Subjective Experiences During Sedation Induced by Equipotent Dose of Dexmedetomidine, Propofol, Sevoflurane and S-ketamine

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Studies conducted in clinical and experimental settings have shown that unresponsive persons undergoing anesthetic infusion often report subjective experiences, such as dreaming, when interviewed afterwards. The aim of the present study was to investigate the presence and quality of subjective experiences in healthy young participants sedated with dexmedetomidine, propofol, sevoflurane or S-ketamine. We addressed how participant's responsiveness (measured as behavioral response to auditory stimulus) during sedation is related to reporting experiences. Further, we explored the differences between anesthetics in the prevalence and nature of subjective experiences. Participants received equisedative doses of either dexmedetomidine (n = 40), propofol (n = 40), sevoflurane (n = 41), or S-ketamine (n = 24) and were interviewed of their subjective experiences immediately after termination of anesthetic administration. The interview transcripts were content analyzed by two independent raters for dream-likeness, incorporations of the experimental setting, awareness of the research environment, and complexity and modalities of experiences. There were no differences in the prevalence or contents of experiences between those classified as unresponsive and responsive. Of all participants who could be interviewed, 49.0% reported subjective experiences, most frequently dreaming (98.0%). Incorporations of the experimental setting were also quite frequent (36.0%) while awareness of the environment was rare (4.1%). Participants receiving dexmedetomidine and S-ketamine reported subjective experiences most often and S-ketamine induced the most multimodal experiences. This study shows that unresponsiveness does not equal unconsciousness, and that participant's responsiveness during sedation with equipotent dose is not associated with the likelihood of reporting subjective experiences. Subjective experiences are frequently reported after sedation and the subjective experiences may slightly differ between anesthetics administered in equipotent doses. Further studies should not consider responsiveness as an indicator of consciousness and should focus on how to distinguish unresponsive individuals who can experience external stimuli from those unresponsive individuals who cannot.

Keywords: consciousness, general anesthesia, responsiveness, subjective experiences, dreaming, awareness, connectedness, disconnectedness

Contents

Introduction

The presence or absence of consciousness (i.e., subjective experiences) cannot be objectively verified just by relying on a person's ability to respond to environmental stimuli. Yet, especially in clinical setting, responsiveness is commonly used as an indicator of the patient's state of consciousness. When a person can respond to external stimuli, the person is conscious and aware of the environment (i.e., connected to the environment). Respectively, unconsciousness in the clinical setting refers to a state where the person cannot respond to even painful stimuli and is therefore considered unable to experience or feel anything. The problem of measuring consciousness becomes evident when the person remains connected to the environment while unresponsive and assumed unconscious. This can manifest as unintended intraoperative awareness (i.e., being aware of one's environment) during surgery and later lead to severe psychological sequalae. Yet, having purely internally generated contents of consciousness, such as dreams, may not be harmful for patient undergoing surgery. Therefore, the problem appears to be how to disconnect the person from the environment rather than how to suppress internally generated experiences.

We would be closer to resolving the problem of consciousness if we could understand how anesthetic agents affect conscious experiences, especially connectedness to the environment. Carrying out such investigations in the surgical setting is, however, complicated, given the patients suffer from various medical conditions, receive multiple drugs, and cannot be interviewed immediately after the operation. The presence and contents of subjective experiences during sedation and unresponsiveness have been sparsely studied. Thus, investigating the effects of different anesthetics on subjective experiences could lead to new information on, for example, whether some drugs are more prone to induce disconnectedness.

In this study, we utilized nonsurgical experimental setting. Subjective experiences were investigated in unresponsive and responsive sedative state, induced to healthy young participants by using equipotent dose of dexmedetomidine, propofol, sevoflurane and S-ketamine. The participants were interviewed about their subjective experiences immediately after termination of the anesthetic administration. The aim was to investigate the prevalence and contents of subjective experiences during responsive and unresponsive sedative state and how the experiences differ between the four anesthetic agents.

Problems of Defining and Measuring Consciousness

One of the challenges of studying consciousness is that it is difficult to define, and it is not always clear what phenomena is even addressed when the term 'consciousness' is used. Consciousness refers to subject's inner world of experiences which cannot be directly observed by outsiders (Revonsuo & Arstila, 2011). Revonsuo (2006) distinguishes between the concepts of phenomenal and reflective consciousness. Phenomenal consciousness is the most fundamental part of consciousness and refers to the ability to feel or experience subjective states in memorable way, such as pain, feelings or sensations. Phenomenal consciousness is challenging for research because of its subjective nature. Nagel (1974) rises the problem of measuring phenomenal consciousness: Only the being experiencing his or her consciousness knows what it is like. Science still does not have objective method of capturing contents of consciousness from outside of the subject having the experiences and thus we must rely on indirect measures of conscious experiences, such as verbal reports collected after the experiences has passed. Indirect information about the contents of phenomenal consciousness can be acquired when the contents may later be exposed to cognitive processing through reflective consciousness. Reflective consciousness refers to a form of consciousness which functions in attentional and working memory circuits. Through reflective consciousness, we direct selective attention to some specific contents in phenomenal consciousness and thus these contents can be reported to external observers. However, the report produced is not completely reliable source of information as it is limited by the ability of the subject to remember, reflect and report the experiences.

Further concepts linked to consciousness which should be separated include: *connectedness* and *responsiveness* (Sanders, Tononi, Laureys, & Sleigh, 2012). When consciousness is connected to the environment we are able to experience external stimuli, for example, such as when we are awake (Sanders et al., 2012). In contrast, the content of consciousness can be innate and occur without being connected to the environment, such as dreaming during sleep. Additionally, responsiveness refers to how we interact with the external world, and it can be measured through behavior. Responsiveness can be further categorized to two different behavioral categories: goal-directed (e.g. obeying orders) and spontaneous behavior (Sanders et al., 2012).

The dissociation between responsiveness and phenomenal consciousness has led to a new concept used in the science of consciousness; a person who fulfills the clinical criteria of unconsciousness by being unresponsive, but has preserved phenomenal consciousness is considered to be an inverse zombie (a regular zombie would be responsive yet unconscious) (Mashour & LaRock, 2008). There is still no objective measurement to identify an inverse zombie in real time (i.e., does the person have subjective experiences while being unresponsive) (Noreika et al., 2011). This is the reason why measurements based on responsiveness are used in clinical setting, such as Glasgow Coma Scale (Teasdale & Jennett, 1974). If a person cannot respond to a specific stimulus, the person is classified as unconscious. Yet, even the slightest manifestation of subjective experience is a sign of consciousness and the inability to respond to a stimulus or communicate with the environment is not sufficient proof for lack of subjective experiences. This is evidenced, for example, in locked-in syndrome where patients have full consciousness and awareness of the environment but are not responsive. Similarly, studies using functional magnetic resonance imaging show that some of the patients classified to have unresponsive wakefulness syndrome (UWS; previously known as vegetative state) are probably capable of having subjective experiences caused by both innate and external stimuli (Owen et al., 2006). Although UWS is defined as the absence of cognitive functions and being in unconscious wake state, some of the patients with the diagnosis seem to be able to accomplish instructed imagery tasks similarly to healthy controls. The same areas of the brain activate in a similar manner in some of the UWS patients and healthy controls when doing the same task (Owen et al., 2006). By looking at the external behavior, these persons are classified as unconscious and thus, they are probably misdiagnosed due to lack of reliable diagnostic measures. To be able to provide appropriate treatment, it would be important to be able to verify the presence of subjective experiences in patients suffering from disorders of consciousness.

In anesthesiology, a person is classified as unconscious if he or she is not responding meaningfully to stimuli, does not react to painful stimuli and cannot recall the events from during surgery. The most efficient way to suppress awareness during surgery is to induce deep enough anesthesia. However, causing overly deep anesthesia is undesirable, because anesthetics and other medication used in surgeries have effects also on respiratory and cardiovascular functions (Sanders et al., 2012).

General Anesthesia

In general anesthesia, the aim is to induce deep unconscious state to the patient. Patient's brain stem reflexes and responsiveness to pain should be suppressed, the patient's respiration is maintained artificially as well as circulation and thermoregulation are supported (Scheinin, Långsjö, & Scheinin, 2014). General anesthesia includes four main components: amnesia (lack of memory), analgesia (lack of pain), hypnosis (lack of response) and muscle relaxation (lack of movement) (Al-Kadi, Reaz, & Ali, 2013). These occur only when a combination of anesthetics, analgesics, and muscle relaxants is used.

Anesthetics agents that induce general anesthesia can be divided into two groups: inhalational agents and intravenous agents (Al-Kadi et al., 2013). Intravenous agents are used to induce anesthesia while inhalational agents are generally used in maintaining anesthesia (Alkire, Hudetz, & Tononi, 2008). Generally, in surgical anesthesia, various drugs are used in different stages of the surgery.

The action mechanisms of general anesthetics are still somewhat unclear, and the primary neurophysiological or neurochemical event that would explain their effect on consciousness is still unknown (Yli-Hankala & Scheinin, 2015). In general anesthesia, the central nervous system's functions can be suppressed either by inhibiting the vigilance maintaining systems or by strengthening the systems that suppress vigilance (Yli-Hankala & Scheinin, 2015). On one hand, drugs that increase gamma-amino butyric acid (GABA) transmission, such as propofol or inhalational agents, are used to inhibit the activity of vigilance maintaining systems. On the other hand, drugs such as S-ketamine, a glutamatergic NMDA-receptor antagonist, can be used to activate vigilance suppressing systems. Anesthetics do not have a common influence site and they can also act through other receptors than the ones mentioned above (Scheinin et al., 2014). In this study, four different anesthetic agents, propofol, dexmedetomidine, sevoflurane and S-ketamine, were administered to healthy participants in an experimental setting and thus these four anesthetic agents are described below in more detail.

Dexmedetomidine is an alpha-2 adrenergic agonist. It is a sedative and induces a state neurophysiologically very similar to physiological non-rapid eye movement (NREM) sleep (Mashour, 2016). It is also unique in a way that stimulation during dexmedetomidine sedation permits awakening from sedation with rapid orientation to environment (Scharf & Kelz, 2013).

Propofol is one of the most often used anesthetic agents. It has a rapid effect, short action and fewer side effects than other anesthetic agents (Chidambaran, Costandi, & D'Mello, 2015). It activates the release of inhibitory neurotransmitter GABA to cause its hypnotic effects (Chidambaran et al., 2015). Propofol is particularly interesting in consciousness studies as animal studies demonstrate that propofol satisfies rapid eye movement (REM) sleep homeostasis. Rats who received propofol after sleep deprivation had similar recovery sleep characteristics as animals allowed to have normal recovery sleep (Tung, Bergmann, Herrera, Cao, & Mendelson, 2004). REM sleep is the most optimal stage of sleep for dreaming to occur (Nielsen, 2000) and, interestingly, propofol-based anesthesia has been associated with higher incidences of dreaming (Leslie & Skrzypek, 2007).

Sevoflurane is a volatile agent that is thought to facilitate the GABA receptor and the inhibitory glycine receptor (Moppett, 2015). A study done with rodents suggested that sevoflurane anesthesia does not substitute for REM sleep, but seems to substitute for NREM sleep (Scharf & Kelz, 2013).

S-ketamine is an NMDA receptor antagonist. S-ketamine is unique in a way that it has hypnotic, analgesic and amnesic effects. Further, it does not have similar suppressive effects on cardiac and circulatory functions as other anesthetics. Therefore, it is especially suitable for sedation of trauma patients but also for anesthesia (Långsjö et al., 2005). Ketamine is, however, a dissociative anesthetic, since it usually causes the person to have floating sensations, vivid pleasant dreams and hallucinations (Collier, 1972; Marland et al., 2013). Additionally, the person might feel loss-of-self and isolation of mind from body.

Contents of Consciousness During Anesthesia

In anesthesiology, inverse zombies have been studied under the labels of unintended intraoperative awareness and dreaming during anesthesia (Errando et al., 2008). Anesthesia awareness or unintended intraoperative awareness refers to connectedness: sensory and perceptual information from the external world enters consciousness, for example, the patient can hear a conversation carried out by medical staff during surgery (Revonsuo & Arstila, 2011). Dreaming during anesthesia, however, refers to experiencing subjective phenomena during unresponsiveness which are not associated with the external world. They are dreamlike hallucinations occurring in the absence of physical stimuli (Revonsuo & Arstila, 2011) and thus a sign of disconnected consciousness.

Existence of inverse zombies raises the problem of how to identify the presence of a subjective experience and especially connectedness to the environment. The problem is fundamentally clinical and practical because there is no reliable meter to identify or predict intraoperative awareness. Considering the challenges in relation to measuring consciousness, in anesthesiology it might be more important to concentrate on how we can disconnect a person from the environment to prevent intraoperative awareness rather than to suppress all conscious experiences. After all, having internally generated subjective experiences (such as dreams) during surgery does not seem to be a clinical problem, as long as the person is not connected to the environment during surgery.

The incidence of anesthesia awareness ranges from 0,007 to 1% (Mashour, Orser, & Avidan, 2011). A review study by Ghoneim et al. (2009) concluded that the risk factors for being aware during anesthesia were light anesthesia and having experienced awareness during anesthesia before. Awareness during anesthesia can lead to immediate consequences and later to psychological sequalae. The inability to move and the feelings of hopelessness, anxiety and fear during anesthesia were strongly associated with later psychological symptoms, such as insomnia, flashbacks and nightmares (Bruchas, Kent, Wilson, & Domino, 2011; Ghoneim, Block, Haffarnan, & Mathews, 2009). Memory of the experience during anesthesia can be traumatic or otherwise trouble the patient depending on the length of the awareness and how fearful the experience was. Avoidance behaviors, which are the diagnostic criteria for posttraumatic stress syndrome (PTSD) (Aceto et al., 2013), can also occur, such as avoiding environments or things that are related to hospitals. Additionally, it has been shown that retrospective amnesia is not a guarantee of unconsciousness as anesthetized patients can show goal-directed behaviors during surgery and not remember these afterwards (Sanders et al., 2012). Therefore, intraoperative awareness, and the symptoms of PTSD, can occur through implicit memory in the absence of explicit recall (Wang, Messina, & Russell, 2012), which is why it would be important to recognize intraoperative awareness in real time.

Dreaming during anesthesia refers to any experience (excluding awareness) that the person thinks happened between the onset of anesthesia and the first moment of regaining awareness of the environment (Hobbs, Bush, & Downham, 1988). Dreaming is usually disconnected from the environment, thus it is considered to be pure form of phenomenal consciousness (Mashour, 2011; Revonsuo, 2006). Dreaming during anesthesia has been reported by approximately 20 to 50% of patients (Leslie & Skrzypek, 2007; Errando et al., 2008). Similar incidence (19%) is reported in patients under sedation (Eer, Padmanabhan, & Leslie, 2009). Factors that associate with the reported incidence of dreaming include, for example, patient's age and gender, the choice of anesthetic agent, the depth of anesthesia, and when the person is interviewed (Leslie & Skrzypek, 2007).

Since typically in clinical anesthesia more than one anesthetic agent is administered, along with other drugs, most of the studies on subjective experiences during anesthesia have used patient data and thus, studied the effects of drug cocktails (Noreika et al., 2011). What is further problematic in these studies is that information about experiences during anesthesia are acquired by interviews after the recovery period, and thus after the effects of the anesthetics have dissipated. Therefore, it is impossible in the case of dreaming to distinguish whether the dreams have taken place during the anesthetic administration or during the recovery period. Given the time interval between the anesthesia and the interview, and the amnestic effects of anesthetic drugs, the patients might not be able to recall dreams or other experiences that they actually experienced during anesthesia. This suggests that the incidence of subjective experiences may be even higher (Revonsuo & Arstila, 2011). Also, the clinical condition of the patients, and combination of anesthetic agents and other drugs might affect the incidence and recall of dreaming and other experiences (Noreika et al., 2011).

Only few controlled experimental studies on the effects of a single drug on subjective experiences have been done. The two single-drug experimental studies of experiences during anesthesia conducted to date found the incidence of recalling subjective experiences to be higher than in clinical patient studies. In a study by Noreika et al. (2011), 58.6% of the participants reported experiences after regaining responsiveness. Additionally, in a study by Radek et al. (2018), 83.9% of participants reported experiences from the unresponsiveness period. Most of these were dream-like (85.9%) or memory incorporation of the experimental setting (76.9%) while awareness reports were rare (16.7%) and all awareness experiences were linked to brief arousals. In both studies, the incidence of reporting subjective experiences was higher for those receiving dexmedetomidine than propofol.

The contents of dreams during anesthesia have been systemically addressed in only a few studies. Usually the contents of dreams during anesthesia resemble those of dreaming during natural sleep (Leslie & Skrzypek, 2007). They are short and pleasant and are related to everyday events. In the two single-drug experimental studies addressing experiences during anesthesia, the contents of experiences were categorized using the Subjective Experiences During Anesthesia Coding System (SEDA) (Noreika et al., 2011) or a modified version of SEDA (Radek et al., 2018). Noreika et al. (2011) concluded that the subjective experiences ranged from simple sensations to complex dream-like stories. Additionally, Radek et al. (2018) concluded that dream-like experiences were brief, mostly static, and emotionally slightly more positive than negative. When the contents of subjective experiences between drugs have been compared, Noreika et al. (2011) found that laboratory experiences related to the operating room and hospital were more frequent when participants received sevoflurane than dexmedetomidine whereas Radek et al. (2018) did not find any differences in report contents between dexmedetomidine and propofol.

Since patients who have undergone surgery can be interviewed only after recovery period, it has been suggested that dreaming does not occur during the actual anesthetic infusion, but during the recovery period when the anesthetic-induced unresponsiveness transforms to natural sleep (Leslie, Skrzypek, Paech, Kurowski, & Whybrow, 2007). In an experimental study by Radek et al. (2018), the participants were roused during constant infusion and also interviewed after recovery, and they reported dreams equally often during the anesthetic infusion and after recovery period. This indicates that dreaming is not only limited to the recovery period but also present during anesthetic infusion.

The dreams experienced during anesthesia have also been correlated with measures of the depth of anesthesia, such as BiSpectral Index (BIS). BIS is based on electroencephalography (EEG), and by using an algorithm it reduces a complex EEG signal into a number which indicates the depth of anesthesia in the patient (Alkire et al., 2008). The meter provides, as an indicator of anesthesia depth, a number from hundred (wake) to zero (no electrical brain activity). It is, however, unclear whether dreaming can be predicted by this kind of a monitor. Leslie et al. (2007) concluded that the depth of anesthesia is unrelated to dreaming. However, in a study by Noreika et al. (2011) BIS values were associated with subjective experiences during anesthesia, although different drugs had differential correlations with BIS values. In the Noreika et al. (2011) study, the BIS values were higher during the unresponsive phase (i.e., closer to wake state) in dexmedetomidine-receiving participants who reported dreams. On the contrary, in participants receiving propofol BIS values were lower (deeper anesthesia) in those who reported dreaming after recovery. These results support the fact that subjective experiences can occur during the unresponsive phase and that differences between drugs and their effects should be analyzed separately.

The Purpose of The Present Study

The first aim of this study was to compare the prevalence and contents of subjective experiences in responsive and unresponsive sedative states (participants were divided to two groups based on their responsiveness at the end of the experiment); how does responsiveness affect subjective experiences and are the experiences of responsive participants more often related to the environment? Second, we investigated the prevalence and contents of subjective experiences during sedation; how often are subjective experiences reported after sedation, and are most of the contents disconnected (i.e., dream-like)? Finally, we explored the similarities and differences in subjective experiences between anesthetic agents; does the anesthetic agent influence the prevalence of reporting subjective experiences and are some anesthetic agents more likely to lead to dream-like (disconnected) vs. awareness (connected) experiences?

Most of the studies on dreaming and awareness during anesthesia have been conducted with surgical patients. This study aims to avoid the problems of clinical studies by using healthy young participants who are anesthetized with single anesthetic agent and not with a drug cocktail of anesthetics, analgesics, and muscle relaxants. We further extend the previous experimental studies on subjective experiences during experimental anesthesia by utilizing four different anesthetic agents: dexmedetomidine, propofol, sevoflurane and S-ketamine. Additionally, unlike in previous experimental studies, we use here an equipotent anesthetic dose for each participant within a drug group (i.e., the plasma target concentration is the same for all participants while drug dose is adjusted for body weight) and responsiveness varies individually. We also use an equipotent dose of the different anesthetics (i.e., the administered doses of dexmedetomidine, propofol, sevoflurane and S-ketamine are equally sedative). We control carefully the participant's responsiveness during the experiment with responsiveness testing and compare experiences during unresponsive and responsive sedation, acquired by interviews conducted immediately after termination of drug infusion.

Methods

The current study is a part of the Academy of Finland funded "Conscious Mind" -project. The study was conducted in Turku PET Centre, Finland, it was registered in ClinicalTrials.gov (NCT02624401) and approved by the Ethics Committee of the Hospital District of Southwest Finland and the Finnish Medicines Agency Fimea (EudraCT 2015-004982-10). A written informed consent was acquired from all the participants according to the Declaration of Helsinki.

Participants

In addition to anesthesia and interviews, the participants underwent Positron Emission Tomography (PET) imaging. Because of exposure to radioactive fluorodeoxyglucose tracer [^{18}F]FDG, the participants were required to be male, 18-30 years, in good general health (American Society of Anesthesiologists status class I) and have normal results in physical examination and laboratory tests including drug screening. Due to experimental demands, they were also right handed, had normal hearing, and were fluent in Finnish. The participants were instructed not to use any medication or alcohol for 48 and caffeine products for 10-12 h prior to the study session and fasted from the previous midnight. The participants were informed that they may withdraw their consent to participate at any time during the study. Each participant was compensated with 340 euros for participating. Altogether 166 participants were recruited (dexmedetomidine (n = 40, age = 20-30), propofol (n = 40, age = 18-28), sevoflurane (n = 41, age = 19-30), S-ketamine (n = 24, age = 20-30) and saline placebo (n = 21, age = 20-28). Participants were randomized with balanced permuted block sizes of 16 to receive one of the four anesthetic agents or saline placebo. To ensure random allocation, the person in charge of participant recruitment was not responsible for randomization. As the aim of this study was to investigate subjective experiences induced by four different anesthetics, participants receiving saline placebo were omitted from all the analyses.

Materials and Procedure

This was a controlled, parallel-group study, and conducted in a nonsurgical setting during one session. The preparations for the experiment included inserting two venous cannulas in the right forearm, one for administration of the anesthetic and Ringer's acetate, and the other one for injecting the radioactive tracer. Further, the radial artery in the left wrist was cannulated for blood sampling. Electroencephalogram (EEG) with 64 channels was recorded throughout the experiment (NeurOne 1.3.1.26 software and Tesla #MRI 2013011 and #MRI 2013012 amplifiers; Mega Electronics Ltd.). An active electrode cap (EasyCap GmbH, Herrsching, Germany) was placed on the participants' scalp, four electrodes were used to measure eye movements, and two electrodes to measure electrocardiogram. The participants also filled in a questionnaire regarding their emotional states before and after the experiment. PET, EEG, and questionnaire results will be reported elsewhere. An overview of the study procedure is shown in Figure 1.

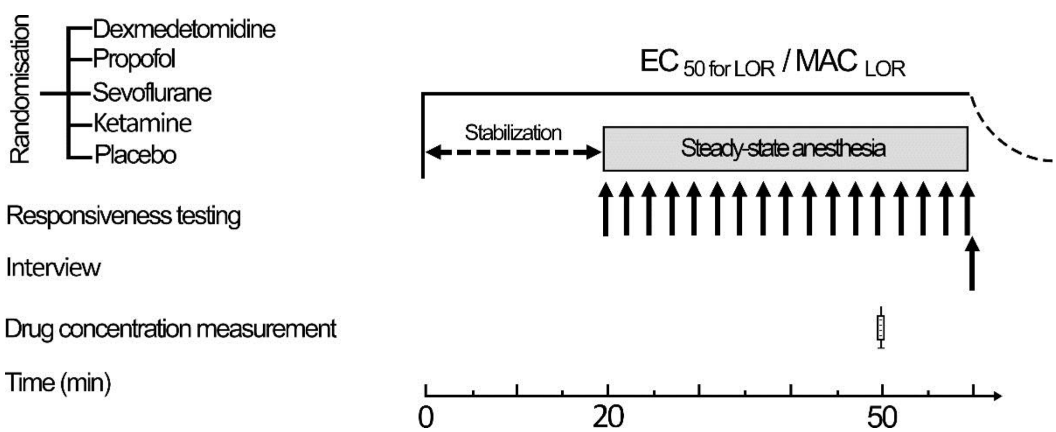

Figure 1. Anesthesia procedure, sequence of events, and the timing of responsiveness tests, interview and the last drug concentration measurement.

After the preparations, data collection was initiated by collecting 5 min of baseline EEG recording with eyes closed. Then the target controlled infusion (or inhalation in the case of sevoflurane) was started. The drug administration protocol included a 20 min stabilization phase, followed by 40 min steady-state anesthesia (i.e., total duration of administration was 1 hour). Within the drug groups, each participant received an equipotent dose of anesthetic, and the dose was equisedative between drug groups. The effective concentration (EC) for dexmedetomidine, propofol, and S-ketamine, and the minimum alveolar concentration

(MAC) for sevoflurane, were administered at equisedative doses to achieve loss of responsiveness (LOR) in 50% of participants. The aim in each drug group was to achieve, with the same dosage of anesthetic, a sample where half of the participants would become unresponsive, and the other half would maintain their responsiveness, due to individual thresholds needed to induce unresponsiveness. The rationale was to compare brain glucose metabolism, EEG changes and subjective experiences in responsive and non-responsive subjects after a standard dose of different anesthetics (i.e., omitting the effects of varying drug doses on the measures). $EC_{50 \text{ for LOR}}$ (1.5 ng ml^{-1} for dexmedetomidine, 1.7 µg ml^{-1} for propofol, and 0.75 µg ml^{-1} for S-ketamine) and MAC_{LOR} (end-tidal target of 0.9%) doses were based on previous studies (Kaskinoro et al., 2011; Långsjö et al., 2005, 2012).

The responsiveness testing (r-testing) was performed from the beginning of the experiment at 2.5 min intervals. A pre-recorded request “press the handles twice” was delivered via headphones, with Presentation 17.0 stimulus delivery and experimental control software system (Neurobehavioral Systems Inc., Berkeley, CA, USA). The custom-made response handles were secured to the participant’s wrists with velcro so that the handles would not fall off. When the subject squeezed his fingers in response to stimuli, a time-locked trigger was saved to the digital EEG tracing. Additionally, every unexpected and/or potentially disturbing event (e.g., phone ringing or researcher sneezing) was manually marked to the EEG tracing.

After 60 minutes, drug administration was terminated, and the participants were roused by calling their name and shaking them gently. If awakening was successful, they were interviewed about their experiences using a semi-structured interview (Table 1.). After the interview, the participants were transported to PET scanner for imaging which lasted for 30 min. The participants were monitored in the study unit until all signs of anesthesia/sedation had disappeared but at least for 2 hours. The participants were then released with an escort.

Table 1.
The interview questions

Did you dream during sedation?
Did you experience anything related to the research environment during sedation?
Did you hear anything during sedation?
Did you sense anything (else) during sedation?
Do you remember anything else that you have not already mentioned?
What is the last thing you remember before falling asleep?
What is the first thing you remember after awakening?

Note. If the participant answered yes to any question, he was asked to describe the experience in as much detail as possible

Data Analyses

Responsiveness of participants receiving anesthetics during the experiment was addressed. For clarification, Figure 2. highlights the responsiveness analysis process and explicates, for example, participants with missing data on responsiveness tests (due to error during experimentation, for example, the participant had managed to shake the response handles off).

To investigate the effect of responsiveness on reporting experiences, we used r-test results to divide the participants into two groups depending on whether they had been responsive in the last two r-tests (tests presented 2.5 minutes before the awakening attempt, and just prior to awakening attempt). Participants who were not responsive in the penultimate or the last r-tests were classified as *unresponsive*, and participants who were responsive in both last r-tests were classified as *responsive*. Notably, we assumed that if the participants have reported experiences in the interview, the experiences most likely originate from the last minutes of the anesthetic infusion, as most recent experiences are the ones most likely to be recalled and thus reported. Of course, the exact timing of the experiences cannot be determined. Further, except for these last two r-tests, the participant could have been responsive or unresponsive in any of the other preceding r-tests during experiment.

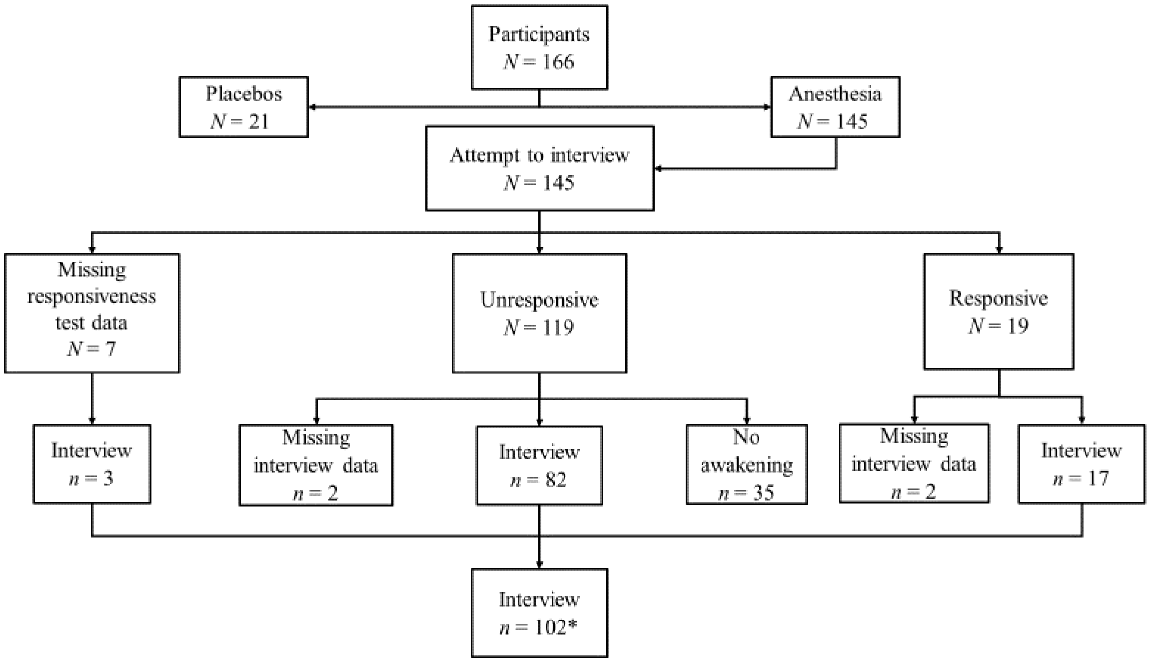

Figure 2. The process of analyzing responsiveness and acquiring interviews for the content analysis
*One participant did not wake up immediately after termination of anesthetic infusion, however, he reported experiences later and was included in the analysis

Interview transcripts were systemically content analyzed by two independent judges using a slightly modified version of a previously published scale (Radek et al., 2018). In the first phase, the judges categorized whether the participants had reported experiences from during the administration of the anesthetic agent and distinguished *anesthetic reports* (experiences that occurred during the administration of the anesthetic) from *white reports* (the participant believes he had experiences during anesthesia but cannot recall any content) and from *no recall reports* (see Table 2. for description of the scale and definitions).

In the second phase, anesthetic reports were categorized according to whether they included *dream-like experiences* (i.e., internally generated content of consciousness), *memory incorporation of the research environment* (experiences related to things/persons that have been present or events that have occurred during the anesthesia session), or *awareness of the environment* (experiences related to verifiable stimuli that the participant cannot have expected to occur during the anesthesia session). Distorted experiences of the research environment, such as dreaming of a researcher in an imaginary environment were scored as dreaming.

In phase three, the judges categorized the anesthetic reports according to perceptual complexity and dynamics of experiences. Perceptual experiences were categorized either as *static* (isolated, fragmentary percept) or *dynamic* (temporal progression, narrative structure, typically multiple sensory modalities), and separately for dream-like, memory incorporation and awareness experiences.

In the final phase, the judges categorized the nature of sensory-perceptual experiences (e.g., visual, auditory etc.), affective states (positive, negative), cognition (thinking and remembering), out of body experiences and sense of presence, again separately for dream-like, memory incorporation and awareness experiences. After each phase, the inter-rater reliability was calculated, and the judges settled the disagreements by discussion.

Table 2.
The content analysis scale for the classification of the interview reports

Phase 1. All interviews were coded as follows	
No awakening	The participant could not be woken up for interview immediately after drug infusion was terminated
No recall report	The participant regains responsiveness but does not recall any experiences.
White report	The participant reports having had experiences during anesthetic administration/unresponsiveness but has no recall of explicit content (i.e., fails to recall any aspects of content while retaining a strong impression of having experienced something).
Anesthetic report	The participant reports having had experiences that have most evidently taken place during the period of anesthetic administration/unresponsiveness.
Phase 2. Anesthetic reports were further coded as follows	
Dreaming	Purely internally-generated hallucinatory experiences (i.e., reports of content of consciousness that is not directly related to or does not originate from the research environment).
Memory incorporation	Experiences which realistically depict objects or persons that have been present, events that have occurred, or sensations/feelings related to the events, during the experimental session. The experiences are not coded as dreaming although may be mixed with the dream environment. Timing the experience to anesthetic administration/unresponsive period cannot be verified as the report includes references to elements that have been present during the experimental session also beyond the confines of the administration/unresponsiveness periods.
Awareness of environment	Externally-generated experiences which are related to objects/persons that have been present, or events that have occurred, during anesthetic administration/unresponsiveness, and the occurrence of which the participant could not anticipate, and which thus cannot be memory incorporation.
Phase 3. Dreaming, memory incorporation and awareness of environment reports were separately categorized by perceptual complexity and dynamics of experiences.	
Static	An isolated, fragmentary percept or several unconnected or interconnected percepts with typically only one sensory modality are present, with no temporal progression or narrative structure
Dynamic	An experience that amounts to a world-simulation. Some change or movement or action or interaction occurs between several interconnected experiences within a scene, so that typically there are at least two sensory modalities present (although can be only visual), temporal progression and/or narrative structure.
Phase 4. Dreaming, memory incorporation and awareness of environment reports were separately categorized by modality of the experience	
Sensations and perceptions	Visual, auditory, interoceptive, tactile, pain and temperature, kinesthetic, olfactory and gustatory experiences.
Affective states	Positive or negative emotions, feelings or moods.
Cognition	Inner speech, thinking, thoughts, remembering, planning and silent reflection of content in phenomenal consciousness.
Out-of-body experience	Observing one’s body and/or the experimental situation from an outsider position.
Sense of presence	Feeling a sense of presence of another person or being without perception of the person or being.

For clarification, Table 3. shows examples of experiences the participants reported after sedation and how the experience was content analyzed. As evident in the examples, the same report may include both dreaming and memory incorporation.

Table 3.
Examples of subjective experiences and content analysis

Drug	Type of anesthetic report	Complexity	Modalities	Summary
Dex	Dream, memory incorporation	Dynamic dream, static memory incorporation	Visual	The participant reports short dreams where "there was a labyrinth in a hospital" and "real drugs, real doctors and a hamster dressed in gold came from there".
Pro	Dream	Static	Visual, kinesthetic, negative emotion	The participant describes "he was in a cafeteria and saw some people who might have looked like hackers and he walked past them". He felt the dream was a little unpleasant and he felt threatened.
Sev	Dream	Static	Visual, auditory, positive emotion	The participant reports "he was sitting with two people somewhere and they talked to him. He tried to listen the conversation but could not comprehend what they were saying". He reported the experience to be positively rather than negatively toned.
Ket	Anesthesia awareness	Static	Auditory	The participant reports hearing the sentence stimuli during anesthesia: "there were elements when suddenly I had to respond to someway and I heard them all clearly" and "they felt little external to the dream". He did press the handles when the sentence stimulus was presented. Additionally, he recalls hearing "murmuring" at some point. (There was a continuous silent peeping sound during the first 10 minutes of the experiment from unknown origin).
Ket	Dream, memory incorporation	Dynamic dream, static memory incorporation	Visual, cognition	The participant reports "the world spun over, there was a black color which was as black as it could be and then the dream popped on its place" He said that "I was concentrating what was happening in my head and wondering who am I, and then I was like I am who I am, and I can't understand the reality". He also reported that he saw the corner of the experimental room in the dream.

Statistical Methods

Statistical analyses were performed with IBM SPSS version 25 for Windows™ software. The inter-rater reliability between the two independent judges was measured with Cohen's Kappa coefficient (κ). Kappa values <.00 indicates poor agreement, .00-.20 slight agreement, .21-.40 fair agreement, .41-.60 moderate agreement, .61-.80 substantial agreement, and .81-1 almost perfect agreement (Landis & Koch, 1977). The data were analyzed with nonparametric methods due to modest sample size and skewed distributions, tested with Kolmogorov-Smirnov normality test. The association of measured drug concentrations with awakening, and differences between drugs in the prevalence of awakenings, report types, perceptual complexity and dynamics, and modalities were analyzed with Kruskal-Wallis test (*H*), Mann-Whitney U-test (*U*), Chi square test (χ^2), and with Fisher's Exact Test (*FET*; when expected counts were too low for χ^2). Dunn's Multiple Comparison Test was used as a post hoc test for Kruskal-Wallis test. As a post hoc test for chi square test, the proportions were compared using z-test. Bonferroni correction was used for the *p* values when multiple comparisons were conducted. For Kruskal-Wallis and Mann-Whitney tests, eta squared (η^2) was used as a measure of effect size, values between .000-.003 indicate no effect, .01-.039 small effect, .06-.110 intermediate effect, and values over .14 indicate large effect (Lenhard & Lenhard, 2016). For Chi square test, Cramer's V was used as an effect size. Cramer's *V* values .00-.09 indicate negligible association, .10-.19 weak association, .20-.39 moderate association, .40-.59 relatively strong association, .60-.79 strong association, and .80-1.00 very strong association (Rea & Parker, 1992).

Results

Responsiveness

The number of participants who were categorized as unresponsive or responsive based on the last two r-tests, and how many of them were interviewed are shown in Table 4. The anesthetic agent and whether the participant could be roused for the interview had a relatively strong association, $\chi^2(3, N = 117) = 37.787$, $p < .001$, Cramer's $V = .568$. The difference in proportions of unresponsive participants between drug groups was tested with z-test. Greater proportion of unresponsive participants were rousable for the interview in dexmedetomidine group than in sevoflurane and S-ketamine groups (both *p* values < .001), and greater proportion of unresponsive participants in propofol group were rousable for the interview than participants in sevoflurane and S-ketamine groups (both *p* values = .001).

Table 4.
The number of responsive and unresponsive participants and how many were interviewed

	Dex *n*/*N* (%)	Pro *n*/*N* (%)	Sev *n*/*N* (%)	Ket *n*/*N* (%)	Total *n*/*N* (%)
Responsive	3/40 (7.5)	9/40 (22.5)	4/38 (10.5)	3/20 (15.0)	19/138[a] (13.8)
Interview	3/3 (100)	8/8 (100)	3/3 (100)	3/3 (100)	17/17[b] (100)
Unresponsive	37/40 (92.5)	31/40 (77.5)	34/38 (89.5)	17/20 (85.0)	119/138[a] (86.2)
Interview	35/37 (94.6)	27/31 (87.1)	14/33 (42.4)	5/16 (31.2)	81/117[c] (69.2)
No awakening	2/37 (5.4)	4/31 (12.9)	19/33 (57.6)	11/16 (68.8)	36/117[c] (30.8)

[a] There was no information on the last two r-test results from seven participants
[b] Two participants classified as responsive did not have information about the interview
[c] Two participants classified as unresponsive did not have information about the interview

The mean (*SD*) drug concentration at 50 min (last concentration measurement) for dexmedetomidine was 2.06 (0.34) ng ml^{-1}, for propofol 1.73 (0.37) µg ml^{-1}, for sevoflurane 0.91 (0.04) end-tidal%, and for S-ketamine 1.03 (0.23) µg ml^{-1}. The only significant difference between drug concentration and rousability, with large effect size, was found in participants receiving S-ketamine. The measured concentration at 50 min was greater for those who could not be woken up for the interview immediately after termination of anesthetic administration (Mdn = 1.12, n = 11) than for those who could be roused for the interview (Mdn = .88, n = 8), U = 8.000, p = .002, η^2 = .465.

Interviews and Inter-rater Reliability

The interviews took place immediately after the administration of the anesthetic had been terminated, and in case of return of responsiveness. Of all participants, 35 could not be roused for the interview. Notably, three participants who received S-ketamine reported experiences during or after the PET imaging, and these three reports were included in the anesthetic report analyses. One of these participants did not wake up after termination of anesthetic infusion but later recalled his experiences, another participant first reported that he did not experience anything but later recalled experiences, and a third participant first gave a white report, but later recalled the contents of the experience. Altogether, interviews could be obtained from 102 participants, and these were further content analyzed. The process of content analysis is shown in Figure 3.

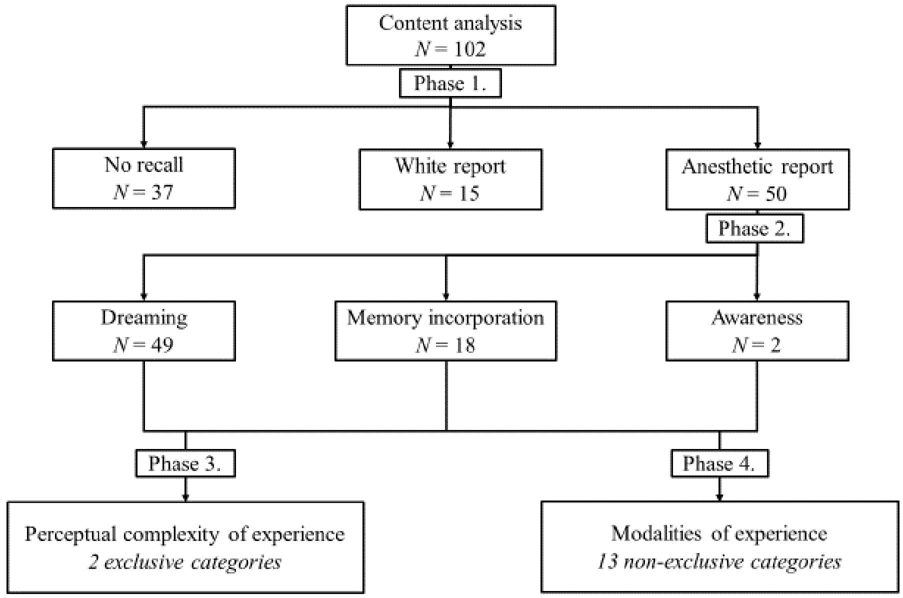

Figure 3. The frequency of report types and the process of content analysis

Two independent judges content analyzed the reports. Inter-rater reliability ranged from substantial to almost perfect agreement, and the overall inter-rater agreement was κ = .888, p <.001, 95% Cl[.868, .908]. The reliability for categorizations of the report type (no recall, anesthetic report, white report) was κ = .947, $p < .001$, 95% Cl[.906, .988], for the anesthetic report experiences to include dream-like imagery, memory incorporation or awareness of the environment κ = .895, $p < .001$, 95% Cl[.824, .965], for the perceptual complexity and dynamic of experiences κ = .742, $p < .001$, 95% Cl[.651, .832], and for the modality of experiences κ = .724, $p < .001$, 95% Cl[.663, .785].

Subjective Experiences in Anesthetic Reports

Of those interviewed, nine participants categorized as responsive (52.9%) gave an anesthetic report, while 38 unresponsive participants (46.3%) gave an anesthetic report. In responsive group, nine anesthetic reports (100%) included dream-like imagery, one report (11.1%) included memory incorporation, and none included awareness. In unresponsive group, 37 anesthetic reports (97.4%) included dream-like imagery, 15 reports (39.5%) included memory incorporation, and one report (2.7%) included awareness. There were no statistically significant differences between responsive and unresponsive groups in the prevalence of reports $\chi^2(2, N = 99) = .308$, $p = .878$, Cramer's $V = .056$, or in the type of experience in the anesthetic reports (all *p* values > .138, *FET*). Thus, the groups were pooled together, and the content analysis results are reported for pooled reports. Prevalence of report types in those who were interviewed and who reported experiences are shown in Table 5.

A moderate association was found between report type and drugs, $\chi^2(3, N = 102) = 13.622$, $p = .003$, Cramer's $V = .365$. Z-test was used to evaluate the proportions between drugs in reporting anesthetic reports. Participants receiving dexmedetomidine gave more anesthetic reports than participants receiving propofol ($p = .004$), or sevoflurane ($p = .044$) (Table 5.). No differences were found between drugs in reporting dreaming, but there was an association between drugs and reporting memory incorporations ($p = .003$, *FET*), *FET* analyses were conducted as a series of bivariate comparisons to investigate the differences in reporting memory incorporations between drugs. Participants receiving S-ketamine reported more memory incorporations than participants receiving propofol ($p < .001$, *FET*).

Table 5.
Prevalence of report types and experiences in anesthetic reports

Report type	Dex *n*/*N* (%)	Pro *n*/*N* (%)	Sev *n*/*N* (%)	Ket *n*/*N* (%)	Total *n*/*N* (%)
No recall	6/38 (15.8)	21/35 (60.0)	7/18 (38.9)	3/11 (27.3)	37/102 (36.3)
White report	5/38 (13.2)	3/35 (8.6)	5/18 (27.8)	2/11 (18.2)	15/102 (14.7)
Anesthetic report	27/38 (71.1)	11/35 (31.4)	6/18 (33.3)	6/11 (54.5)	50/102 (49.0)
Type of experience in the anesthetic report					
Dreaming	26/27 (96.3)	11/11 (100)	6/6 (100)	6/6 (100)	49/50 (98.0)
Memory incorporation	10/27 (37.0)	0/11 (0.0)	3/6 (50.0)	5/6 (83.3)	18/50 (36.0)
Awareness	0/27 (0.0)	0/11 (0.0)	0/6 (0.0)	2/6 (33.3)	2/50 (4.0)

Perceptual Complexity and the Modality of Anesthesia Experiences

Perceptual complexity and modality of experiences were analyzed separately for dreaming, memory incorporation and awareness reports. The frequencies of complexity and modality in anesthetic reports are shown in Table 6. Out of 50 reports, two included references to awareness of the environment, both were reported in S-ketamine group, and both were static auditory experiences, thus complexity and modality of awareness experiences are not shown in Table 6.

Anesthetic agent had a large effect on how complex the dream-like experience was, $H(3, 49) = 11.017$, $p = .012$, $\eta^2 = .178$. Dunn's pairwise tests indicated that there was a significant difference between S-ketamine ($n = 6$) and dexmedetomidine ($n = 26$), $p = .006$; participants receiving S-ketamine had more dynamic dream-like experiences than those who received dexmedetomidine (Table 6.).

To compare modalities between drugs, the modalities were grouped into three sum variables: sensations (visual, auditory, interoception, gustatory, pain and temperature, kinesthesia and balance, olfactory and tactile), emotions (positive and negative) and cognition (thoughts and memories). Anesthetic agent had a large effect on how much there were thoughts and memories in dreams, $H(3, 49) = 10.132$, $p = .017$, $\eta^2 = .158$. Dunn's pairwise tests showed significant difference between propofol ($n = 11$) and S-ketamine ($n = 6$), $p = .018$; participants receiving S-ketamine had more cognitive aspects in their dream-like experiences (Table 6.).

There were no statistical differences between anesthetic agents in the complexity of perceptual content in the memory incorporations ($p = 1$, *FET*). Kruskal-Wallis test was conducted to evaluate the differences between drugs in the modalities of memory incorporation experiences. Anesthetic agent had a large effect to how much there were sensations in the memory incorporation experience, $H(2, 18) = 6.889$, $p = .032$, $\eta^2 = .326$. Dunn's pairwise tests indicated that there was a significant difference between dexmedetomidine ($n = 10$) and S-ketamine ($n = 5$), $p = .029$; participants receiving S-ketamine had more sensations in their memory incorporations (Table 6.).

Table 6.
Perceptual complexity and modality of experiences in anesthetic reports

	Dex *n/N* (%)	Pro *n/N* (%)	Sev *n/N* (%)	Ket *n/N* (%)
	Dream-like experiences			
Perceptual complexity				
No perceptual content	**2/26 (7.7)**	0/11 (0.0)	**1/6 (16.7)**	0/6 (0.0)
Static report	**18/26 (69.2)**	**7/11 (63.6)**	**2/6 (33.3)**	0/6 (0.0)
Dynamic report	**6/26 (23.1)**	**4/11 (36.4)**	**3/6 (50.0)**	**6/6 (100)**
Sensory-perceptual experiences				
Visual	**24/26 (92.3)**	**10/11 (90.9)**	**5/6 (83.3)**	**6/6 (100)**
Auditory	**3/26 (11.5)**	**3/11 (27.3)**	**4/6 (66.7)**	**3/6 (50.0)**
Interoceptive	0/26 (0.0)	**1/11 (9.1)**	**1/6 (16.7)**	0/6 (0.0)
Tactile	0/26 (0.0)	**2/11 (18.2)**	0/6 (0.0)	0/6 (0.0)
Pain and temperature	**1/26 (3.8)**	0/11 (0.0)	0/6 (0.0)	0/6 (0.0)
Kinesthetic	**1/26 (3.8)**	**2/11 (18.2)**	**1/6 (16.7)**	**2/6 (33.3)**
Olfactory	0/26 (0.0)	0/11 (0.0)	0/6 (0.0)	0/6 (0.0)
Gustatory	0/26 (0.0)	0/11 (0.0)	**1/6 (16.7)**	0/6 (0.0)
Affective states				
Positive	**14/26 (53.8)**	**7/11 (63.6)**	**5/6 (83.3)**	**4/6 (66.7)**
Negative	**3/26 (11.5)**	**1/11 (9.1)**	0/6 (0.0)	0/6 (0.0)
Cognition	**3/26 (11.5)**	0/11 (0.0)	0/6 (0.0)	**3/6 (50.0)**
Out-of-body	0/26 (0.0)	0/11 (0.0)	0/6 (0.0)	**1/6 (16.7)**
Sense of presence	0/26 (0.0)	0/11 (0.0)	**1/6 (16.7)**	0/6 (0.0)
	Memory incorporation			
Perceptual complexity				
No perceptual content	0/10 (0.0)	0/11 (0.0)	0/3 (0.0)	0/5 (0.0)
Static report	**9/10 (90.0)**	0/11 (0.0)	**3/3 (100)**	**4/5 (80.0)**
Dynamic report	**1/10 (10.0)**	0/11 (0.0)	0/3 (0.0)	**1/5 (20.0)**
Sensory-perceptual experiences				
Visual	**10/10 (100)**	0/11 (0.0)	**2/3 (66.7)**	**4/5 (80.0)**
Auditory	0/10 (0.0)	0/11 (0.0)	**1/3 (33.3)**	**4/5 (80.0)**
Interoceptive	0/10 (0.0)	0/11 (0.0)	0/3 (0.0)	0/5 (0.0)
Tactile	0/10 (0.0)	0/11 (0.0)	0/3 (0.0)	0/5 (0.0)
Pain and temperature	0/10 (0.0)	0/11 (0.0)	0/3 (0.0)	0/5 (0.0)
Kinesthetic	0/10 (0.0)	0/11 (0.0)	0/3 (0.0)	**1/5 (20.0)**
Olfactory	0/10 (0.0)	0/11 (0.0)	**1/3 (33.3)**	0/5 (0.0)
Gustatory	0/10 (0.0)	0/11 (0.0)	0/3 (0.0)	0/5 (0.0)
Affective states				
Positive	0/10 (0.0)	0/11 (0.0)	0/3 (0.0)	0/5 (0.0)
Negative	0/10 (0.0)	0/11 (0.0)	0/3 (0.0)	0/5 (0.0)
Cognition	**2/10 (20.0)**	0/11 (0.0)	0/3 (0.0)	0/5 (0.0)
Out-of-body	0/10 (0.0)	0/11 (0.0)	0/3 (0.0)	0/5 (0.0)
Sense of presence	0/10 (0.0)	0/11 (0.0)	0/3 (0.0)	0/5 (0.0)

Note. The reported contents are bolded to make the results more easily detectable

Discussion

The results of the present study show that there were no differences in the prevalence or contents of experiences between those categorized as unresponsive (no responsiveness on the penultimate or the last r-test) and responsive (responsive on both of the last r-tests), indicating that responsiveness is not directly related to the prevalence or the contents of subjective experiences. Second, subjective experiences were often reported after sedation and the contents of these experiences varied from static images to dynamic multimodal dreaming. Finally, subjective experiences were most often reported when participants were sedated by either dexmedetomidine or S-ketamine, and S-ketamine induced the most multimodal experiences. These results confirm that responsiveness should not be considered as an indicator of consciousness, that disconnected subjective experiences (categorized as dreaming) were the most often reported type of experience, and that anesthetic agents have differential effects on the prevalence and contents of these experiences.

Responsiveness

There were no differences in the prevalence or contents of anesthetic reports between responsive and unresponsive participants, which suggests that responsiveness is not directly related to the occurrence or contents of subjective experiences. Given that memory incorporation may signal awareness of the environment in some cases, it was reasonable to expect that responsive participants would have experienced more memory incorporations or direct awareness, however, this was not the case. Additionally, unresponsive participants who received dexmedetomidine or propofol were more often rousable compared to participants who received sevoflurane or S-ketamine. In the case of dexmedetomidine, this is typical, as the agent is sedative and allows return of responsiveness with stimulation. In the case of propofol this may indicate faster recovery than for participants receiving sevoflurane and S-ketamine. Notably, participants receiving S-ketamine were in some cases unable to answer the interview questions immediately due to speech difficulties, even though they were responsive.

In this study, the target concentration used was equipotent so that every participant was targeted with equisedative dosage of the drug, while for instance in the study by Radek et al. (2018) the concentration was titrated individually to just exceed the person’s threshold of unresponsiveness. The mean concentrations were greater in Radek et al. (2018) study than in this study (3.13 ng ml^{-1} vs 2.06 ng ml^{-1} in dexmedetomidine groups, 2.6 µg ml^{-1} vs 1.73 µg ml^{-1} in propofol groups) and all participants were unresponsive before the interview, which might influence the occurrence and/or reporting of anesthesia experiences. In this study, the only significant connection between rousability and drug concentration level was found in the S-ketamine group, where the concentration of S-ketamine had a large effect on whether not the participant woke up and gave an interview. Notably, participants who did not wake up had almost the same concentration (1.12 µg/ml) required for the minimum anesthetic concentration (approximately 1.2 µg/ml) (Långsjö et al., 2005).

Reports and Contents

Of the 145 participants receiving anesthetics, 102 gave an interview. Of the 102 participants, almost half of the participants reported having subjective experiences (49.0%), while previous studies have found that dreaming occurs around one fifth of clinical patients, even up to 53% (Leslie & Skrzypek, 2007; Errando et al. 2008). The result of the present study thus fits in the scope of previous findings observed in clinical populations. Additionally, comparing this result to the other two experimental studies, the occurrence was similar with the study by Noreika et al. (2011) (58.6%), however lower than in the study by Radek et al. (2018) (83.6%). When comparing single anesthetic agent's association to the occurrence of reported experiences, a similar trend in the different studies is evident: participants receiving dexmedetomidine tend to report experiences more often than participants receiving propofol. In the study by Noreika et al. (2011), the occurrence of reported anesthesia experiences in dexmedetomidine group was 73.7% and 36.8% in propofol group, while in the study by Radek et al. (2018), the occurrence was 89.8% for dexmedetomidine and 73.5% in propofol group. In this study the occurrence was 71.1% for dexmedetomidine and 31.4% in propofol group.

In this study, participants receiving dexmedetomidine or S-ketamine reported more experiences than participants receiving propofol or sevoflurane. This is in line with previous studies showing that after dexmedetomidine sedation and S-ketamine anesthesia, dreams are often reported (Leslie & Skrzypek, 2007; Noreika et al., 2011; Radek et al., 2018). Almost all of the subjective experiences (except one) contained dream-like content with no difference between drugs. Memory incorporations were also quite common phenomena. However, in the propofol group, none of the reports included memory incorporations which was a surprising finding because in the previous study the occurrence of memory incorporations was much higher with propofol (Radek et al. 2018: 87.5%). This could result from differences in how persistently the participants were interviewed about memory incorporations or how strictly the content analysis criteria were applied in this study versus the study by Radek et al. Another explanation could be that the participants were roused several times in the experiment by Radek et al., thus having more chances for memories to be incorporated into experiences, or the participants were possibly more used to being interviewed and reporting experiences. Notably, only two participants reported experiences related to awareness and both were reported by participants receiving S-ketamine. This finding is similar to that of Noreika et al. and Radek et al. observations with dexmedetomidine and propofol, while in this study participants receiving other agents than S-ketamine did not report awareness experiences.

The dreams during sedation were classified more often as static (55.1%) while fewer dynamic dreams (38.8%) were reported. Previous studies have described dreaming during anesthesia and sedation as simple in nature (Leslie & Skrzypek, 2007; Radek et al., 2018). Our findings show that over third of the dreams were dynamic which is, however, probably explained by the fact that we used S-ketamine which is known to cause highly vivid dreams. Further, all anesthesia reports in the S-ketamine group were classified as dynamic and containing multimodal experiences which corroborates the previous ketamine studies showing that it causes vivid dreams, floating sensations, and audiovisual perturbations (Collier, 1972; Marland et al., 2013; Vlisides et al., 2018). Dream reports in the S-ketamine participants had more cognitive aspects than in propofol participants and more sensations in their memory incorporations than in dexmedetomidine participants. The two reports by participants receiving S-ketamine which included references to awareness were static auditory experiences. One of them was most likely related to concentration level, since the participant had the lowest concentration of S-ketamine compared to others. The other participant experiencing awareness did not have r-test results, but the experiment was terminated after 40 minutes due to the participant screaming and moving. The participant did not feel discomfort, on the contrary, he reported that the experience was positive. He also said that he was in “a borderline state” where he thought he was aware of what was happening, and he could influence what was happening. This dissociative state seemed to be a common theme for the participants receiving S-ketamine and could explain the prevalent memory incorporations and references to awareness.

Limitations

In this study, some participants reported dream-like experiences which were mixed with incorporated experiences related to the experiment, such as the environment or the feeling of cannulation. One of the limitations of this study was that we cannot be sure whether the memory incorporations actually were awareness experiences or just memories from before the anesthetic administration. Such experiences have previously been assumed to reflect disconnected consciousness and incorporation of previous events from memory (Radek. et al. 2018) rather than real awareness.

One of the aims of this study was that with the chosen anesthetic dose half of the participants should remain responsive throughout the experiment and the other half should become and remain unresponsive. However, this did not happen. When the participants were divided into groups based on the last two r-tests, most were unresponsive (86.2%). Thus, the number of participants in the responsive group was small. Regardless, even though the responsive group was small, the prevalence and contents of reports were similar to those who were considered unresponsive, indicating that responsiveness is not directly related to the ability to have and report subjective experiences. The decision to divide participants based on their responsiveness on the last two r-tests was done because responsiveness varied in some participants during the experiment. Thus, instead of comparing those who were responsive and unresponsive for the whole experiment, we based our division on the assumption that normally the most recent experiences are the ones most likely to be remembered whereas earlier experiences are more likely to be forgotten. Also, as anesthetics have amnesic effects, the division surely is reasonable but perhaps not the most optimal.

The biggest problem of this study, as it is for all studies that address experiences retrospectively, is the problem of memory. It is possible, due to the amnesic effects of anesthetics, that all of the sedated participants had subjective experiences at some point during the 40-minute steady-state anesthesia, but just could not recall them in the interview anymore. Thus, the absence of recall is not unambiguous marker of unconsciousness. Furthermore, in the present study, white reports were quite frequently given, demonstrating that it is not easy to recall and report subjective experiences especially after anesthesia, and this might hamper the validity of our results. Additionally, participants receiving S-ketamine usually felt like they wanted to tell more about their experiences but were not able to do so.

Finally, the findings of this study should be interpreted with caution when generalizing the results to the clinical environment. This was purely an experimental study with healthy participants, we used only one anesthetic agent for the same participant, and anesthetic doses were lower than those used in surgeries. Thus, these results cannot be directly generalized to apply to deep surgical anesthesia.

Future Directions

Future studies in clinical settings are needed to determine whether these results apply to general anesthesia. Such studies should consider not to use responsiveness as an indicator of consciousness, as the lack of responsiveness does not indicate that the person is not experiencing anything. Further, amnesia of the experiences should not be the aim as posttraumatic experiences can emerge without explicit recall of the events (Wang et al., 2012).

Memory incorporations were frequently reported in this study. Therefore, it would be advantageous in clinical settings that the anesthesiologist would inform the patient that during anesthesia or when recovering from it, dreaming can occur and that the dreams can be related to the surgery or the hospital, but they are not a sign of experiencing intraoperative awareness. This way, the patient would not be left with the wrong impression of experiencing awareness and possible later psychological consequences would be avoided. Additionally, in intensive care units the patients are often sedated but not anesthetized. Therefore, they may be more prone to be in a borderline state of being connected to the environment and thus their experiences might have more incorporated environmental stimuli, or they may experience awareness. Thus, it would be important to at least interview the patient after recovery from sedation whether he remembers any dreams or other experiences and assess what kind of contents the patient recalls.

Notably, in future studies in a clinical setting the relation between consciousness, responsiveness and memory could be assessed using the isolated forearm technique (IFT). In IFT, after the anesthetic administration a tourniquet is placed around arm before administration of muscle relaxants. The tourniquet prevents the arm to be paralyzed, and therefore the patient can communicate with specific hand movements to the observer while the anesthetic drug affects the central nervous system. Typically, the patient is asked to respond to simple questions at first and later to more complex questions to find out the patient's cognitive level. Usually, when IFT works, the patient shows almost normal cognitive functioning (Sanders et al., 2012). The interesting part is that they show goal-oriented responsiveness and seldom spontaneous responsiveness, and they do not remember the operation or answering the questions afterwards.

As the isolated forearm technique and the results of this study show, future studies should focus on the overall understanding of how and when consciousness is connected to the environment. This way, we could monitor in real time whether the experiences are related to the surgery or are they disconnected. Additionally, perhaps assessing the differences in the underlying brain activity patterns between S-ketamine and other anesthetics could increase our understanding of what causes the ability to be connected to the environment or in a dissociative state. Understanding what causes connectedness would not be only beneficial for patients undergoing surgery, but also for patients suffering from disorders of consciousness, such as locked-in syndrome or unresponsive wakefulness syndrome.

Furthermore, with brain imaging methods it has been shown that anesthetic-induced unresponsiveness is associated with disturbance in thalamocortical and cortico-cortical connectivity, and when responsiveness returns, the first activations of brain areas are seen in the deeper structures and phylogenetically ancient structures (e.g., brainstem and diencephalon) (Långsjö, et al. 2012). Therefore, it seems that emergence from anesthesia progresses firstly from activation of phylogenetically ancient structures, with limited neocortical involvement, leading emergence of responsiveness, and surprisingly, this was found to occur with both dexmedetomidine and propofol which have different mechanisms of action (Långsjö et al., 2012). The activation of these evolutionary older brain areas later enables the activation of complex network in neocortex and full consciousness (Scheinin, Scheinin, & Långsjö, 2014). Perhaps future studies should particularly focus on imaging the neocortex as this study suggests that different anesthetics have varying effects on subjective experiences and that responsiveness did not affect the prevalence or content of experiences. Especially, as S-ketamine-induced sedation showed such different effects on the contents of subjective experiences in relation to other anesthetic agents in this study, a recent study by Vlisides et al. (2018) could perhaps enlighten why the participants might have had such different experiences. The study suggested that ketamine induced its psychoactive effects by decreasing low-frequency EEG power specifically in precuneus and temporo-parietal junction, and these areas are known to have a role in consciousness, self-representation and integration of information from multiple sensory modalities (Vlisides et al., 2018).

Conclusions

The findings of this study show that independently of whether a person is unresponsive or responsive during sedation, he or she can have subjective experiences that may vary from simple static images to dynamic multimodal dreaming. Subjective experiences are frequently reported when sedated participants are interviewed immediately after terminating drug infusion. The probability of reporting experiences varies between drugs, and the highest prevalence of experiences is reported when dexmedetomidine or S-ketamine is used. In this study, most of the experiences were considered as stimulus-unrelated dreaming (i.e., signs of disconnected consciousness). Disconnected experiences seem to be more prevalent when using dexmedetomidine, propofol or sevoflurane as a sedative while S-ketamine seems to more likely be able to retain connectedness. Especially with S-ketamine, participants reported more memory incorporations, and experiences related to awareness of the environment, suggesting that S-ketamine can cause a state where a person is “in-between” or in a “borderline” state, neither completely disconnected nor fully connected.

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