Validation of Measures of Consciousness Using Propofol Anesthesia

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Abstract

Title: Validation of Measures of Consciousness Using Propofol Anesthesia

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Author statement: This thesis was an independent research project. Idea and design were developed in collaboration with Johan Storm and several members of his group. Hypothesis development, data collection, processing and analysis was done by the author.

Summary:

One of the biggest challenges in the field of consciousness research today is to find a reliable objective measure. The currently most promising measures are perturbational complexity index (PCI), Lempel-Ziv complexity (LZC), amplitude coalition entropy (ACE) and synchrony coalition entropy (SCE). However, all these measures were tested on states where unconsciousness was merely assumed. The current thesis sought to investigate these measures by applying them to data from awake and anesthetized states, while controlling for experiences in unresponsive states. For this we collected electroencephalographic (EEG) data with applied transcranial magnetic stimulation (TMS) from participants while they were awake and under anesthesia. Importantly, participants were woken up intermittently, in order to additional experience reports. In nearly 70% of the awakenings participants reported having dreams. Additionally, results showed a significant difference between measures for awake and anesthetized states, albeit for LZC, ACE and SCE only under eyes open condition during awake state. Further, LZC, ACE and SCE correlated with the vividness of reports given by subjects, while PCI^{ST} did not. While our results indicate that current measures of consciousness can distinguish between awake and non-responsive states, it is not clear whether this truly reflects unconsciousness or what part of consciousness these measures reflect.

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1. Introduction

Consciousness is commonly seen as being the subjective experience of an agent. The phenomenon itself has always fascinated scholars, since the times of the ancient Greeks, over 2000 years ago. Arguably, because it is so inherent to human nature, defining our whole experience and long thought to only be found in humans. Today it becomes more and more apparent that humans might not be the only species that experiences at least some kind of consciousness (Storm et al., 2017; Tononi & Koch, 2015).

However, although the importance and relevance of consciousness to the human species is unquestionable, the scientific study of the phenomenon only recently became recognized. Because of its subjective nature, research on consciousness has long been condemned and not taken seriously. Especially, considering how during the 20th Century, the time of behaviorism, subjectivity was shunned in the field of psychology. In fact, trying to follow a scientific career on the study of consciousness was equal to a career suicide, until about 30 years ago. In 1990 Francis Crick and Christoph Koch rediscovered the field with their paper "Towards a neurobiological theory of consciousness". Since then, research on consciousness has seen a steep increase in publications each year, in addition to the emergence of consciousness-specific conferences (e.g. by the Association for the Scientific Study of Consciousness). Furthermore, the questions of what consciousness is and how it emerges have been dubbed "the ultimate intellectual challenge of this new millennium" (Dehaene & Changeux, 2004).

1.1 Consciousness

But what exactly is consciousness? Since Crick and Koch (1990) published their paper several theories have emerged claiming to explain what consciousness is and how it emerges from brain activity. While these theories come to different conclusions as to how consciousness emerges there is a general consensus that consciousness itself can be described as being any kind of subjective experience (e.g. LeDoux et al., 2020; Oizumi et al., 2014; Storm et al., 2017). Importantly, this follows that a person can not only be considered conscious while being awake, but also during various other states. For example, during dreaming or in a so-called locked in syndrome. This is a disorder of consciousness where patients are fully aware of their own thoughts and surroundings while having no means of communicating themselves to the outside world (see Owen, 2008 for more information on disorders of consciousness).

The phenomenon of consciousness is classically separated into two distinct aspects: the content of consciousness (also referred to as local state of consciousness) and the level or global state of consciousness (Laureys, 2005). Conscious content refers to the actual percept or the features of the experience, for example the bodily and visual sensations and the thoughts associated with a specific experience. In contrast, conscious states address the cognitive and behavioral abilities that an agent is capable of at a given moment. These two aspects are in close relationship to each other, depicted in Figure 1. However, it has been argued that conscious states should not be thought of as moving only along one dimension, but rather as a multi-dimensional construct (Bayne et al., 2016).

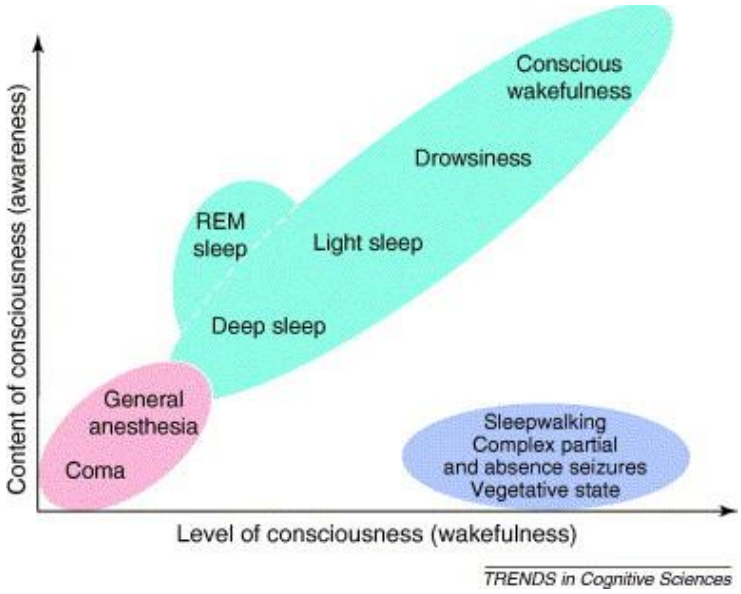


Figure 1: **Classical representation of Conscious content and Conscious state**. *Reprinted from "The neural correlate of (un)awareness: lessons from the vegetative state ", by Steven Laureys (2005). Copyright © 2005 Elsevier Ltd.*

One prominent theory that tries to explain consciousness is the Integrated Information Theory (IIT; Oizumi et al., 2014; Tononi et al., 2016), mainly developed by Giulio Tononi. The IIT postulates that there are several axioms that are true of every conscious system. It claims that consciousness arises from the integration of information in a system. In terms of brain activation this integration can be thought of as some initial activity (e.g. some sensory input) that gets spread throughout different brain regions in a diverse manner. Importantly, this activation does not need to arise from external stimuli, but can be generated by the system, giving it cause-effect power upon itself (i.e. the system itself can be the cause for an effect that changes the systems state; Albantakis and Tononi 2015). In the framework of the IIT this integration of information can be quantified using a measure called Φ (Greek letter Phi). Φ can, according to theory, give an indication of how conscious a system is in a particular state, as well as why conscious content feels the way it does (Haun & Tononi, 2019). While the theory is certainly not perfect (e.g. see Cerullo 2015 for critique), it has directly led to the development of the currently most promising measures of consciousness (Casali et al., 2013; Schartner, 2017).

1.2 Measuring Consciousness

One of the biggest challenges of the science of consciousness today, is the question of measurement. As the famous philosopher René Descarte already noted, "I think, therefore I am" (Wohlers & Descartes, 2009), this follows that the only thing that I can be certain of is, that I am conscious. However, how do I know that others around me are conscious?

In the past one could only rely on behavioral signs to determine that someone else is conscious. But does that really suffice? It is quite possible to imagine a fully functioning human being, showing every sign of behavior, while having no conscious experience at all. Every movement, every behavioral output is just an automatic deterministic reaction. In the field of philosophy this idea is referred to as a "Zombie" (Kirk, 2006). However, even if one disregards the possibility of these "zombies" (see Dennett 1995 for an argument against their existence) certain problems arise without a reliable objective measure of consciousness, especially in the medical profession.

Every year millions of people undergo surgery in hospitals around the world, during which many receive general anesthesia, putting them into a seemingly unconscious state (WHO, n.d.). Even with an anesthesiologist present to monitor the depth of the anesthesia, several patients a year report some form of awareness during the procedure (Sandin et al., 2000). Experiences range from having some vague dreams to being fully aware of the operation going on while feeling imprisoned in their own body, without being able to move. The latter being called connected consciousness as the experiences are connected to out of body stimuli (Sanders et al., 2012, 2016). The magnitude of these instances is still being debated, with some sources speaking of 1 to 2 cases in 1000 (Gropper, 2019; Sebel et al., 2004), and others speaking of 9 in 1000 patients (Lewis et al., 2019). These numbers may seem small (0,01% at the most), however, there is evidence from studies using the isolated forearm technique[1] suggesting that between 4,7% and 37% of all patients experience connected consciousness during anesthesia (Sanders et al., 2017). The low instances of recall are explained by the amnesic effects of the drugs. In the last decades, several methods for assessing depth of anesthesia have emerged, with the bispectral index (BIS) being the most prominent method,

[1] The isolated forearm technique is a way to assess awareness under the influence of anesthesia. Before start of the anesthetic procedure the blood-flow of a patient's arm is restraint, so that anesthetics and muscle relaxants will not affect the arm. Thus, a doctor can ask the patient to squeeze their hand if they experience awareness of the environment.

relying on electroencephalographic (EEG) activity (Medical Advisory Secretariat, 2004). In short, BIS measures brain activity through two electrodes placed on the forehead. It then converts the measured activity to a score between 0 and 100, allegedly indicating the depth of anesthesia. However, meta studies suggest that BIS has little to no effect on being able to detect awareness (i.e. connected consciousness) during general anesthesia (Lewis et al., 2019).

Another area where measuring consciousness is of utmost importance is during the assessment of patients with disorders of consciousness. Based on the clinician's judgement relatives might decide to turn off life supporting machines, effectively ending the patient's life. However, can one really be sure, based on traditional behavioral assessment like the Glasgow Coma Scale (Teasdale & Jennett, 1974), that a comatose patient has no awareness? A state characterized by complete absence of arousal, meaning patients do not show any signs of response beyond reflexes after stimulation (Laureys et al., 2004). Owen et al. (2006) showed that this is not the case. They asked a patient to imagine either playing tennis or walking through multiple rooms in her home, during which they measured her brain activity through fMRI. However, this patient had been diagnosed as being in a vegetative state. This state is defined by cycles of eyes opening and closure, giving the impression of sleep/wake cycles, however no signs of voluntary behavior is observed (Owen, 2008). Despite this condition recordings of said patient resulted in brain activation patterns that were indistinguishable from healthy subjects doing the same task. They concluded that this patient, despite being diagnosed as vegetative, had awareness of her surroundings and could voluntarily follow verbal commands.

However, fMRI is a is an expensive and time-consuming method, which in many situations is not feasible and often not available on site. EEG on the other hand is relatively cheap, easy and mobile in its use, which results in a high motivation to find a reliable objective measure for consciousness based on EEG activity. In the last two decades measures have emerged showing some form of success when it comes to distinguishing between conscious and unconscious states. The most promising all reflect some sort of signal diversity in the recorded brain signals (e.g. Casali et al., 2013; Comolatti et al., 2019; Sarasso et al., 2015; M. Schartner et al., 2015). The basic assumption, in line with the IIT, for all these measures is that a system needs to be both integrated and differentiated at the same time in order for consciousness to arise (Oizumi et al., 2014). Some of these measures use complexity, perturbational complexity index (PCI) and Lempel-Ziv complexity (LZC), as a proxy to capture signal diversity. While others use information entropy, amplitude coalition entropy

(ACE) and synchrony coalition entropy (SCE), to capture the amount of information inherit to a signal.

1.2.1 Perturbational Complexity Index

Developed by Casali et al. (2013) the perturbational complexity index(PCI) seems to be the most promising measure for conscious states. It has been reliably shown that PCI can distinguish between awake and anesthetized states of consciousness (Casali et al., 2013; Sarasso et al., 2015) and classify unresponsive patients into different states (Casarotto et al., 2016; Sarasso et al., 2014). In its original form PCI utilizes transcranial magnetic stimulation (TMS) to activate/perturb one part of the brain and then looking at how this perturbation spreads throughout the cortex via EEG and source reconstruction. One can think of it as a sonar to assess the instantaneous connectivity of the brain. Through this, one can assess at the same time how integrated (to which parts of the brain the activation spreads) and how differentiated (in what manner the activation spreads over time) the brain is in a given state. Figure 2 shows a schematic representation of how activation would spread in systems of different complexity and Figure 3 shows actual EEG recorded brain response to perturbation via TMS in two distinct brain states.

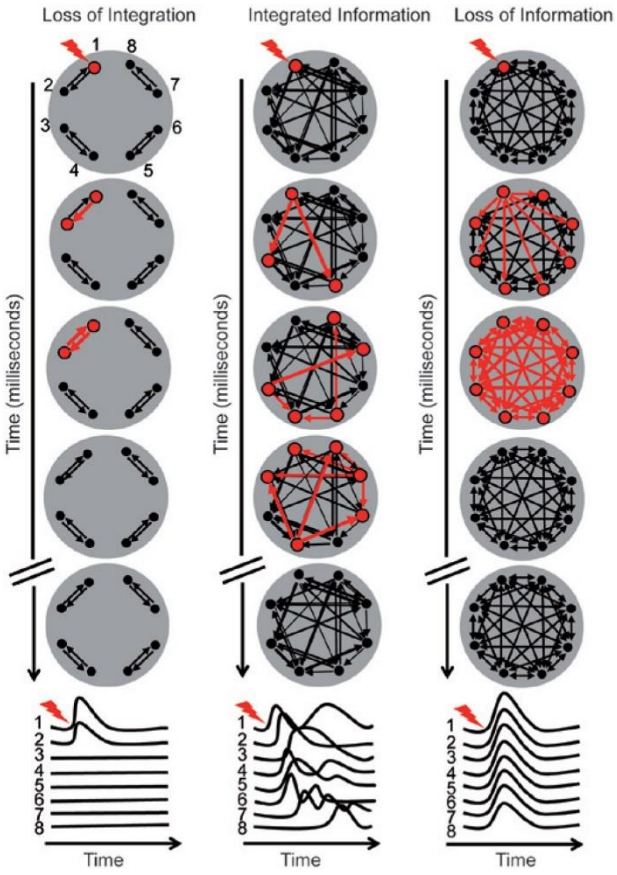


Figure 2: **Schematic representation of differently integrated systems**. Activation of one node of the system only results in local activity around the activation if a system is not integrated (left); If the system is not differentiated the same activation spreads through the whole system in an equal manner (right); Is the system both integrated and differentiated activation spreads in a complex manner throughout the system (middle); (Bottom row) abstraction of EEG response to activation of the different systems. *Reprinted from "Quantifying Cortical EEG Responses to TMS in (Un)Consciousness",* by Simone Sarasso et al. (2014). *Copyright © 2014, © SAGE Publications*

However, especially due to its utilization of source reconstruction PCI is computationally very heavy. Instead one can utilize the more recently developed PCIST (where

ST = state transition), which has been shown to result in comparable outcomes and is about 380 times faster than PCI (Comolatti et al., 2019). As the name suggests, this version of PCI utilizes so called state transitions along the time dimension to capture the complexity of a TMS evoked potential. These state transitions can be roughly understood as amplitude fluctuations between time points (see below, Section 2.5.1, for a more detailed explanation). Importantly, these amplitude fluctuations are not explored on the EEG signal itself, but on components obtained through dimensionality reduction (i.e. principal component analysis). These components are more likely to reflect the underlying brain signal of the EEG recording.

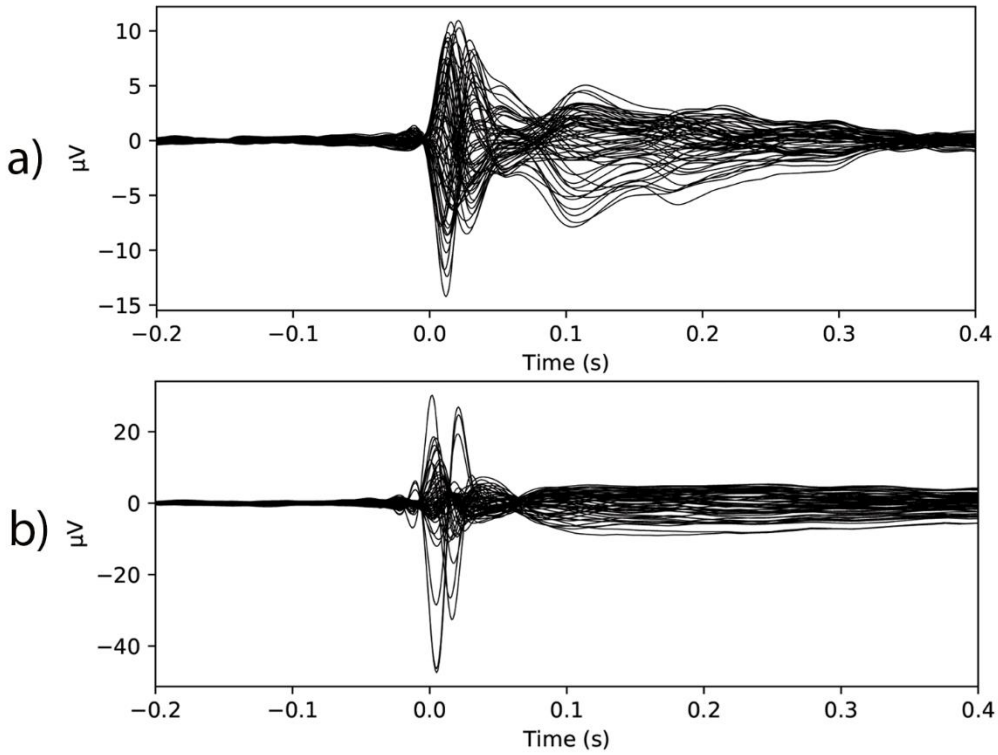


Figure 3: **TMS evoked potentials during wakeful state (a) and under anesthesia (b)**

1.2.2 Lempel-Ziv-Complexity

In search of a measure that circumvents the drawbacks utilizing TMS during recording Schartner (2017) applied three methods that can be used on relatively short recordings of continuous EEG data. One of these measures is Lempel-Ziv-Complexity (LZC). As the name suggests, it is based on an algorithm by A. Lempel and J. Ziv, which is usually used to compress data of binary strings (i.e. to format data into a .zip format on normal computers) (Lempel & Ziv, 1976). In short, the algorithm takes a given binary string and searches front-to-back for repetitions of "words", i.e. repetitions of the same sequence of ones and zeros. These "words"

are then put into a “dictionary” and the size of this dictionary then gives an indication of how compressible the data is. In other words a fully uniform string would have the lowest number of “words”, while a fully random string would have the maximum number of “words” in its “dictionary”.

The idea behind applying this algorithm to brain activity is as follows. If applied to a multitude of channels that are spatially distributed over the scalp, then a brain with uniformly distributed activation (indicating low diversity) can be compressed to just a few “words”, thus obtaining a low score. While on the other hand, if a brain shows disparate activations over a multitude of channels (i.e. showing a diverse activation pattern) the score will indicate a high value, since more “words” are necessary to explain its compressibility.

LZC has been shown to be able to discern between awake and anesthetized states (Juel et al., 2018; M. Schartner et al., 2015; Varley et al., 2019), and between awake and non-REM sleep states (Schartner, Pigorini, et al., 2017). Additionally, LZC scores are elevated under psychedelic conditions (Schartner, Carhart-Harris, et al., 2017), which are thought to represent heightened states of consciousness, and even following the time-course of the subjective intensity of the psychedelic experience (HorizonsConference, 2020).

1.2.3 Measures of Entropy

Amplitude coalition entropy (ACE) and Synchrony coalition entropy (SCE) are the two additional methods introduced by Schartner (2017). Entropy is seen here as part of information theory (also known as information entropy) and quantifies the average “surprise” or “uncertainty” of a signal (Shannon, 1948). In other terms it gives a mathematical measure of how much a given signal can be compressed without losing any information, and thus how diverse the signal is.

ACE, first introduced by Shanahan (2010; as coalition entropy) and modified for use on EEG data by Schartner (2017), measures the entropy of a community (coalition) of active channels (for an explanation of how channels are classified as active or inactive see methods below, section 2.5.3).

SCE on the other hand captures the diversity of a coalition of channels that are in synchrony. In short SCE assumes that channels can be abstracted as oscillators, and these

oscillators can then be classified as either being in synchrony or out of synchrony based on their phase information (see methods, section 2.5.3, for a more in-depth explanation).

Both measures have been shown to decrease under anesthetic conditions (Schartner et al., 2015), increase during psychedelic states (Farnes et al., 2019; Schartner, Carhart-Harris, et al., 2017) and to distinguish those states from normal wakeful states. Additionally, while not using specifically using ACE or SCE Vivot et al. (2020) recently showed that entropy increases during the practice of meditation in certain frequency bands, which might indicate that meditation can be seen as an altered state of consciousness.

1.3 Subjective Reports

Despite these recent developments in finding an objective measure for consciousness all these measures have only been validated by correlating them against responsiveness in certain states. In other words, the most valid assessment in healthy humans to date might still be to ask for their subjective experience. Employing subjective reports certainly comes with a set of problems (Tsuchiya et al., 2015), however, given its subjective nature there is no better standard of which to test novel measures of subjective experience on (Noreika et al., 2011). Dreams, as a special form of subjective experiences, have been even more in question of being trustworthy. Dennet's cassette theory being a famous critique on the subject, where he postulates that dreams are merely instantaneous memory insertions (Dennett, 1976). However, with more recent empirical evidence and developments it has been argued that dreams indeed occur during sleep and are a trustworthy source for assessing experience during unresponsive states (Windt, 2013).

1.4 Consciousness & (Propofol) Anesthesia

General anesthesia is used in hospitals around the world each day to reversibly "switch-off" consciousness in patients undergoing surgery and is generally considered by clinicians to result in complete unconsciousness. However, more and more evidence emerges showing that it can result in either unconsciousness (complete absence of awareness/experience), disconnected consciousness (no conscious awareness of surroundings, while having inner experiences, i.e. dreams), or connected consciousness (experiencing inner thoughts as well as surrounding stimuli; Bonhomme et al. 2019). Being able to alter states of consciousness in such diverse

ways makes it an important tool in the search of neural correlates of consciousness (Crick & Koch, 1990; Walsh, 2018).

Propofol (2, 6-disopropylphenol) is one of the most favored anesthetics today, with usage on 30 – 50 million patients each year, in the US alone (Walsh, 2018). As anesthetic it shows significant advantages such as minimal side effects, fast onset and emergence and easily adjustable anesthetic state (Glen & Hunter, 1984). Most common side effects are lowered blood pressure, pain/rash around the area of needle injection, shortened breath, headache and dizziness after anesthesia (Felleskatalogen, n.d.). Given that propofol modulates gammaaminobutyric acid (GABA A) receptors it might reduce pain at sub-anesthetic levels, making the drug a possible analgesic (see Vasileiou et al., 2009 for a review of its sub-anesthetic effects). However, one of the most prominent side effects of Propofol is amnesia. It has been shown that amnesic effects occur even under sub-anesthetic conditions (Veselis et al., 1997). These effects seem to arise from a rapid memory decay rather than from problems during encoding (Veselis et al., 2009; Veselis & Pryor, 2010). Because of this strong amnesic effect and its white color, coming from the soy compound in the drug, Propofol is frequently dubbed the "milk of amnesia" (Walsh, 2018).

1.5 Current Study

1.5.1 Aims

Although the presented measures seem promising, there remain doubts as to whether or not these measures truly reflect conscious states. For instance, the measures have been tested on differences between sleep stages, and have been shown to differ between with higher scores during REM sleep and lower scores during non-REM (Casali et al., 2013; Comolatti et al., 2019; Schartner, 2017). However, it has been shown that dreams occur in 23-74% of awakenings during non-REM sleep (Nir & Tononi, 2010; Sanders et al., 2012; Siclari et al., 2018). Given that dreams are seen as subjective experiences (i.e. consciousness) instances where dreams occur should result in higher scores of conscious state.

The same argument can be applied to validation through anesthetic intervention. While it is true that somewhere in the transition from a wakeful brain to brain death (i.e. flat EEG signals) there should be a point of unconsciousness, it is not clear when that point is reached. Further, during this transition it is likely that an agent will also transit through different states of consciousness, some of which allow for dreams to happen. This gradual transition is

evidenced by findings that up to 37% of people undergoing anesthesia show signs of connected consciousness (Sanders et al., 2017) and dreams occur in at least 27% (Leslie et al., 2009) and up to 60% of cases (Noreika et al., 2011).

These facts place a problem on the original studies (Casali et al., 2013; Comolatti et al., 2019; Schartner, 2017), which worked on data where reports of experiences were either not available or obtained up to two hours after the session. To forgo this problem, and to revalidate these measures, we wanted to obtain nearly immediate dream reports from people under anesthesia. This was done by keeping participants in a steadily sedated state while they were still arousable by a noxious stimulus. Importantly, the level of the anesthetic agent should not be changed once the desired level is found, to keep the brain in a steady state. Based on the problems and literature presented above three different hypotheses were developed for this thesis.

1.5.2 Hypotheses

- H1: Up to 60% of participants will experience dreams under the influence of anesthesia.
- H2: Due to amnesic effects, participants will forget their experience after emergence, resulting in a drop of recalled dreams to around 30%.
- H3: Measures of signal diversity (PCI^{ST}, LZC, ACE, SCE) should show a decline in scores ranging from awake reports (high scores) to no report awakenings (lowest scores).

2. Methods

2.1 Participants

The study included 11 healthy participants (8 female), aged 21 – 32 (mean age = 27). All participants were screened for MRI compatibility according to local standards, TMS compatibility in accordance with safety guidelines by Rossi et al. (2009) and showed no signs of neurological disease. One participant had to be excluded from analysis due to complications during the procedure. Further, due to either time constrains, artefactual muscle twitches or a motor threshold > 80% of the maximum stimulation output of the TMS machine, 4 participants were excluded from the TMS part of the study. Lastly, due to the closing of research activities during the Covid-19, pandemic further recordings of at least three more participants had to be cancelled. Participants fasted 8h before anesthesia from solids, 2h before from liquids, were monetarily reimbursed and gave written consent. The study was ethically approved by the Regional komite for medisinsk forskningsetikk (Saksnr. hos REK (2015/1520)).

2.2 Procedure

The study consisted of two different sessions. First participants came in for an MRI scan to get T1 weighted images used for neuro-navigation during TMS application. During this session participants were also screened for TMS compatibility, which involved finding a rough estimate of their motor threshold (MT). We then applied several TMS pulses at 130% of the MT estimation to brain areas likely to be used as a spot for the PCI procedure (either frontal or parietal regions). Participants with a MT estimation higher than 80% of the maximum of the machines output as well as any participant giving feedback about or showing visible muscle twitches were excluded from the TMS part of the study. The whole session lasted for roughly 1.5 hours.

One week before the second session participants were send information about the questions asked during the experiment. Additionally, they were advised to ask themselves these questions after awakening from sleep and any misunderstandings were cleared up. The second session consisted of combined EEG/TMS measures during awake and anesthetized states. After setup and preparation of the EEG and neuro-navigation system single TMS pulses with increasing intensity were applied over the motor area until a slight twitch was visible in their thumb. The motor threshold was then estimated with the help of two electrodes placed on the thumb muscle and an algorithm, which calculates the intensity, based on EMG activity, at

which a muscle response is elicited 50% of the time. Actual stimulation intensity was then set to 120-130% of the motor threshold, adjusted online to provide a strong TMS evoked potential, which was defined as a minimum of 10μV peak-to-peak difference in the first 50ms after TMS stimulation and no sign of muscle artefacts. Depending on the participants response to TMS, stimulation was applied over either frontal or parietal regions. With the preparations finished we then recorded baseline measures during the awake state, consisting of resting state EEG with eyes opened and with eyes closed, five minutes each, and recording of 300 TMS pulses (intertrial interval jittered between 1.7 – 2.3 sec.), lasting about 10 min. During the recording participants listened to a TMS masking noise to not elicit an auditory response to the TMS sound. The masking noise was made by randomly repeating the TMS sound in an infinite loop, making the resulting noise comparable to white nose. After TMS application the participant was interviewed based on the questions that were asked during awakenings (see table 1).

Anesthesia was then initiated by either an anesthetic doctor or a trained anesthetic nurse, using a CareFusion Alaris^{tm} PK plus (Becton, Dickinson and Company; Franklin Lakes, NJ, USA) anesthetic pump following the Schnider model. Initially a bolus dose was given to sedate the participants during which they were asked to count upwards. Five minutes after the participants discontinued counting their sedation level was assessed according to the Richmond agitation scale (Sessler et al., 2002). This was done by first calling out their name, and then, if no response was given, by squeezing their trapezius (shoulder) muscle, (see appendix A for the full scale). If no response was given, the Propofol dosage was lowered and sedation level was assessed again after five additional minutes. Reversely if the participants were too easily arousable (i.e. participants showed reaction to being called by name) the dosage was increased. This was done until the right sedation level was found, defined as being deeply sedated but still arousable to noxious stimuli (Richmond agitation score = -4). On average participants received a dosage of 1.7 μg/h propofol (mean total amount administered = 598 mg); EEG was recorded during the whole induction phase.

Table 1: **Questionnaire for interviews during awakenings and after emergence from anesthesia**

Sedation questions	1. Report questions	(1) What did you experience? (1.2) Did you experience anything at all?
	2. Memory questions	(2) I will name five word, please repeat these words. (3) I will name six cities, please name the country of you know. Say next otherwise.
Emergence questions	1. Report questions	(1) Can you tell us about your experience during anesthesia? (2) Do you remember anything related to the experiment itself? (3) Do you remember any dreams? (4) What was the last thing you remember before falling asleep. (4.2) What is the last number you remember?
	2. Additional question	(5) Is there anything else?

After the last induction awakening we waited another five minutes to let the participant get to a steady anesthetic state. We then recorded five minutes of resting state EEG and 300 pulses of TMS applied at the same spot and intensity as during the awake condition, plus one-minute resting state EEG. After TMS application participants were woken up by noxious stimulus and verbally interviewed according to the questionnaire (see table 1, Sedation questions). This procedure was repeated three times in total.

After the last awakening, injection of Propofol was shut off and participants were allowed to emerge naturally from anesthesia. At the first sign of responsiveness the participants were asked additional questions regarding their experience during the procedure (see table 1, Emergence questions).

After the procedure participants were under observation for two more hours. During these two hours free talk about the experiment and experiences continued between the experimenters and the participant. For a schematic representation of the experiment see Figure 4.

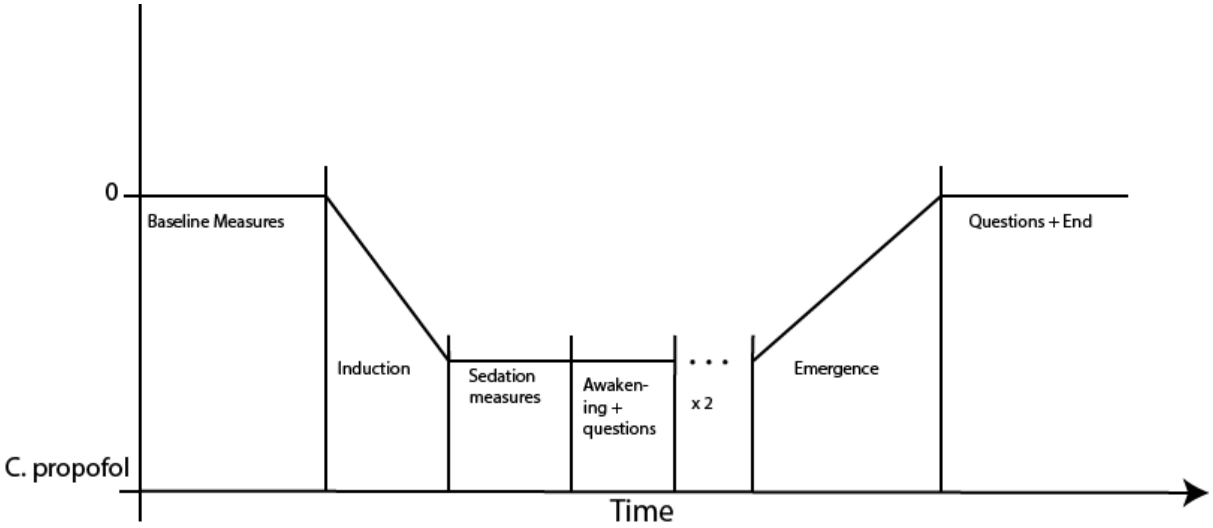


Figure 4: **Schematic procedure of the Experiment with propofol concentration over time.**

2.3 Data Acquisition

2.3.1 EEG System

EEG was recorded using multi-channel amplifiers (BrainAmp, BrainProducts GmbH, Gilching Germany) with 62 passive electrodes placed according to the international 10-10 system (EasyCap, BrainProducts GmbH, Gilching Germnay). Reference and ground electrode were placed on the forehead, slightly above the nasion. Additionally, two electrodes were placed slightly to the side and above the right outer canti and next to the left outer canti to record vertical and horizontal eye movements respectively. Impedances were held below 10kΩ and data was online filtered at 1000Hz with a sampling rate of 5000Hz. Recording was done via the BrainVision recorder (BrainProducts GmbH, Gilching Germany).

2.3.2 TMS & Neuronavigation

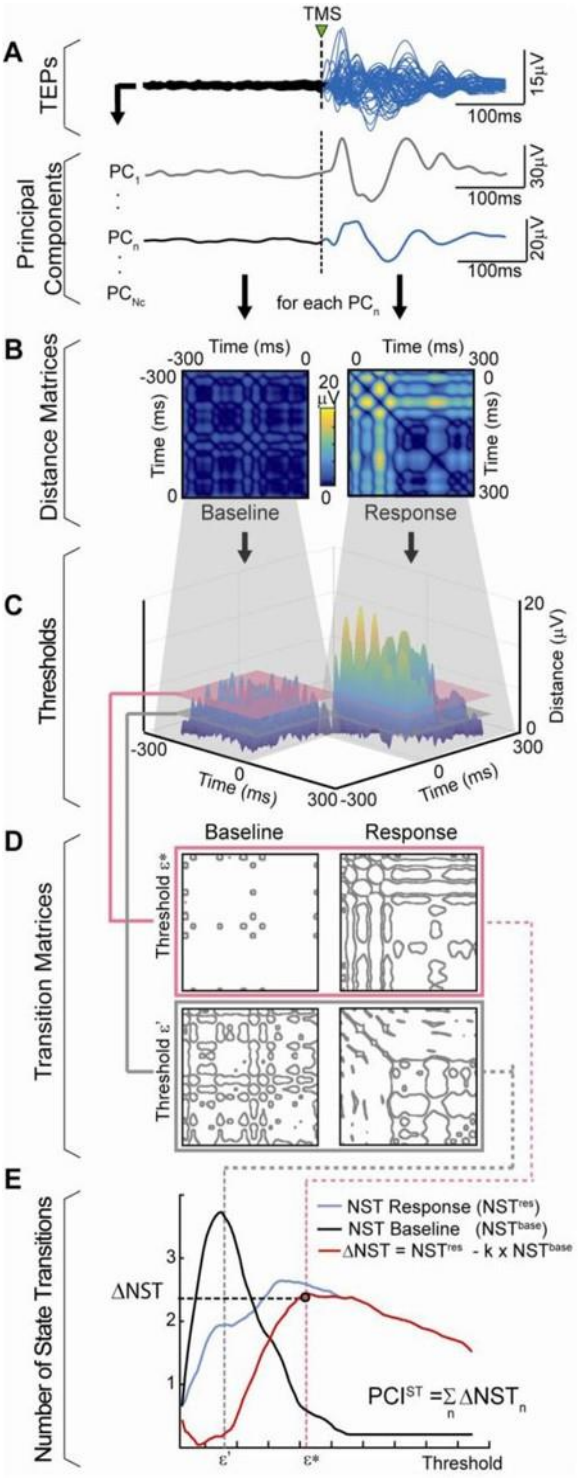
TMS pulses were applied using the PowerMag Research 100 stimulator (MAG & More GmbH, München, Germany) in conjunction with a figure of eight coil (Double coil PMD70-pCool, MAG & More GmbH, München, Germany). Pulses were guided via neuronavigation using individually obtained T1 weighted MRI images (Philips 3.0T Ingenia MR system, Philips

Healthcare, Netherlands). Position of TMS coil and the participants head in a 3D space was tracked using the PowerMag View! (MAG & More GmbH, München, Germany) software.

2.4 Preprocessing

All EEG analysis was done in Python (v.3.7; (Python Sotware Foundation, n.d.)) using the MNE-python package (v. 0.20.5; (Eric Larson et al., 2020; Gramfort et al., 2013)) and custom-made scripts. For the spontaneous data we first inspected channels by eye and interpolated those deemed as being bad (mean = 3). Data was resampled at 1000Hz, filtered with a 5^{th} order Butterworth filter at 0.5-45Hz and notch-filtered at 50Hz to attenuate line-noise. ICA was then computed on the continuous data and components were inspected by eye; any artefactual components were removed. Subsequently, reference was set to average reference. Data was then cut into even epochs with a length of five seconds and epochs deemed artefactual based on the autoreject algorithm (Jas et al., 2017) were rejected from further analysis. In short, this algorithm uses a Bayesian approach via cross–validating the Root Mean Squared Error of different amplitude thresholds to estimate the optimal threshold for a dataset above which epochs should be rejected. However, if the threshold is surpassed in only a minor number of channels (calculated based on number of total channels) instead of rejecting the whole epoch the artefactual channels will be interpolated by the algorithm.

TMS datasets were preprocessed in a similar way, with the exception that the artefact evoked by the TMS pulse was interpolated before channel interpolation. This was done by linearly interpolating the TMS pulse at a defined range around the event code (-2 – 7 ms) using the MNE fix_stim_artefact function. The raw data was then inspected for bad channels, bad channels were interpolated (mean = 4) and data was filtered using a 5^{th} order Butterworth filter (0.5-45Hz) in addition with a 50Hz notch filter attenuate line noise. Data was then epoched from -1 to 2 seconds around the TMS pulse to compute ICA on epoched data, so that ICA components would more robustly reflect components during the time of interest. Any artefactual components were zeroed out from further analysis. After ICA, epochs were shortened to -400 to 400 ms and any artefactual epochs were removed, based on the autoreject algorithm (Jas et al., 2017).



2.5 Measures of Signal Diversity

2.5.1 PCIST

Figure 4 shows a schematic of how PCIST is computed. First epochs are extracted from the data, time-locked around the TMS pulse and averaged over epochs to generate a TMS evoked potential (TEP). This TEP is then decomposed into N_C components, where N_C is the number of components explaining at least 99% of the response strength measured in terms of the square mean field power minus those components that showed low signal-to-noise ratio. The complexity of each component (ΔNST) is then the maximized difference in state transitions of a component C_N compared to its baseline, where state transitions are defined as the voltage-amplitude distances between all time-points that surpass a threshold ε (see Comolatti et al., 2019 for a detailed description). PCIST is then defined as the sum of the complexity of all components:

$$PCI^{ST} = \sum_{n=1}^{N_C} \Delta\mathrm{NST}_n$$

*Figure 5.***Calculation of PCIST***: A) A TMS evoked potential is decomposed into N different components; B) For each component amplitude difference matrices are calculated for both baseline and response windows; C) Distance matrices are thresholded at different levels; D) For each threshold transition matrices are calculated and used to obtain the average number of state transitions for both baseline and response window; E) The maximum difference in average state transitions is then taken as the complexity of that component. Reprinted from "A fast and general method to empirically estimate the complexity of brain responses to transcranial and intracranial stimulations", Renzo Comolatti et al. (2019). Copyright © 2019 Elsevier Inc*

PCIST was calculated using code obtained from Comolatti (2019).

2.5.2 LZC

To apply the Lempel-Ziv algorithm (Lempel & Ziv, 1976) to continuous EEG, the data must first be binarized. This is done by first decomposing it into its analytical signal via the so-called Hilbert-transformation. This mathematical formula takes a real value signal and transforms it into a time-series of complex numbers, which can then be decomposed into the analytical signal containing only positive values. Each time-point of a channel is then binarized by assigning it either a one or a zero whether it is above or below a threshold, defined as the mean value of the analytical signal of that channel. In a next step, the binarized time-series data of each channel are concatenated along their time-dimension into a one-dimensional array. Lastly, the Lempel-Ziv algorithm is then applied to this array. As mentioned above the Lempel–Ziv algorithm searches for repeating patterns in this binary string, so called "words". These words are then put into a "dictionary". The complexity is then the size of the resulting "dictionary". For normalization the score is divided by a score obtained from the same data, where the value of each time-point is randomly shuffled along the time dimension, resulting in a complexity score between 0 and 1.

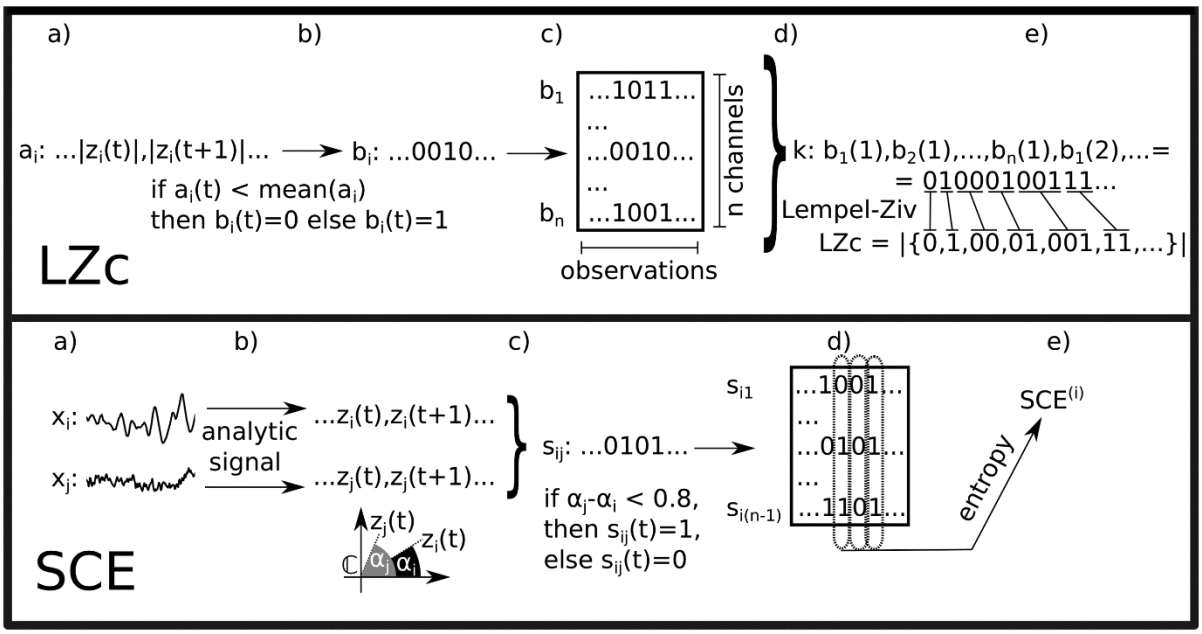


Figure 6: Schematic vizualization of LZC and SCE computation. LZC: a) The signal of a channel i is decomposed into its analytic signal a_i; b) a_i is binarized at time point t, based on its mean amplitude; c) Binarization is done for all n channels; d) binarized time series are concatenated along the time dimension to obtain one binarized string k; e) Lempel – Ziv algorithm is applied to k. SCE: a) The signals from channel Xi and Xj; b) Signals are decomposed into their analytic signals; c) Both analytic signals are binarized into one binarized string, based on their phasic information α; d) binarization is done for all channel pairs in the analysis e) Shannon entropy is calculated on coalitions of those binarized strings Reprinted from " Global and local complexity of intracranial EEG decreases during NREM sleep", by Michael M. Schartner et al. (2017). Copyright 2017 Schartner et al. (open access, distributed under the Creative Commons Attribution License)

2.5.3 Entropy

Shannon entropy was calculated for both measures using applications developed by Shanahan (2010) and Schartner (2017). Importantly, those applications take in binary data as well. For ACE data was binarized by categorizing a channel, at a given time point, as either active or inactive, based on the same binarization scheme used for LZC. SCE on the other hand is binarized based on the phase synchrony between two channels. Two channels are defined as being in synchrony if the phase information of their analytic signal differs no more than 0.8 radians from each other (see Figure 6, lower panel).

LZC, ACE and SCE, were calculated using functions from the pyconscious toolbox (Nilsen, 2020/2020), which adapted code shared by Schartner et al. (2015). In short, these functions take in a three-dimensional array (channel x times x epoch) and apply the above-mentioned methods (section 2.5.2 to 2.5.3) to each of the epochs. The overall score for each of the measures is then the mean value over all epochs.

2.6 Statistics

Differences between awakes scores and sedation scores as within-subject effect were tested using the non-parametric Wilcoxon-Rank sum test. p–values were corrected for false discovery rate using the Benjamini-Hochburg procedure. To test for positive correlations between vividness of reports and scores a Spearman rank correlation analysis was conducted, where each score got paired with a corresponding report score. Since the higher scores during awake recordings would skew the correlation to one side those values were excluded from this analysis. Additionally, since it could not be assessed with certainty in which state participants were when they did not respond or did not wake up, those instances were excluded from further analysis. Statistical analysis was done in R (version 4.0).

3. Results

3.1 Signal Diversity Scores

Due to bad data quality, PCI^{ST} analysis of one sedation recording in one participant was excluded from analysis (Participant 5, recording 3; see figure 7). Wilcoxon rank sum test yielded no significant differences between any of the PCI^{ST} scores when corrected for multiple comparisons (see table 2).

Table 2: **Wilcoxon rank sum test between PCI^{ST} scores of different recordings**

Recording 1	*Recording 2*	*W*	*p*	*p.adj*	*p.adj.signif*
Awake	SED 1	21	0.02	0.09	ns
Awake	SED 2	15	0.03	0.16	ns
Awake	SED 3	6	0.12	0.50	ns

Sed 1-3 = Sedation recordings 1 – 3; p.adj = p-values after Benjamini – Hochburg adjustment

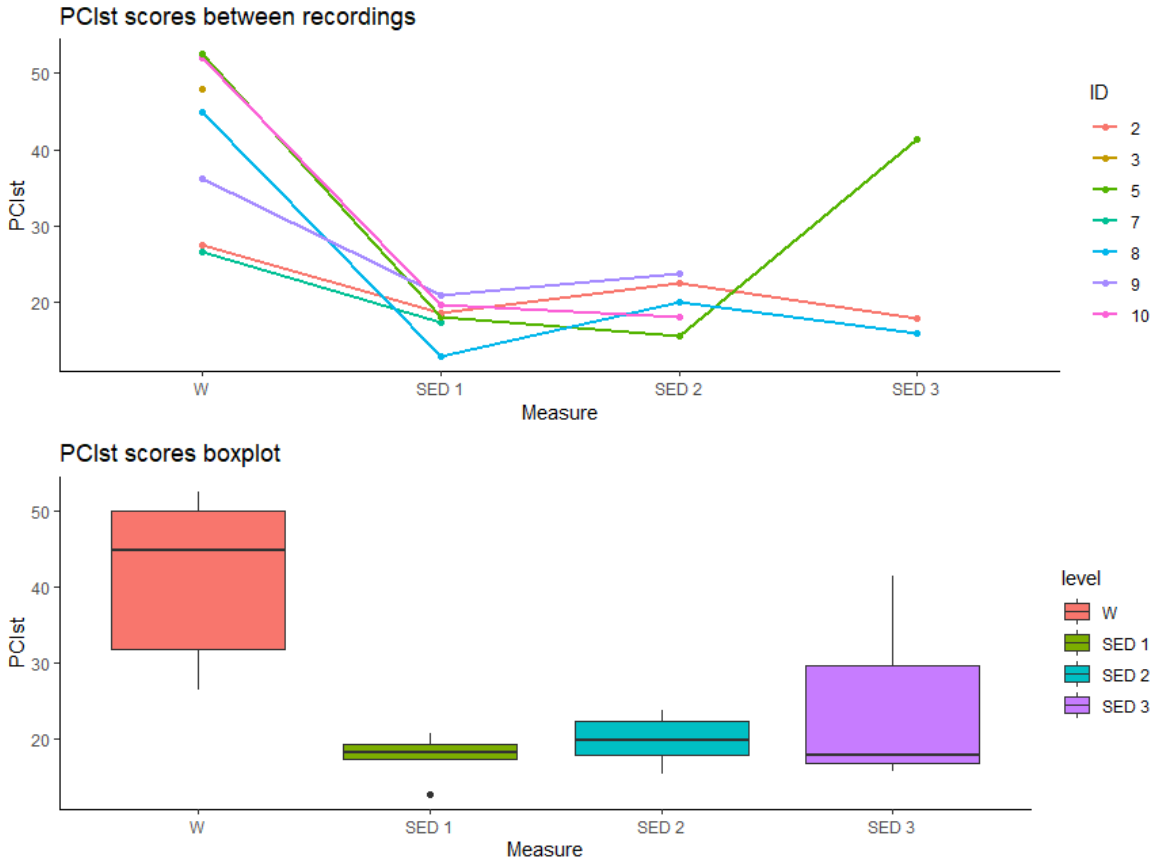


Figure 7*:* **PCIST scores between recordings. Top) Individual PCIST scores for all participants; Bottom) Boxplot with error bars for PCIST scores between different recordings**. W = Wakeful recording; SED 1 – 3 = Sedation recordings 1 – 3

Table 3: **Wilcoxon rank sum test between scores of continuous data**

Recording 1	*Recording 2*	*LZC p*	*LZC adj.*	*ACE p*	*ACE adj.*	*SCE p*	*SCE adj.*
W/O	W/C	0.03**	0.29	0.00***	0.01**	0.00***	0.02**
W/O	SED 1	0.12	0.75	0.00***	0.01**	0.00***	0.02**
W/O	SED 2	0.15	0.75	0.01**	0.08*	0.01**	0.08*
W/O	SED 3	0.03**	0.29	0.02**	0.11	0.02**	0.11
W/C	SED 1	0.65	0.75	0.05	0.32	0.16	0.80
W/C	SED 2	0.59	0.75	0.18	0.84	0.46	0.91
W/C	SED 3	0.42	0.75	0.22	0.84	0.42	0.91

W/O = wakeful, eyes open; W/C = wakeful, eyes closes; SED 1-3 = sedation recordings; adj. = adjusted p – score after Benjamini – Hochburg correction; * = $p < 0.1$; ** = $p < 0.05$; *** = $p < 0.01$

Similarly, there were no differences found in LZC scores in-between recordings. ACE scores, on the other hand, differed significantly ($p < 0.05$) when comparing scores of awake recordings with eyes open against eyes closed ($p = 0.01$), as well as between awake eyes open and the first sedation ($p = 0.01$) after multiple comparison correction. SCE scores showed a similar pattern as ACE scores, yielding a significant difference between awake eyes open versus eyes closed ($p = 0.02$), as well as between awake eyes open versus first sedation recording ($p = 0.02$); see table 3 for a full list of p-values between recordings. Interestingly, one participant showed abnormal behavior in LZC scores, with scores gradually increasing from wakeful eyes open to the last sedation recording. See subject 3 in Figure 9(a).

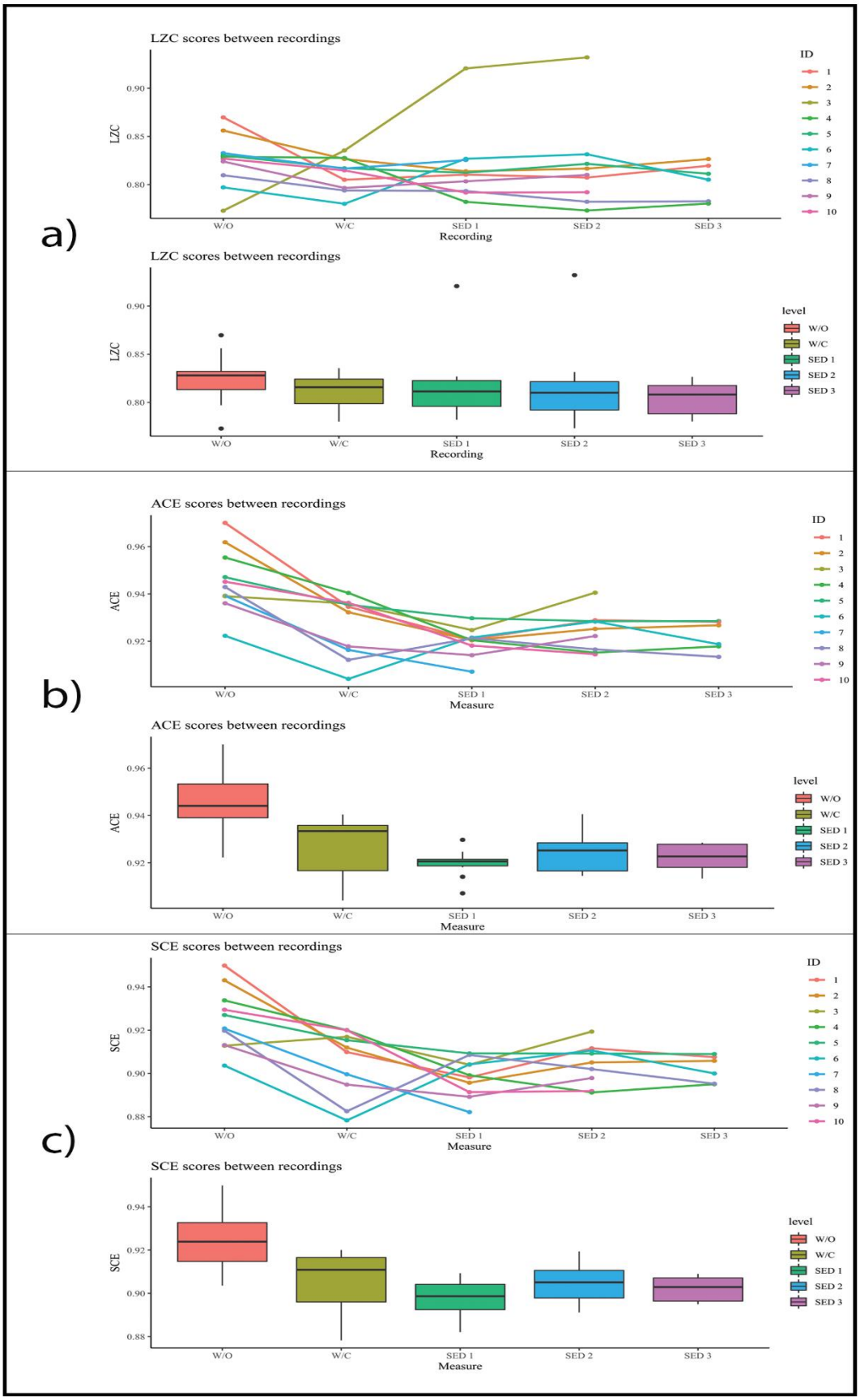


Figure 8**: Individual scores (top) and boxplots (bottom) of different recordings for LZC (a), ACE (b) and SCE (c) scores**

3.2 Reports

Due to time constrains during the experiment we could not obtain all three reports from all participants, i.e. 5 out of 10 participants were awakened two instead of three times. This resulted in a total number of 26 awakenings across all subjects. Out of these 26 awakenings there were 8 instances where participants did not respond to the question "Did you experience anything?". Interestingly however, participants were still able to answer the memory questions in those instances, and some participants (n = 3) still reported being sure about having dreamed after emergence from sedation although their reports consisted of either no reports or no responsiveness. Out of the remaining 18 reports, 13 (72%) included having at least some kind of vague experience. These ranged from "I have dreamed something, but don't remember what", to vivid stories including scenes an persons (see appendix B for examples of experience reports). On the other hand, of the 18 reports, 5 (27%) reported no experiences. Table 4 shows the total number of reports classified to each category.

Table 4: **Number of reports in each category**

	Number of Reports (total = 26)					
N subjects (with TMS)	*Did not awake*	*No Response*	*No Report*	*White Report*	*Vague Report*	*Vivid Report*
10(6)	1 (4%)	7 (27%)	4 (15%)	2 (8%)	5 (19%)	7 (27%)

Spearman rank correlation revealed no correlation between PCI^{st} scores and vividness of report ($R = 0.22$, $p = 0.54$). However, analysis showed a positive correlation between reports and LZC ($R = 0.68$, $p < 0.01$), ACE ($R = 0.76$, $p < 0.001$) and SCE ($R = 0.69$, $p < 0.01$) respectively, as shown in table 5 and see figure 7 for corresponding scatter plots with linearly fitted lines.

Table 5: **Spearman rho and p values of correlation analysis between Reports and Scores**

	Report - PCI^{st}	Report - LZC	Report - ACE	Report - SCE
Rho	0.22	0.68	0.76	0.69
p	0.54	< 0.01	< 0.001	< 0.01

After the experiment, out of ten participants three reported having no dreams or experiences during the experiment, six remembered having dreamed but did not remember what and one remembered vivid scenes from their dreams.

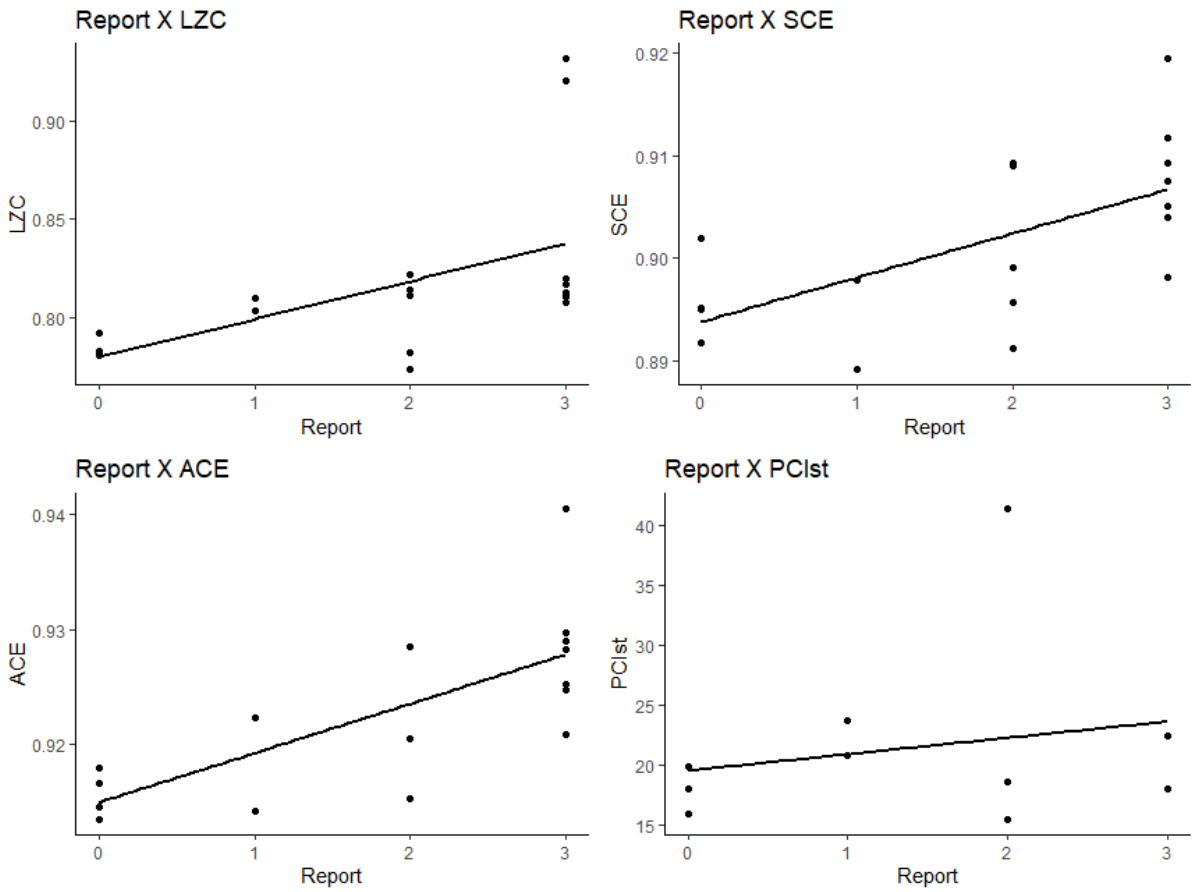


Figure 9: **Scatterplot with linearly fitted line for LZC (top, left), SCE (top, right), ACE(bottom, left) and PCIst (bottom, right) compared with vividness of report**. X – axis: 0 = no experience; 1 = white experience ("feeling of experience without remembering details"); 2 = vague experience ("vaguely remembered faces, places etc."); 3 = vivid experiences (Reports included details stories and descriptions)

4. Discussion

In this study we wanted to investigate whether current measures of consciousness truly reflect different conscious states. For this we measured brain activity from participants during awake and unresponsive (i.e. anesthetized) states. Based on previous findings we expected values of PCI^{ST}, LZC, ACE and SCE to drop in anesthetized compared to wakeful states (Comolatti et al., 2019; Schartner, 2017). However, unexpectantly, our findings deviated from previous results.

4.1 PCI^{ST}

Contrary to previous findings of Comolatti et al (2019), the results presented above indicate no differences in scores between awake and sedated participants. However, when looking at the distribution of scores between recordings, as shown in figure 8, there seems to be a clear drop between awake and sedation scores, making it likely that the non-significant findings are due to a low sample size. Further p-values are only non-significant after false discovery rate adjustment. Based on this assumption PCI^{ST} can robustly distinguish between awake and non-responsive participants.

It has been noted before that this drop in PCI^{ST} values, as observed in figure 8, during sedation recordings is likely due to break down in long range functional connectivity (Casali et al., 2013). Which, in turn, has been shown to be important in distinguishing conscious from (seemingly) unconscious patients (Sitt et al., 2014). Propofol especially was found to break down thalamocortical connectivity (A. G. Hudetz, 2012), a structure often referred to as a relay center of information, because of its reciprocal connection to the cortex (Mai & Forutan, 2012). Breakdown of these connections are unlikely to be an epiphenomenon, but more likely a causing factor of anesthetic induced unconsciousness (Mashour & Alkire, 2013). That is, because modification of the connectivity between low-level sensory and high-order brain areas, induced through anesthesia, seem to be necessary for the perception of stimuli, and thus building a conscious experience (Boveroux et al., 2010).

4.2 Continuous Measures

Except for a difference in ACE and SCE scores in the eyes open condition versus the eyes closed condition, as well as between eyes open and the first sedation recording continuous

measures did not yield any significant results. These findings suggest that LZC, ACE and SCE are not able to distinguish between awake and non-responsive states.

On a more methodological level our findings might differ from previous ones since we did not compute a surface Laplacian during analysis as a spatial filter (Farnes et al., 2019; Schartner, Carhart-Harris, et al., 2017). In short, this computation assigns weight to activities at channels around a given channel (Kayser & Tenke, 2015). It then subtracts this weighted activity, thereby aiming to increase spatial specificity. In other words, it reduces the effect of volume conductivity in order for the resulting signal to more closely reflect the true signal at a given channel. Additionally, the surface Laplacian foregoes a uni-polar reference. However, this procedure might result in favoring more local and close-to-surface activity at the expense of more widespread activity generated more subcortically (Yao et al., 2019). Since it has been argued that consciousness might rely on thalamocortical activity (Llinás & Ribary, 2001) and evidence suggests that thalamocortical connections play an important role in the loss and recovery of consciousness during anesthesia (Ching et al., 2010; Mashour & Alkire, 2013; Redinbaugh et al., 2020) it was hence decided not to use a surface Laplacian approach during analysis. This might, however, have led to different results. Additionally, to control for this, we applied MNE's preprocessing function to calculate the current-spectral density, by using a surface Laplacian, on our epoched data and recalculated LZC values, which resulted in an unreasonable drop of those values (see appendix C for a comparison).

Interestingly, we could in part recreate findings from Farnes et al. (2019) showing that scores during wakeful states with eyes open differ from the same state but with eyes closed (see figure 9). Logically, given that it has long been shown that sensory input is distributed to different parts of the brain over time, these measures are susceptible to sensory input by design. For example, visual input will first arrive in the occipital lobe and from there will be distributed via two distinct pathways, the ventral and dorsal pathway, throughout the cortex (Banich & Compton, 2018). This should in theory be reflected in a more diverse spontaneous brain activity compared to conditions with less sensory input. Additionally, Barry et al. (2007) found significant differences in alpha, beta, theta and delta power between EEG recordings with opened and closed eyes, likely reflecting more complex brain activity. Thus, the findings of this thesis support the hypothesis by Farnes et al. (2019) that the continuous measures proposed by Schartner (2017) seem to rather reflect the richness of conscious content rather than conscious states.

The difference between eyes open and eyes closed condition could be another explanation for the inconsistent findings between this study and that of Schartner et al. (2015), as they never state in their paper whether the awake recordings where recorded with opened or closed eyes. Thus, the differences could be traced back to a difference in conditions. We are currently in the process of contacting Schartner to inquire about this.

Lastly, one participant showed rather deviating LZC scores (see Figure 9(a), Participant 3) by having increased LZC scores over time. We could not explain this behavior, however, the participant experienced a critically low pulse (at times < 40bpm) which might have caused abnormal brain activity. It has been shown that cardiac arrest can lead to a surge in gamma frequency with high levels of feedback connectivity and interregional coherence in rats (Borjigin et al., 2013). We reasoned that our participant might have experienced a similar situation during bradycardia. However, this does not explain the elevated scores from eyes open to eyes closed in this participant.

4.3 Reports

Additionally, we wanted to control for experiences during unresponsive states as indicator for retained consciousness. For this we intermittedly woke participants up from anesthesia to obtain dream reports. Based on previous definitions of consciousness (e.g. Laureys 2005; Seth et al. 2008) we expected PCI^{ST}, LZC, ACE and SCE to indicate higher values in recordings preceding reports of dream versus recordings preceding no dream or les vivid dream reports. This assumption could be met for LZC, ACE, and SCE, but not for PCI^{ST}.

4.3.1 Prevalence

Our findings show that participants experienced dreams under the influence of anesthesia in 72% of the cases. This is in line with previous findings (Noreika et al., 2011) and thus H1 could be verified.

However, the majority of participants (7 out of 10) had at least a vague feeling of having dreamed during the experiment, thus H2 could not be verified. This can be explained by the short time-interval between emergence from anesthesia and the interview. In other words, the amnesic effects of the drug might not have taken effect at the time of the interview. It has been shown that amnesic effects are severe as soon as 10 minutes after patients regain normal mental status (Miner et al., 2005), however in our study interviews happened as soon as signs of

responsiveness were noticed. Additionally, during the free talk phase after the experiment participants frequently forgot having been interviewed. This further strengthens the claim that amnesia did not commence at the time of the interview. However, the free talk was not recorded and thus no specific conclusions can be drawn.

4.3.2 PCI^{ST}

Using Spearman's correlation analysis, it could be shown that PCI^{ST} did not correlate with the vividness of dream reports. Thus H3 (Expectancy of gradual decline of consciousness scores over reports) could not be verified for PCI^{ST}. These results might originate from several factors. First and foremost, given that the number of reports in the different categories range from one to seven, one possible explanation could be that the sample size in this study was too small. Second is the question of when dreams occur and whether or not one can trust dream reports. From a philosophical perspective some describe dreaming as a mere insertion of memory (Dennett, 1976), however others hold current thought experiments and empirical evidence against this (Windt, 2013). From a more physiological perspective it has been argued that dreams under anesthesia occur most likely during emergence phase (Leslie et al., 2009). The study found that people are more likely to report dreams if they show more high-frequency and less spindle activity (i.e. burst-like activity at 10-15Hz) during emergence from anesthesia. However, in this study we did not let participants wake up on their own, but rather woke them by noxious stimuli. This in turn did not give the participants time to develop a dream during an emergence phase. Based on findings presented in this study it seems more plausible that the reduction in spindle activity recorded by Leslie et al. (2009) lead to increased memory consolidation and thus leading to better recall of dreams, which is in accordance with previous research (Chellappa et al. 2011; Nielsen et al. 2017; and see Fernandez and Luthi 2019 for an extensive review of spindles).

Yet, there is still the problem of the length of the recording. One sedation recording (resting state plus recording of 300 TMS pulses) in our study lasted for roughly 15 minutes. From this the question arises whether the reports given by participants truly reflect a span of this length. It is possible that the reported experiences only reflect on a margin of the recordings and as PCI^{ST} is computed as an average over epochs (i.e. over ten minutes), to control for noise, the measure might not be able to reflect dreams. However, there is currently no method to control for this factor, thus making it impossible to accept or deny this point.

One additional point that should be mentioned is the frequency of experiences occurring during anesthesia. As mentioned above dreams occur in up to 60% of cases during anesthesia (Noreika et al., 2011) and our data suggests that they can occur in even higher instances. Because of this, it is reasonable to assume that a high percentage of participants in the original studies (Casali et al., 2013; Comolatti et al., 2019) experienced dreams during anesthesia. In the results presented above, the PCI^{ST} values fell into the expected range and one can thus speculate PCI^{ST} is able to reflect an unresponsive brain state. In other words, PCI^{ST} can potentially indicate where functional thalamocortical connectivity is broken while individuals are still capable of having experiences. This is further strengthened by the condition of hydranencephaly, where patients lack most to all of their cortex (Contro et al., 2018). While no thalamocortical connectivity is able to develop these patients still seem to retain some form of consciousness and awareness (Merker, 2007). By its design, PCI^{ST} would not be able to reflect conscious content in states where consciousness arises from subcortical structures, since it only quantifies cortical activity directly caused by the TMS pulse. Thus, PCI^{ST} seems to reflect long range connectivity, however, it is not clear whether this is truly necessary for conscious experiences.

4.3.3 Continuous Measures

On the contrary to PCI^{ST} values, our findings showed that all continuous scores correlated positively with the vividness of reports. This finding is probably due to the fact that diversity measures of spontaneous brain activity are strictly speaking not reflecting instantaneous functional connectivity (like PCI^{ST} does). This is because they do not rely on a perturbation (i.e. TMS) that can be traced in time throughout the brain. This makes them susceptible to changes in experiences that are projected to the cortex, which is reflected in the above reported difference between recordings done with opened eyes and with closed eyes during wakefulness. Given that anesthesia can be regarded as a different conscious state, caused in part by the breakdown of long range thalamocortical connectivity (Sitt et al., 2014), it seems to be a state where some form of experience is still possible, as evidenced by our findings as well as by Noreika (2011). These experiences might arise from more localized brain activity, which would then be reflected in a spatially more diverse whole brain activity; however, more research is needed on this subject.

4.4 Dimensionality

Many consciousness researchers today assume states of consciousness can be described by a single graded dimension (Casali et al., 2013; Seth et al., 2008). Classically following the conception by Laureys (2005) that conscious states follow a continuous scale ranging from no consciousness at all to being able to perceive vivid experiences. However, the results of this study suggest differently. While certain aspects of consciousness clearly fade away under anesthesia, others persist. Because of this, it might be more plausible to think of consciousness as a multi-dimensional construct (Bayne et al., 2016, 2017; Bayne & Carter, 2018). This would mean however, that it might not be possible to capture consciousness in a single measure, and all measures presented here capture some aspect of it, but not the construct itself.

5. Limitations and Future Studies

The study of consciousness itself comes with a few limitations, where some have already been elucidated. However, in the following section, these limitations will be discussed more in-depth. Some drawbacks that arose during the experiment and analyses will also be considered.

As briefly mentioned previously in this thesis, the use of subjective dream reports might have its limitations. By their very nature those reports cannot be immediate and thus it is possible that those reports are merely memory insertions (Dennett, 1976). However, it has been found that brain activity during sleep show many similarities to wakeful activity through which dreams could arise (e.g. see Louie and Wilson 2001 for a review on the concept of replay and reconsolidation). Some researchers have even reported some success in decoding visual imagery from brain activity (Horikawa et al., 2013). Future studies could build on this work and uphold the validity of dreams and their reports by developing objective measures of brain activity that reflect dreams.

Second, as there is currently no consensus on the preprocessing steps to obtain reliable scores, the measures and methods must be discussed as limitations. During our analysis it became apparent that PCI^{ST}, LSC, ACE and SCE, but especially those three computed on continuous data will drastically change depending on the chosen processing steps. Future studies should address this by comparing different processing pipelines within as well as between different datasets.

Yet another limitation is the high percentage of participants (~50%) that could not partake in the TMS part of the study. For the most part, this was due to time constrains while finding a stimulation spot suitable to evoke a visible TMS response. Future studies should consider taking an additional session with participants to find a suitable spot that can be reused on the day of the experiment to forgo this. In this way one could also investigate how PCI^{ST} changes over time.

Another possible future investigation comes from the interesting finding that measures of spontaneous EEG activity differ between the eyes open and eyes closed condition. It seems that LZC, ACE and SCE are highly susceptible to sensory input. This could be tested via a study that utilizes methods of sensory deprivation. If it could be shown that LZC, ACE and SCE indicate lower scores during conditions where subjects are deprived of certain senses it could strengthen the claim that they are influenced by sensory input. Further, if an experiment

that utilized masking of stimuli, i.e. preventing stimuli from reaching conscious awareness, could show lower scores for conditions where participants did not perceive a stimulus it could strengthen the claim that LZC, ACE and SCE reflect richness of conscious content rather than sensory input.

Finally, the concentration levels of Propofol over time should be discussed. While we controlled the induction rate via a model driven pump it seemed that Propofol effects changed slightly over time. This was reflected in some participants by being more difficult or not able to wake up (Richmond scale = -5), and in others by being too easily arousable (Richmond scale > -4). Unfortunately, in our study we would only realize this after the recording, as we only tested responsiveness during the induction period and then assumed a steady state to not arouse participants during recordings. Although this was in line with previous studies (Murphy et al., 2011) future studies might want to test for responsiveness to verbal command at multiple time points throughout the recording. Additionally, future studies could utilize the isolated forearm technique to control for connected consciousness during anesthesia. In that way it could be controlled whether connected consciousness leads to higher scores of PCI^{ST}, LZC, ACE or SCE.

6. Conclusion

The present study investigated the currently most promising measures of consciousness while controlling for experiences in unresponsive states. By applying PCI^{ST}, LZC, ACE and SCE to high density EEG/TMS recordings during awake and anesthetized states we showed that only PCI^{ST} is able to reliably distinguish between those states. However, despite certain limitations it could not be shown that recordings yielding low PCI^{ST} values were truly during unconscious states. Based on results presented here it can be argued that PCI^{ST} reflects responsiveness rather than consciousness. On the other hand, LZC, ACE and SCE values positively correlate with vividness of report, and it can thus be argued that these measures seem to rather reflect the richness of experiences.

Furthermore, over the course of the study several drawbacks related to the measures became apparent. On the one hand, there is currently no consensus about processing steps involved in obtaining these measures. Especially LZC, ACE and SCE seem to be highly dependent on the different steps chosen during analysis. On the other hand, all four measures assume that consciousness can be measures on a single scale. However, our data suggests that consciousness is rather a multi-dimensional construct that cannot be measured by a single measure.

While the validity of PCI^{ST}, LZC, ACE and SCE as measures of consciousness could not be supported, they are a promising start in the development of means to measure consciousness, as these measures indeed correlate with states of impaired consciousness. Based on this, future studies can further investigate how these measures relate to specific aspects of consciousness. This can ultimately contribute to our understanding of consciousness as a concept and potentially have clinical implications in the assessment of patients with disorders of consciousness.

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APPENDIX

Appendix A

The Richmond-Agitation-Sedation-Scale, as described in Sessler et al. (2002)

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour toward staff
+2	Agitated	Frequent non-purposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and Calm	
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Appendix B

Examples of experience reports

Vague report:

Experimenter: “Did you experience anything?”

Subject: “Yes! Politics!”

Vivid report:

“I was prepping for exams…. But I don’t have exams, and I was really stressed out…. [he] (name changed) helped me”

Appendix C