wong KFK, Pierce ET, Harrell PG, Walsh JL, Salazar-Gomez AF, Cash SS, Eskandar EN, Weiner VS, Brown EN, Purdon PL. 2014. A transition in brain state during propofol-induced unconsciousness. J. Neurosci. 34: 839–845.

Münte S, Münte TF, Grotkamp J, Haeseler G, Raymondos K, Piepenbrock S, Kraus G. 2003. Implicit memory varies as a function of hypnotic electroencephalogram stage in surgical patients. Anesth. Analg. 97: 132–138.

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

Murphy C, Krause B, Banks M. 2019. Selective effects of isoflurane on cortico-cortical feedback afferent responses in murine non-primary neocortex. Br. J. Anaesth. 123: 488–496.

Muthukumaraswamy SD, Shaw AD, Jackson LE, Hall J, Moran R, Saxena N. 2015. Evidence that subanesthetic doses of ketamine cause sustained disruptions of NMDA and AMPA-mediated frontoparietal connectivity in humans. J. Neurosci. 35: 11694–11706.

Muzur A, Pace-Schott EF, Hobson JA. 2002. The prefrontal cortex in sleep. Trends Cogn. Sci. 6: 475–481.

Myles PS, Leslie K, McNeil J, Forbes A, Chan MT V. 2004. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet (London, England) 363: 1757–1763.

Naccache L, Sitt J, King J-R, Rohaut B, Faugeras F, Chennu S, Strauss M, Valente M, Engemann D, Raimondo F, Demertzi A, Bekinschtein T, Dehaene S. 2016. Reply: Replicability and impact of statistics in the detection of neural responses of consciousness. Brain 139: e31.

Naccache L. 2018. Minimally conscious state or cortically mediated state? Brain 141: 949–960.

Naci L, Cusack R, Anello M, Owen AM. 2014. A common neural code for similar conscious experiences in different individuals. Proc. Natl. Acad. Sci. U. S. A. 111: 14277–14282.

Naci L, Sinai L, Owen AM. 2017. Detecting and interpreting conscious experiences in behaviorally non-responsive patients. Neuroimage 145: 304–313.

Naci L, Haugg A, MacDonald A, Anello M, Houldin E, Naqshbandi S, Gonzalez-Lara LE, Arango M, Harle C, Cusack R, Owen AM. 2018. Functional diversity of brain networks supports consciousness and verbal intelligence. Sci. Rep. 8: 13259.

Nagel T. 1974. What is it like to be a bat? Philos. Rev. 83: 435–450.

National Institute for Clinical Excellence NICE Diagnostics Guidance. 2012. Depth of anaesthesia monitors – Bispectral Index (BIS), E-Entropy and Narcotrend-Compact M. https://www.nice.org.uk/guidance/dg6 (Accessed April 8, 2022).

Ní Mhuircheartaigh R, Warnaby C, Rogers R, Jbabdi S, Tracey I. 2013. Slow-wave activity saturation and thalamocortical isolation during propofol anesthesia in humans. Sci. Transl. Med. 5: 208ra148.

Nicolaou N, Hourris S, Alexandrou P, Georgiou J. 2012. EEG-based automatic classification of “awake” versus “anesthetized” state in general anesthesia using Granger causality. PLoS One 7: e33869.

Nielsen TA. 2000. A review of mentation in REM and NREM sleep: “covert” REM sleep as a possible reconciliation of two opposing models. Behav. Brain Sci. 23: 851–66; discussion 904-1121.

Nieminen JO, Gosseries O, Massimini M, Saad E, Sheldon AD, Boly M, Siclari F, Postle BR, Tononi G. 2016. Consciousness and cortical responsiveness: a within-state study during non-rapid eye movement sleep. Sci. Rep. 6: 30932.

Nieuwland MS, Barr DJ, Bartolozzi F, Busch-Moreno S, Darley E, Donaldson DI, Ferguson HJ, Fu X, Heyselaar E, Huettig F, Matthew Husband E, Ito A, Kazanina N, Kogan V, Kohút Z, Kulakova E,

Mézière D, Politzer-Ahles S, Rousselet G, Rueschemeyer S-A, Segaert K, Tuomainen J, Von Grebmer Zu Wolfsthurn S. 2020. Dissociable effects of prediction and integration during language comprehension: evidence from a large-scale study using brain potentials. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 375: 20180522.

Nimmo AF, Absalom AR, Bagshaw O, Biswas A, Cook TM, Costello A, Grimes S, Mulvey D, Shinde S, Whitehouse T, Wiles MD. 2019. Guidelines for the safe practice of total intravenous anaesthesia (TIVA): Joint Guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia. Anaesthesia 74: 211–224.

Nishiyama T. 2013. Composite auditory evoked potentials index is not a good indicator of depth of anesthesia in propofol-fentanyl anesthesia: Randomized comparative study. J. Anaesthesiol. Clin. Pharmacol. 29: 333–336.

Noreika V, Valli K, Lahtela H, Revonsuo A. 2009. Early-night serial awakenings as a new paradigm for studies on NREM dreaming. Int. J. Psychophysiol. 74: 14–18.

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

Northoff G, Lamme V. 2020. Neural signs and mechanisms of consciousness: Is there a potential convergence of theories of consciousness in sight? Neurosci. Biobehav. Rev. 118: 568–587.

Nourski K V., Steinschneider M, Rhone AE, Kawasaki H, Howard MA, Banks MI. 2018. Auditory predictive coding across awareness states under anesthesia: An intracranial electrophysiology study. J. Neurosci. 38: 8441–8452.

Nourski K V., Steinschneider M, Rhone AE, Krause BM, Mueller RN, Kawasaki H, Banks MI. 2021. Cortical responses to vowel sequences in awake and anesthetized states: A human intracranial electrophysiology study. Cereb. Cortex 31: 5435–5448.

Nunez PL, Srinivasan R. 2006. Measures of EEG Dynamic Properties. In: Electric Fields of the Brain. Oxford, England: Oxford University Press, p 353–431.

Obert DP, Schweizer C, Zinn S, Kratzer S, Hight D, Sleigh J, Schneider G, García PS, Kreuzer M. 2021. The influence of age on EEG-based anaesthesia indices. J. Clin. Anesth. 73: 110325.

Odegaard B, Knight RT, Lau H. 2017. Should a few null findings falsify prefrontal theories of conscious perception? J. Neurosci. 37: 9593–9602.

Oostenveld R, Fries P, Maris E, Schoffelen JM. 2011. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput. Intell. Neurosci. 2011: 156869.

Orlinsky D. 1962. Psychodynamic and cognitive correlates of dream recall. Unpublished doctoral dissertation.

Overgaard M, Overgaard R. 2010. Neural correlates of contents and levels of consciousness. Front. Psychol. 1: 164.

Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. 2006. Detecting awareness in the vegetative state. Science 313: 1402.

Pal D, Dean JG, Liu T, Li D, Watson CJ, Hudetz AG, Mashour GA. 2018. Differential role of prefrontal and parietal cortices in controlling level of consciousness. Curr. Biol. 28: 2145-2152.e5.

Pal D, Li D, Dean JG, Brito MA, Liu T, Fryzel AM, Hudetz AG, Mashour GA. 2020. Level of consciousness is dissociable from electroencephalographic measures of cortical connectivity, slow oscillations, and complexity. J. Neurosci. 40: 605–618.

Palanca BJA, Mitra A, Larson-Prior L, Snyder AZ, Avidan MS, Raichle ME. 2015. Resting-state functional magnetic resonance imaging correlates of sevoflurane-induced unconsciousness. Anesthesiology 123: 346–356.

Palva S, Palva JM. 2007. New vistas for alpha-frequency band oscillations. Trends Neurosci. 30: 150–158.

Palva S, Palva JM. 2012. Discovering oscillatory interaction networks with M/EEG: Challenges and breakthroughs. Trends Cogn. Sci. 16: 219–230.

Palva JM, Wang SH, Palva S, Zhigalov A, Monto S, Brookes MJ, Schoffelen JM, Jerbi K. 2018. Ghost interactions in MEG/EEG source space: A note of caution on inter-areal coupling measures. Neuroimage 173: 632–643.

Pandit JJ. 2013. Isolated forearm - or isolated brain? Interpreting responses during anaesthesia - or "dysanaesthesia". Anaesthesia 68: 995–1000.

Pandit JJ, Andrade J, Bogod DG, Hitchman JM, Jonker WR, Lucas N, Mackay JH, Nimmo AF, O'Connor K, O'Sullivan EP, Paul RG, Palmer JHM, Plaat F, Radcliffe JJ, Sury MRJ, Torevell HE, Wang M, Cook TM. 2014a. 5th National Audit Project (NAP5)on accidental awareness during general anaesthesia: Protocol, methods, and analysis of data. Br. J. Anaesth. 113: 540–548.

Pandit JJ, Andrade J, Bogod DG, Hitchman JM, Jonker WR, Lucas N, Mackay JH, Nimmo AF, O'Connor K, O'Sullivan EP, Paul RG, Palmer JHMG, Plaat F, Radcliffe JJ, Sury MRJ, Torevell HE, Wang M, Hainsworth J, Cook TM, Armstrong J, Bird J, Eddy A, Harrop-Griffiths W, Love N, Mahajan R, Mallick A, Barker I, Kirkpatrick A, Molodynski J, Poonnusamy K, Moonesinghe R, Weatherill D, Smith D, Grocott M, Humphrey M, Casserly M, Drake S, Rangasami J. 2014b. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: Summary of main findings and risk factors. Br. J. Anaesth. 113: 549–559.

Pandit JJ, Cook TM eds. 2014. Accidental awareness during general anaesthesia in the United Kingdom and Ireland: Report and findings. London, UK: The Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland.

Papana A, Kugiumtzis D, Larsson PG. 2011. Reducing the bias of causality measures. Phys. Rev. E 83: 036207.

Pappas I, Adapa RM, Menon DK, Stamatakis EA. 2019. Brain network disintegration during sedation is mediated by the complexity of sparsely connected regions. Neuroimage 186: 221–233.

Perrin F, Pernier J, Bertrand O, Echallier JF. 1989. Spherical splines for scalp potential and current density mapping. Electroencephalogr. Clin. Neurophysiol. 72: 184–7.

Perrin F, García-Larrea L, Mauguière F, Bastuji H. 1999. A differential brain response to the subject's own name persists during sleep. Clin. Neurophysiol. 110: 2153–2164.

Perrin F, Bastuji H, Garcia-Larrea L. 2002. Detection of verbal discordances during sleep. Neuroreport 13: 1345–1349.

Pesonen H, Kallionpää RE, Scheinin A, Sandman N, Laitio R, Scheinin H, Revonsuo A, Valli K. 2019. A novel Bayesian linear regression model for analysing event-related potentials: technical report. https://github.com/hpesonen/Bayesian-linear-regression-for-ERPs (Accessed January 28, 2022).

Phillips JM, Kambi NA, Redinbaugh MJ, Mohanta S, Saalmann YB. 2021. Disentangling the influences of multiple thalamic nuclei on prefrontal cortex and cognitive control. Neurosci. Biobehav. Rev. 128: 487–510.

Piastra MC, Nüßing A, Vorwerk J, Clerc M, Engwer C, Wolters CH. 2021. A comprehensive study on electroencephalography and magnetoencephalography sensitivity to cortical and subcortical sources. Hum. Brain Mapp. 42: 978–992.

Picard-Deland C, Nielsen T, Carr M. 2021. Dreaming of the sleep lab. PLoS One 16.

Picchioni D, Pixa ML, Fukunaga M, Carr WS, Horovitz SG, Braun AR, Duyn JH. 2014. Decreased connectivity between the thalamus and the neocortex during human nonrapid eye movement sleep. Sleep 37: 387–397.

Plourde G. 2006. Auditory evoked potentials. Best Pract. Res. Clin. Anaesthesiol. 20: 129–139.

Plourde G, Belin P, Chartrand D, Fiset P, Backman SB, Xie G, Zatorre RJ. 2006. Cortical processing of complex auditory stimuli during alterations of consciousness with the general anesthetic propofol. Anesthesiology 104: 448–57.

Pockett S. 1999. Anesthesia and the electrophysiology of auditory consciousness. Conscious. Cogn. 8: 45–61.

Pollard RJ, Coyle JP, Gilbert RL, Beck JE. 2007. Intraoperative awareness in a regional medical system: A review of 3 years' data. Anesthesiology 106: 269–274.

Prerau MJ, Brown RE, Bianchi MT, Ellenbogen JM, Purdon PL. 2017. Sleep neurophysiological dynamics through the lens of multitaper spectral analysis. Physiology (Bethesda). 32: 60–92.

Price CJ. 2012. A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. Neuroimage 62: 816–847.

Pruvost-Robieux E, Marchi A, Martinelli I, Bouchereau E, Gavaret M. 2022. Evoked and event-related potentials as biomarkers of consciousness state and recovery. J. Clin. Neurophysiol. 39: 22–31.

Pryor KO, Reinsel RA, Mehta M, Li Y, Wixted JT, Veselis RA. 2010. Visual P2–N2 complex and arousal at the time of encoding predict the time domain characteristics of amnesia for multiple intravenous anesthetic drugs in humans. Anesthesiology 113: 313–326.

Pryor KO, Root JC, Mehta M, Stern E, Pan H, Veselis RA, Silbersweig DA. 2015. Effect of propofol on the medial temporal lobe emotional memory system: a functional magnetic resonance imaging study in human subjects. Br. J. Anaesth. 115 Suppl 1: i104–i113.

Puglia MP, Vlisides PE, Kaplan CM, Jewell ES, Therrian M, Mashour GA, Li D. 2022. Constrained functional connectivity dynamics in pediatric surgical patients undergoing general anesthesia. Anesthesiology 137: 28–40.

Pujol J, Blanco-Hinojo L, Gallart L, Moltó L, Martínez-Vilavella G, Vilà E, Pacreu S, Adalid I, Deus J, Pérez-Sola V, Fernández-Candil J. 2021. Largest scale dissociation of brain activity at propofol-induced loss of consciousness. Sleep 44: zsaa152.

Pullon RM, Warnaby CE, Sleigh JW. 2022. Propofol-induced unresponsiveness is associated with a brain network phase transition. Anesthesiology 136: 420–433.

Purdon PL, Pierce ET, Mukamel EA, Prerau MJ, Walsh JL, Wong KF, Salazar-Gomez AF, Harrell PG, Sampson AL, Cimenser A, Ching S, Kopell NJ, Tavares-Stoeckel C, Habeeb K, Merhar R, Brown EN. 2013. Electroencephalogram signatures of loss and recovery of consciousness from propofol. Proc. Natl. Acad. Sci. U. S. A. 110: E1142-51.

Purdon PL, Sampson A, Pavone KJ, Brown EN. 2015. Clinical electroencephalography for anesthesiologists: Part I: Background and basic signatures. Anesthesiology 123: 937–960.

Putois B, Leslie W, Asfeld C, Sierro C, Higgins S, Ruby P. 2020. Methodological recommendations to control for factors influencing dream and nightmare recall in clinical and experimental studies of dreaming. Front. Neurol. 11: 724.

Rabovsky M, McRae K. 2014. Simulating the N400 ERP component as semantic network error: insights from a feature-based connectionist attractor model of word meaning. Cognition 132: 68–89.

Rabovsky M, Hansen SS, McClelland JL. 2018. Modelling the N400 brain potential as change in a probabilistic representation of meaning. Nat. Hum. Behav. 2: 693–705.

Rabs E, Delogu F, Drenhaus H, Crocker MW. 2022. Situational expectancy or association? The influence of event knowledge on the N400. Lang. Cogn. Neurosci. 37: 766–784.

Radek L, Koskinen L, Sandman N, Laaksonen L, Kallionpää RE, Scheinin A, Rajala V, Maksimow A, Laitio T, Revonsuo A, Scheinin H, Valli K. 2021. On no man's land: Subjective experiences during unresponsive and responsive sedative states induced by four different anesthetic agents. Conscious. Cogn. 96: 103239.

Rämä P, Relander-Syrjänen K, Öhman J, Laakso A, Näätänen R, Kujala T. 2010. Semantic processing in comatose patients with intact temporal lobes as reflected by the N400 event-related potential. Neurosci. Lett. 474: 88–92.

Ramaswamy SM, Kuizenga MH, Weerink MAS, Vereecke HEM, Struys MMRF, Nagaraj SB. 2019. Novel drug-independent sedation level estimation based on machine learning of quantitative frontal electroencephalogram features in healthy volunteers. Br. J. Anaesth. 123: 479–487.

Ramaswamy SM, Weerink MAS, Struys MMRF, Nagaraj SB. 2021. Dexmedetomidine-induced deep sedation mimics non-rapid eye movement stage 3 sleep: large-scale validation using machine learning. Sleep 44: zsaa167.

Rampil IJ. 1998. A primer for EEG signal processing in anesthesia. Anesthesiology 89: 980–1002.

Ranft A, Golkowski D, Kiel T, Riedl V, Kohl P, Rohrer G, Pientka J, Berger S, Thul A, Maurer M, Preibisch C, Zimmer C, Mashour GA, Kochs EF, Jordan D, Ilg R. 2016. Neural correlates of sevoflurane-induced unconsciousness identified by simultaneous functional magnetic resonance imaging and electroencephalography. Anesthesiology 125: 861–872.

Ranta SOV, Laurila R, Saario J, Ali-Melkkilä T, Hynynen M. 1998. Awareness with recall during general anesthesia: Incidence and risk factors. Anesth. Analg. 86: 1084–1089.

Raz A, Grady SM, Krause BM, Uhlrich DJ, Manning KA, Banks MI. 2014. Preferential effect of isoflurane on top-down vs. bottom-up pathways in sensory cortex. Front. Syst. Neurosci. 8: 191.

Real RGL, Kotchoubey B, Kübler A. 2014. Studentized continuous wavelet transform (t-CWT) in the analysis of individual ERPs: real and simulated EEG data. Front. Neurosci. 8: 279.

Redinbaugh MJ, Phillips JM, Kambi NA, Mohanta S, Andryk S, Dooley GL, Afrasiabi M, Raz A, Saalmann YB. 2020. Thalamus modulates consciousness via layer-specific control of cortex. Neuron 106: 66-75.e12.

Relander K, Rämä P, Kujala T. 2009. Word semantics is processed even without attentional effort. J. Cogn. Neurosci. 21: 1511–1522.

Revonsuo A, Portin R, Juottonen K, Rinne JO. 1998. Semantic processing of spoken words in Alzheimer's disease: an electrophysiological study. J. Cogn. Neurosci. 10: 408–420.

Revonsuo A. 2006. Inner presence: Consciousness as a biological phenomenon, 1e. MIT Press.

Revonsuo A, Kallio S, Sikka P. 2009. What is an altered state of consciousness? Philos. Psychol. 22: 187–204.

Rhodes SM, Donaldson DI. 2008. Association and not semantic relationships elicit the N400 effect: electrophysiological evidence from an explicit language comprehension task. Psychophysiology 45: 50–59.

Rohaut B, Faugeras F, Chausson N, King JR, Karoui IE, Cohen L, Naccache L. 2015. Probing ERP correlates of verbal semantic processing in patients with impaired consciousness. Neuropsychologia 66: 279–292.

Rokos A, Mah R, Boshra R, Harrison A, Choy TL, Blain-Moraes S, Connolly JF. 2021. Eliciting and recording event related potentials (ERPs) in behaviourally unresponsive populations: A retrospective commentary on critical factors. Brain Sci. 11: 835.

Rolke B, Heil M, Streb J, Hennighausen E. 2001. Missed prime words within the attentional blink evoke an N400 semantic priming effect. Psychophysiology 38: 165–174.

Ruby PM. 2020. The neural correlates of dreaming have not been identified yet. Commentary on "The neural correlates of dreaming. Nat Neurosci. 2017". Front. Neurosci. 14: 585470.

Ruby P, Eskinazi M, Bouet R, Rheims S, Peter-Derex L. 2021. Dynamics of hippocampus and orbitofrontal cortex activity during arousing reactions from sleep: An intracranial electroencephalographic study. Hum. Brain Mapp. 42: 5188–5203.

Russell IF. 1979. Auditory perception under anaesthesia. Anaesthesia 34: 211.

Russell IF, Wang M. 2001. Absence of memory for intra-operative information during surgery with total intravenous anaesthesia. Br. J. Anaesth. 86: 196–202.

Russell IF. 2006. The Narcotrend "depth of anaesthesia" monitor cannot reliably detect consciousness during general anaesthesia: An investigation using the isolated forearm technique. Br. J. Anaesth. 96: 346–352.

Russell IF. 2013. Fourteen fallacies about the isolated forearm technique, and its place in modern anaesthesia. Anaesthesia 68: 677–681.

Ryu J-H, Kim P-J, Kim H-G, Koo Y-S, Shin TJ. 2017. Investigating the effects of nitrous oxide sedation on frontal-parietal interactions. Neurosci. Lett. 651: 9–15.

Salmi E, Laitio RM, Aalto S, Maksimow AT, Långsjö JW, Kaisti KK, Aantaa R, Oikonen V, Metsähonkala L, Någren K, Korpi ER, Scheinin H. 2008. Xenon does not affect gamma-aminobutyric acid type A receptor binding in humans. Anesth. Analg. 106: 129–134.

Samuelsson P, Brudin L, Sandin RH. 2008a. Intraoperative dreams reported after general anaesthesia are not early interpretations of delayed awareness. Acta Anaesthesiol. Scand. 52: 805–809.

Samuelsson P, Brudin L, Sandin RH. 2008b. BIS does not predict dreams reported after anaesthesia. Acta Anaesthesiol. Scand. 52: 810–814.

Sanders RD, Tononi G, Laureys S, Sleigh JW. 2012. Unresponsiveness ≠ Unconsciousness. Anesthesiology 116: 946–959.

Sanders RD, Raz A, Banks MI, Boly M, Tononi G. 2016. Is consciousness fragile? Br. J. Anaesth. 116: 1–3.

Sanders RD, Gaskell A, Raz A, Winders J, Stevanovic A, Rossaint R, Boncyk C, Defresne A, Tran G, Tasbihgou S, Meier S, Vlisides PE, Fardous H, Hess A, Bauer RM, Absalom A, Mashour GA, Bonhomme V, Coburn M, Sleigh J. 2017. Incidence of connected consciousness after tracheal intubation: A prospective, international, multicenter cohort study of the isolated forearm technique. Anesthesiology 126: 214–222.

Sanders RD, Banks MI, Darracq M, Moran R, Sleigh J, Gosseries O, Bonhomme V, Brichant JF, Rosanova M, Raz A, Tononi G, Massimini M, Laureys S, Boly M. 2018. Propofol-induced unresponsiveness is associated with impaired feedforward connectivity in cortical hierarchy. Br. J. Anaesth. 121: 1084–1096.

Sanders RD, Casey C, Saalmann YB. 2021. Predictive coding as a model of sensory disconnection: relevance to anaesthetic mechanisms. Br. J. Anaesth. 126: 37–40.

Sandin RH, Enlund G, Samuelsson P, Lennmarken C. 2000. Awareness during anaesthesia: A prospective case study. Lancet 355: 707–711.

Sanz Perl Y, Pallavicini C, Pérez Ipiña I, Demertzi A, Bonhomme V, Martial C, Panda R, Annen J, Ibañez A, Kringelbach M, Deco G, Laufs H, Sitt J, Laureys S, Tagliazucchi E. 2021. Perturbations in dynamical models of whole-brain activity dissociate between the level and stability of consciousness. PLoS Comput. Biol. 17: e1009139.

Sarasso S, Boly M, Napolitani M, Gosseries O, Charland-Verville V, Casarotto S, Rosanova M, Casali AG, Brichant JF, Boveroux P, Rex S, Tononi G, Laureys S, Massimini M. 2015. Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine. Curr. Biol. 25: 3099–3105.

Sattin D, Duran D, Visintini S, Schiaffi E, Panzica F, Carozzi C, Rossi Sebastiano D, Visani E, Tobaldini E, Carandina A, Citterio V, Magnani FG, Cacciatore M, Orena E, Montano N, Caldiroli D, Franceschetti S, Picozzi M, Matilde L. 2021. Analyzing the loss and the recovery of consciousness: functional connectivity patterns and changes in heart rate variability during propofol-induced anesthesia. Front. Syst. Neurosci. 15: 652080.

Sauseng P, Klimesch W. 2008. What does phase information of oscillatory brain activity tell us about cognitive processes? Neurosci. Biobehav. Rev. 32: 1001–1013.

Scalici F, Caltagirone C, Carlesimo GA. 2017. The contribution of different prefrontal cortex regions to recollection and familiarity: a review of fMRI data. Neurosci. Biobehav. Rev. 83: 240–251.

Scarpelli S, D'Atri A, Gorgoni M, Ferrara M, De Gennaro L. 2015. EEG oscillations during sleep and dream recall: state- or trait-like individual differences? Front. Psychol. 6: 605.

Scheeringa R, Petersson KM, Kleinschmidt A, Jensen O, Bastiaansen MC m. 2012. EEG Alpha Power Modulation of fMRI Resting-State Connectivity. Brain Connect. 2: 254–264.

Scheinin H, Långsjö JW. 2013. Why does bispectral index monitoring not perform better? Anesthesiology 118: 1233–1234.

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

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. 2021. Foundations of human consciousness: Imaging the twilight zone. J. Neurosci. 41: 1769–1778.

Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, Fritz B, Eisenberg B, O'Connor J, Kobylarz EJ, Farris S, Machado A, McCagg C, Plum F, Fins JJ, Rezai AR. 2007. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 448: 600–603.

Schiff ND, Nauvel T, Victor JD. 2014. Large-scale brain dynamics in disorders of consciousness. Curr. Opin. Neurobiol. 25: 7–14.

Schmidt GN, Bischoff P, Standl T, Hellstern A, Teuber O, Schulte J. 2004. Comparative evaluation of the Datex-Ohmeda S/5 entropy module and the Bispectral Index® monitor during propofol-remifentanil anesthesia. Anesthesiology 101: 1283–1290.

Schnakers C, Perrin F, Schabus M, Majerus S, Ledoux D, Damas P, Boly M, Vanhaudenhuyse A, Bruno MA, Moonen G, Laureys S. 2008. Voluntary brain processing in disorders of consciousness. Neurology 71: 1614–1620.

Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, Moonen G, Laureys S. 2009. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol. 9: 35.

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

Schoenle PW, Witzke W. 2004. How vegetative is the vegetative state? Preserved semantic processing in VS patients – evidence from N 400 event-related potentials. NeuroRehabilitation 19: 329–334.

Schredl M, Atanasova D, Hörmann K, Maurer JT, Hummel T, Stuck BA. 2009. Information processing during sleep: The effect of olfactory stimuli on dream content and dream emotions. J. Sleep Res. 18: 285–290.

Schroeder KE, Irwin ZT, Gaidica M, Bentley JN, Patil PG, Mashour GA, Chestek CA. 2016. Disruption of corticocortical information transfer during ketamine anesthesia in the primate brain. Neuroimage 134: 459–465.

Schröter MS, Spoormaker VI, Schorer A, Wohlschläger A, Czisch M, Kochs EF, Zimmer C, Hemmer B, Schneider G, Jordan D, Ilg R. 2012. Spatiotemporal reconfiguration of large-scale brain functional networks during propofol-induced loss of consciousness. J. Neurosci. 32: 12832–40.

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

Sculthorpe-Petley L, Liu C, Hajra SG, Parvar H, Satel J, Trappenberg TP, Boshra R, D'Arcy RC. 2015. A rapid event-related potential (ERP) method for point-of-care evaluation of brain function: development of the Halifax Consciousness Scanner. J. Neurosci. Methods 245: 64–72.

Sebel PS, Bowdle TA, Ghoneim MM, Rampil IJ, Padilla RE, Gan TJ, Domino KB. 2004. The incidence of awareness during anesthesia: A multicenter United States study. Anesth. Analg. 99: 833–839.

Seeber M, Cantonas L-M, Hoevels M, Sesia T, Visser-Vandewalle V, Michel CM. 2019. Subcortical electrophysiological activity is detectable with high-density EEG source imaging. Nat. Commun. 10: 753.

Seel RT, Sherer M, Whyte J, Katz DI, Giacino JT, Rosenbaum AM, Hammond FM, Kalmar K, Pape TL-B, Zafonte R, Biester RC, Kaelin D, Kean J, Zasler N, for American Congress of Rehabilitation Medicine Brain Injury-Interdisciplinary Special Interest Group Disorders of Consciousness Task Force. 2010. Assessment scales for disorders of consciousness: Evidence-based recommendations for clinical practice and research. Arch. Phys. Med. Rehabil. 91: 1795–1813.

Seth AK, Bayne T. 2022. Theories of consciousness. Nat. Rev. Neurosci. 23: 439–452.

Seubert CN, Herman M. 2017. Auditory-evoked potentials. In: Koht A, Sloan TB, Toleikis JR, editors. Monitoring the Nervous System for Anesthesiologists and Other Health Care Professionals, 2e. Cham, Switzerland: Springer International Publishing, p 35–49.

Shao YR, Kahali P, Houle TT, Deng H, Colvin C, Dickerson BC, Brown EN, Purdon PL. 2020. Low frontal alpha power is associated with the propensity for burst suppression: An electroencephalogram phenotype for a "vulnerable brain." Anesth. Analg. 131: 1529–1539.

Siclari F, Baird B, Perogamvros L, Bernardi G, LaRocque JJ, Riedner B, Boly M, Postle BR, Tononi G. 2017. The neural correlates of dreaming. Nat. Neurosci. 20: 872–878.
Siclari F, Bernardi G, Cataldi J, Tononi G. 2018. Dreaming in NREM sleep: A high-density EEG study of slow waves and spindles. J. Neurosci. 38: 9175–9185.
Signorelli CM, Szczotka J, Prentner R. 2021. Explanatory profiles of models of consciousness - towards a systematic classification. Neurosci. Conscious. 2021: niab021.
Sikka P, Valli K, Virta T, Revonsuo A. 2014. I know how you felt last night, or do I? Self- and external ratings of emotions in REM sleep dreams. Conscious. Cogn. 25: 51–66.
Sikka P, Revonsuo A, Sandman N, Tuominen J, Valli K. 2018. Dream emotions: a comparison of home dream reports with laboratory early and late REM dream reports. J. Sleep Res. 27: 206–214.
Sikka P, Valli K, Revonsuo A, Tuominen J. 2021. The dynamics of affect across the wake-sleep cycle: From waking mind-wandering to night-time dreaming. Conscious. Cogn. 94: 103189.
Simpson TP, Manara AR, Kane NM, Barton RL, Rowlands CA, Butler SR. 2002. Effect of propofol anaesthesia on the event-related potential mismatch negativity and the auditory-evoked potential N1. Br. J. Anaesth. 89: 382–388.
Sleigh JW, Scheib CM, Sanders RD. 2011. General anaesthesia and electroencephalographic spindles. Trends Anaesth. Crit. Care 1: 263–269.
Sleigh J. 2013. The place of the isolated forearm technique in modern anaesthesia: Yet to be defined. Anaesthesia 68: 681–683.
Sleigh JW, Vacas S, Flexman AM, Talke PO. 2018. Electroencephalographic arousal patterns under dexmedetomidine sedation. Anesth. Analg. 127: 951–959.
Smith WD, Dutton RC, Smith NT. 1996a. Measuring the performance of anesthetic depth indicators. Anesthesiology 84: 38–51.
Smith WD, Dutton RC, Smith NT. 1996b. A measure of association for assessing prediction accuracy that is a generalization of non-parametric ROC area. Stat. Med. 15: 1199–215.
Sokoliuk R, Degano G, Banellis L, Melloni L, Hayton T, Sturman S, Veenith T, Yakoub KM, Belli A, Noppeney U, Cruse D. 2021a. Covert speech comprehension predicts recovery from acute unresponsive states. Ann. Neurol. 89: 646–656.
Sokoliuk R, Degano G, Melloni L, Noppeney U, Cruse D. 2021b. The influence of auditory attention on rhythmic speech tracking: Implications for studies of unresponsive patients. Front. Hum. Neurosci. 15: 702768.
Spoormaker VI, Schröter MS, Gleiser PM, Andrade KC, Dresler M, Wehrle R, Sämann PG, Czisch M. 2010. Development of a large-scale functional brain network during human non-rapid eye movement sleep. J. Neurosci. 30: 11379–11387.
Srinivasan R, Winter WR, Ding J, Nunez PL. 2007. EEG and MEG coherence: Measures of functional connectivity at distinct spatial scales of neocortical dynamics. J. Neurosci. Methods 166: 41–52.
Stam CJ, Nolte G, Daffertshofer A. 2007. Phase lag index: Assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum. Brain Mapp. 28: 1178–1193.
Stam CJ, van Straaten ECW. 2012. Go with the flow: Use of a directed phase lag index (dPLI) to characterize patterns of phase relations in a large-scale model of brain dynamics. Neuroimage 62: 1415–1428.
Stender J, Gosseries O, Bruno MA, Charland-Verville V, Vanhaudenhuyse A, Demertzi A, Chatelle C, Thonnard M, Thibaut A, Heine L, Soddu A, Boly M, Schnakers C, Gjedde A, Laureys S. 2014. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: A clinical validation study. Lancet 384: 514–522.
Steppacher I, Eickhoff S, Jordanov T, Kaps M, Witzke W, Kissler J. 2013. N400 predicts recovery from disorders of consciousness. Ann. Neurol. 73: 594–602.
Stickgold R, Malia A, Fosse R, Hobson JA. 2001. Brain-mind states: I. Longitudinal field study of sleep/wake factors influencing mentation report length. Sleep 24: 171–179.

Stonell CA, Leslie K, He C, Lee L. 2006. No sex differences in memory formation during general anesthesia. Anesthesiol. J. Am. Soc. Anesthesiol. 105: 920–926.

Storm JF, Boly M, Casali AG, Massimini M, Olcese U, Pennartz CMA, Wilke M. 2017. Consciousness regained: disentangling mechanisms, brain systems, and behavioral responses. J. Neurosci. 37: 10882–10893.

Strauss M, Dehaene S. 2019. Detection of arithmetic violations during sleep. Sleep 42: zsy232.

Struys MMRF, Jensen EW, Smith W, Smith NT, Rampil I, Dumortier FJE, Mestach C, Mortier EP. 2002. Performance of the ARX-derived auditory evoked potential index as an indicator of anesthetic depth: A comparison with Bispectral Index and hemodynamic measures during propofol administration. Anesthesiology 96: 803–816.

Sumner M, Deng C, Evered L, Frampton C, Leslie K, Short T, Campbell D. 2022. Processed electroencephalography-guided general anaesthesia to reduce postoperative delirium: a systematic review and meta-analysis. Br. J. Anaesth.

Supp GG, Siegel M, Hipp JF, Engel AK. 2011. Cortical hypersynchrony predicts breakdown of sensory processing during loss of consciousness. Curr. Biol. 21: 1988–1993.

Sury MRJ, Palmer JHMG, Cook TM, Pandit JJ. 2014. The state of UK anaesthesia: a survey of National Health Service activity in 2013. Br. J. Anaesth. 113: 575–584.

Suzuki M, Larkum ME. 2020. General anesthesia decouples cortical pyramidal neurons. Cell 180: 666-676.e13.

Tagliazucchi E, Von Wegner F, Morzelewski A, Brodbeck V, Jahnke K, Laufs H. 2013. Breakdown of long-range temporal dependence in default mode and attention networks during deep sleep. Proc. Natl. Acad. Sci. U. S. A. 110: 15419–15424.

Tagliazucchi E, Laufs H. 2015. Multimodal imaging of dynamic functional connectivity. Front. Neurol. 6: 10.

Talke P, Lobo E, Brown R. 2003. Systemically administered α2-agonist-induced peripheral vasoconstriction in humans. J. Am. Soc. Anesthesiol. 99: 65–70.

Talmi D. 2013. Enhanced emotional memory. Curr. Dir. Psychol. Sci. 22: 430–436.

Tart CT. 1972. States of consciousness and state-specific sciences. Science 176: 1203–10.

Tavakoli P, Muller-Gass A, Campbell K. 2015. Partial sleep deprivation does not alter processes involved in semantic word priming: Event-related potential evidence. Brain Cogn. 94: 17–23.

Telenczuk B, Nikulin V V., Curio G. 2010. Role of neuronal synchrony in the generation of evoked eeg/MEG responses. J. Neurophysiol. 104: 3557–3567.

Thibaut A, Bruno MA, Ledoux D, Demertzi A, Laureys S. 2014. TDCS in patients with disorders of consciousness: Sham-controlled randomized double-blind study. Neurology 82: 1112–1118.

Thibaut A, Wannez S, Donneau AF, Chatelle C, Gosseries O, Bruno MA, Laureys S. 2017. Controlled clinical trial of repeated prefrontal tDCS in patients with chronic minimally conscious state. Brain Inj. 31: 466–474.

Thornhill DE, Van Petten C. 2012. Lexical versus conceptual anticipation during sentence processing: frontal positivity and N400 ERP components. Int. J. Psychophysiol. 83: 382–392.

Toker D, Pappas I, Lendner JD, Frohlich J, Mateos DM, Muthukumaraswamy S, Carhart-Harris R, Paff M, Vespa PM, Monti MM, Sommer FT, Knight RT, D'Esposito M. 2022. Consciousness is supported by near-critical slow cortical electrodynamics. Proc. Natl. Acad. Sci. U. S. A. 119.

Tononi G. 2004. An information integration theory of consciousness. BMC Neurosci. 5: 42.

Tononi G, Koch C. 2008. The neural correlates of consciousness: An update. Ann. N. Y. Acad. Sci. 1124: 239–261.

Tononi G, Boly M, Massimini M, Koch C. 2016. Integrated information theory: From consciousness to its physical substrate. Nat. Rev. Neurosci. 17: 450–461.

Trainor LJ. 2007. Event-related potential (ERP) measures in auditory development research. In: Schmidt L, Segalowitz S, editors. Developmental Psychophysiology: Theory, Systems, and Methods. Cambridge, UK: Cambridge University Press, p 69–102.

Troyer M, Kutas M. 2020. Harry Potter and the Chamber of What?: The impact of what individuals know on word processing during reading. Lang. Cogn. Neurosci. 35: 641–657.
Tunstall ME. 1977. Detecting wakefulness during general anaesthesia for caesarean section. Br. Med. J. 1: 1321.
Tzovara A, Simonin A, Oddo M, Rossetti AO, De Lucia M. 2015. Neural detection of complex sound sequences in the absence of consciousness. Brain 138: 1160–1166.
Uhrig L, Janssen D, Dehaene S, Jarraya B. 2016. Cerebral responses to local and global auditory novelty under general anesthesia. Neuroimage 141: 326–340.
Uhrig L, Sitt JD, Jacob A, Tasserie J, Barttfeld P, Dupont M, Dehaene S, Jarraya B. 2018. Resting-state dynamics as a cortical signature of anesthesia in monkeys. Anesthesiology 129: 942–958.
Untergehrer G, Jordan D, Kochs EF, Ilg R, Schneider G. 2014. Fronto-parietal connectivity is a non-static phenomenon with characteristic changes during unconsciousness. PLoS One 9: e87498.
Vaitl D, Gruzelier J, Jamieson GA, Lehmann D, Ott U, Sammer G, Strehl U, Birbaumer N, Kotchoubey B, Kübler A, Miltner WHR, Pütz P, Strauch I, Wackermann J, Weiss T. 2005. Psychobiology of altered states of consciousness. Psychol. Bull. 131: 98–127.
Vakkuri A, Yli-Hankala A, Talja P, Mustola S, Tolvanen-Laakso H, Sampson T, Viertiö-Oja H. 2004. Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. Acta Anaesthesiol. Scand. 48: 145–153.
Vallat R, Nicolas A, Ruby P. 2020. Brain functional connectivity upon awakening from sleep predicts interindividual differences in dream recall frequency. Sleep 43: zsaa116.
Valli K, Radek L, Kallionpää RE, Scheinin A, Långsjö J, Kaisti K, Kantonen O, Korhonen J, Vahlberg T, Revonsuo A, Scheinin H. Subjective experiences during anaesthetic–induced unresponsiveness and non-rapid eye movement sleep in healthy male subjects. Submitted.
van Berkum JJ, Hagoort P, Brown CM. 1999. Semantic integration in sentences and discourse: evidence from the N400. J. Cogn. Neurosci. 11: 657–671.
van den Brink RL, Nieuwenhuis S, van Boxtel GJM, van Luijtelaar G, Eilander HJ, Wijnen VJM. 2018. Task-free spectral EEG dynamics track and predict patient recovery from severe acquired brain injury. NeuroImage Clin. 17: 43–52.
van Erp WS, Lavrijsen JCM, Vos PE, Bor H, Laureys S, Koopmans RTCM. 2015. The vegetative state: prevalence, misdiagnosis, and treatment limitations. J. Am. Med. Dir. Assoc. 16: 85.e9-85.e14.
van Petten C, Rheinfelder H. 1995. Conceptual relationships between spoken words and environmental sounds: Event-related brain potential measures. Neuropsychologia 33: 485–508.
Van Petten C, Kutas M, Kluender R, Mitchiner M, McIsaac H. 1991. Fractionating the word repetition effect with event-related potentials. J. Cogn. Neurosci. 3: 131–150.
Van Petten C, Luka BJ. 2006. Neural localization of semantic context effects in electromagnetic and hemodynamic studies. Brain Lang. 97: 279–293.
van Vliet M, Manyakov N V., Storms G, Fias W, Wiersema JR, Van Hulle MM. 2014. Response-related potentials during semantic priming: the effect of a speeded button response task on ERPs. PLoS One 9: e87650.
Veselis RA, Reinsel RA, Wronski M, Marino P, Tong WP, Bedford RF. 1992. EEG and memory effects of low-dose infusions of propofol. Br. J. Anaesth. 69: 246–254.
Veselis RA, Reinsel RA, Feshchenko VA, Wronski M. 1997. The comparative amnestic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations. Anesthesiology 87: 749–764.
Veselis RA, Reinsel RA, Feshchenko VA, Johnson R. 2004. Information loss over time defines the memory defect of propofol: a comparative response with thiopental and dexmedetomidine. Anesthesiology 101: 831–841.
Veselis RA, Pryor KO, Reinsel RA, Mehta M, Pan H, Johnson R. 2008. Low-dose propofol-induced amnesia is not due to a failure of encoding: Left inferior prefrontal cortex is still active. Anesthesiology 109: 213–224.

Veselis RA, Pryor KO, Reinsel RA, Li Y, Mehta M, Johnson R. 2009. Propofol and midazolam inhibit conscious memory processes very soon after encoding: An event-related potential study of familiarity and recollection in volunteers. Anesthesiology 110: 295–312.

Vijayan S, Kopell NJ. 2012. Thalamic model of awake alpha oscillations and implications for stimulus processing. Proc. Natl. Acad. Sci. U. S. A. 109: 18553–18558.

Vijayan S, Ching S, Purdon PL, Brown EN, Kopell NJ. 2013. Thalamocortical mechanisms for the anteriorization of alpha rhythms during propofol-induced unconsciousness. J. Neurosci. 33: 11070–11075.

Vinck M, Oostenveld R, Van Wingerden M, Battaglia F, Pennartz CMA. 2011. An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. Neuroimage 55: 1548–1565.

Vlisides PE, Bel-Bahar T, Lee U, Li D, Kim H, Janke E, Tarnal V, Pichurko AB, McKinney AM, Kunkler BS, Picton P, Mashour GA. 2017. Neurophysiologic correlates of ketamine sedation and anesthesia: A high-density electroencephalography study in healthy volunteers. Anesthesiology 127: 58–69.

Vlisides PE, Li D, Zierau M, Lapointe AP, Ip KI, McKinney AM, Mashour GA. 2019. Dynamic cortical connectivity during general anesthesia in surgical patients. Anesthesiology 130: 885–897.

Voss JL, Paller KA. 2006. Fluent conceptual processing and explicit memory for faces are electrophysiologically distinct. J. Neurosci. 26: 926–933.

Wais PE, Wixted JT, Hopkins RO, Squire LR. 2006. The hippocampus supports both the recollection and the familiarity components of recognition memory. Neuron 49: 459–466.

Walker EMK, Bell M, Cook TM, Grocott MPW, Moonesinghe SR, Central SNAP-1 Organisation, National Study Groups. 2016. Patient reported outcome of adult perioperative anaesthesia in the United Kingdom: a cross-sectional observational study. Br. J. Anaesth. 117: 758–766.

Walter J. 2021. Consciousness as a multidimensional phenomenon: implications for the assessment of disorders of consciousness. Neurosci. Conscious. 2021: niab047.

Wang M, Messina AG, Russell IF. 2012. The topography of awareness: a classification of intra-operative cognitive states. Anaesthesia 67: 1197–1201.

Wang H, Zhang Y, Cheng H, Yan F, Song D, Wang Q, Cai S, Wang Y, Huang L. 2022. Selective corticocortical connectivity suppression during propofol-induced anesthesia in healthy volunteers. Cogn. Neurodyn. 16: 1029–1043.

Wannez S, Heine L, Thonnard M, Gosseries O, Laureys S, Coma Science Group collaborators. 2017. The repetition of behavioral assessments in diagnosis of disorders of consciousness. Ann. Neurol. 81: 883–889.

Ward LM. 2011. The thalamic dynamic core theory of conscious experience. Conscious. Cogn. 20: 464–486.

Warnaby CE, Seretny M, Ní Mhuircheartaigh R, Rogers R, Jbabdi S, Sleigh J, Tracey I. 2016. Anesthesia-induced suppression of human dorsal anterior insula responsivity at loss of volitional behavioral response. Anesthesiology 124: 766–778.

Warnaby CE, Sleigh JW, Hight D, Jbabdi S, Tracey I. 2017. Investigation of slow-wave activity saturation during surgical anesthesia reveals a signature of neural inertia in humans. Anesthesiology 127: 645–657.

Waterman D, Elton M, Kenemans J. 1993. Methodological issues affecting the collection of dreams. J. Sleep Res. 2: 8–12.

Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. 2017. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin. Pharmacokinet. 56: 893–913.

Weimer NR, Clark SL, Freitas AL. 2019. Distinct neural responses to social and semantic violations: An N400 study. Int. J. Psychophysiol. 137: 72–81.

Wennervirta J, Ranta SOV, Hynynen M. 2002. Awareness and recall in outpatient anesthesia. Anesth. Analg. 95: 72–77.

Whitlock EL, Rodebaugh TL, Hassett AL, Shanks AM, Kolarik E, Houghtby J, West HM, Burnside BA, Shumaker E, Villafranca A, Edwards WA, Levinson CA, Langer JK, Fernandez KC, El-Gabalawy R, Zhou EY, Sareen J, Jacobsohn E, Mashour GA, Avidan MS. 2015. Psychological sequelae of surgery in a prospective cohort of patients from three intraoperative awareness prevention trials. Anesth. Analg. 120: 87–95.

Wickens TD. 2002. Elementary signal detection theory, 1e. New York, NY, USA: Oxford University Press.

Wilf M, Ramot M, Furman-Haran E, Arzi A, Levkovitz Y, Malach R. 2016. Diminished auditory responses during NREM sleep correlate with the hierarchy of language processing. PLoS One 11: e0157143.

Windt JM, Nielsen T, Thompson E. 2016. Does consciousness disappear in dreamless sleep? Trends Cogn. Sci. 20: 871–882.

Winter WR, Nunez PL, Ding J, Srinivasan R. 2007. Comparison of the effect of volume conduction on EEG coherence with the effect of field spread on MEG coherence. Stat. Med. 26: 3946–3957.

Wong W, Noreika V, Móró L, Revonsuo A, Windt J, Valli K, Tsuchiya N. 2020. The Dream Catcher experiment: blinded analyses failed to detect markers of dreaming consciousness in EEG spectral power. Neurosci. Conscious. 2020: niaa006.

Xi C, Sun S, Pan C, Ji F, Cui X, Li T. 2018. Different effects of propofol and dexmedetomidine sedation on electroencephalogram patterns: Wakefulness, moderate sedation, deep sedation and recovery. PLoS One 13: e0199120.

Xu L, Wu A-S, Yue Y. 2009. The incidence of intra-operative awareness during general anesthesia in China: a multi-center observational study. Acta Anaesthesiol. Scand. 53: 873–882.

Xu M, Jia Y, Qi H, Hu Y, He F, Zhao X, Zhou P, Zhang L, Wan B, Gao W, Ming D. 2016. Use of a steady-state baseline to address evoked vs. oscillation models of visual evoked potential origin. Neuroimage 134: 204–212.

Yli-Hankala A, Scheinin H. 2015. Voiko anestesian syvyyttä mitata aivosähkökäyrällä? Duodecim. 131: 1929–1936.

Yoshida A, Fujii K, Yoshikawa T, Kawamata T. 2021. Factors associated with quality of dreams during general anesthesia: a prospective observational study. J. Anesth. 35: 576–580.

Yppärilä H, Karhu J, Westerén-Punnonen S, Musialowicz T, Partanen J. 2002. Evidence of auditory processing during postoperative propofol sedation. Clin. Neurophysiol. 113: 1357–1364.

Yppärilä H, Korhonen I, Tarvainen M, Musialowicz T, Jakob SM, Partanen J. 2004a. N100 auditory potential and electroencephalogram discriminate propofol-induced sedation levels. J. Clin. Monit. Comput. 18: 163–170.

Yppärilä H, Nunes S, Korhonen I, Partanen J, Ruokonen E. 2004b. The effect of interruption to propofol sedation on auditory event-related potentials and electroencephalogram in intensive care patients. Crit. Care 8: R483-90.

Zadra A, Robert G. 2012. Dream recall frequency: impact of prospective measures and motivational factors. Conscious. Cogn. 21: 1695–1702.

Zasler ND, Aloisi M, Contrada M, Formisano R. 2019. Disorders of consciousness terminology: history, evolution and future directions. Brain Inj. 33: 1684–1689.

Zhang J, Wamsley EJ. 2019. EEG predictors of dreaming outside of REM sleep. Psychophysiology 56: e13368.

Zhu Z, Bastiaansen M, Hakun JG, Petersson KM, Wang S, Hagoort P. 2019. Semantic unification modulates N400 and BOLD signal change in the brain: A simultaneous EEG-fMRI study. J. Neurolinguistics 52: 100855.

Zierau M, Li D, Lapointe AP, Ip KI, McKinney AM, Thompson A, Puglia MP, Vlisides PE. 2021. Cortical oscillations and connectivity during postoperative recovery. J. Neurosurg. Anesthesiol. 33: 87–91.

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2023

ISBN 978-951-29-9215-7 (PRINT)
ISBN 978-951-29-9216-4 (PDF)
ISSN 0082-6987 (Print)
ISSN 2343-3191 (Online)