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On no man's land: Subjective experiences during unresponsive and responsive sedative states induced by four different anesthetic agents

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ABSTRACT

To understand how anesthetics with different molecular mechanisms affect consciousness, we explored subjective experiences recalled after responsive and unresponsive sedation induced with equisedative doses of dexmedetomidine, propofol, sevoflurane, and S-ketamine in healthy male participants ($N = 140$). The anesthetics were administered in experimental setting using target-controlled infusion or vapouriser for one hour. Interviews conducted after anesthetic administration revealed that 46.9% ($n = 46$) of arousable participants ($n = 98$) reported experiences, most frequently dreaming or memory incorporation of the setting. Participants receiving dexmedetomidine reported experiences most often while S-ketamine induced the most multimodal experiences. Responsiveness at the end of anesthetic administration did not affect the prevalence or content of reported experiences. These results demonstrate that subjective experiences during responsive and unresponsive sedation are common and anesthetic agents with different molecular mechanisms of action may have different effects on the prevalence and complexity of the experiences, albeit in the present sample the differences between drugs were minute.

1. Introduction

The aim of general anesthesia is to render the patient unaware of invasive medical procedures, ensure immobility and provide analgesia. In the clinical setting, behavioral responsiveness is commonly used as an indicator of the patient's state of consciousness. However, the presence or absence of consciousness cannot be determined by one's behavioral capability to respond to external stimuli (Sanders et al., 2012; Scheinin et al., 2021). The problem of having no reliable objective indicators of consciousness becomes evident

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when one remains aware of external stimuli but is unresponsive and assumed unconscious. Under general anesthesia, this can manifest as unintended intraoperative awareness during surgery. Yet, having purely internally generated contents of consciousness, such as dreams, is conceivably quite common among patients undergoing surgery (Cascella et al., 2017; Huang et al., 2005; Leslie et al., 2007). The consciousness-related goal of general anesthesia could thus be redefined as to either render the patient unconscious or, at the very least, totally disconnected from all external stimuli.

Consequently, it is necessary both scientifically and clinically to understand how and to what extent anesthetic agents disable or disconnect consciousness. In the surgical setting, it is difficult to approach this issue experimentally, as patients often receive multiple drugs, are subject to an invasive medical procedure, and cannot be interviewed immediately after the surgery. Experimental studies, where the presence and contents of subjective experiences during sedation and unresponsiveness can be addressed in a more systematic and controlled way, are relatively sparse. Investigating the effects of different anesthetics on consciousness would increase our understanding about the induced phenomenal states, and perhaps reveal whether different anesthetic drugs modulate consciousness, connectedness and responsiveness in different ways or to different degrees. Therefore, the aim of this study was to compare the subjective experiences during responsive and unresponsive sedative states in a nonsurgical experimental setting in healthy male participants receiving four different anesthetic agents: dexmedetomidine, propofol, sevoflurane and S-ketamine.

1.1. Problems of defining and measuring consciousness

Consciousness in the broadest sense refers to an organism's ability to have subjective experiences. Phenomenal consciousness is the most fundamental aspect of consciousness and describes the ability to feel or experience subjective states, such as pain, feelings or sensations (Revonsuo, 2006). Research on phenomenal consciousness is challenging because of its subjective nature: science still does not have reliable objective methods for detecting the presence or contents of phenomenal consciousness. Thus, we must rely on indirect measures, such as verbal reports, a process involving reflective consciousness. Reflective consciousness refers to the ability to direct selective attention to some specific contents in phenomenal consciousness, then to apply cognitive processes (like language) to them, and thus these contents can become reportable to external observers (Revonsuo, 2006). However, the report produced does not completely reflect the original experiences, as it is reliant on one's ability to remember, reflect and report them.

Connectedness and responsiveness are central concepts to the description of consciousness, but they themselves are independent: unresponsiveness is not necessarily indicative of lack of subjective experiences, nor lack of awareness of the environment (Sanders et al., 2012). This is evidenced, for example, in locked-in syndrome where patients are fully aware and connected to the environment but completely or almost completely unresponsive (Plum & Posner, 1966). Further, purely internally generated contents of consciousness can occur when one is unresponsive and disconnected from the surroundings, such as dreaming during sleep. Responsiveness, in turn, refers to how we interact with the external world and can be measured by behavior. In a clinical setting, an unresponsive person is generally considered unconscious. However, studies using functional magnetic resonance imaging or electroencephalogram have shown that some of the patients diagnosed with unresponsive wakefulness syndrome (UWS), previously known as vegetative state, seem capable of following requests to perform specific mental imagery, that is, show signs of preserved internal consciousness and connectedness to the environment (Cruse et al., 2011; Monti et al., 2010; Owen et al., 2006; Vogel et al., 2013). Isolated forearm technique (IFT) studies have also provided evidence that anesthetized patients may respond appropriately to requests during assumed sufficient general anesthesia, although most of these patients do not move spontaneously even when exposed to a noxious stimulus, such as laryngoscopy (Russell, 2013; Russell & Wang, 2014; Sanders et al., 2017; Tunstall, 1977). Finally, patients receiving neuromuscular blocking agents and high doses of opiates have postoperatively provided convincing reports of accidental awareness during general anesthesia while they have not been able to move during surgery in response to noxious stimuli (Sandin et al., 2000).

1.2. Connected and disconnected consciousness during anesthesia

General anesthesia is based on a combination of anesthetics, analgesics, and muscle relaxants to produce unconsciousness (or disconnectedness), lack of pain sensations, and immobility, respectively. Different anesthetics offer a unique tool to modulate and investigate consciousness and its neural correlates during responsive sedation and unresponsive states, even though the exact neurophysiological and neurochemical mechanisms of different anesthetics, as well as their effects on consciousness, are still somewhat unknown (Alkire et al., 2008). Pharmacologically, the level of consciousness can be suppressed either by inhibiting the systems that maintain vigilance or by stimulating the systems that suppress it. Drugs that increase gamma-aminobutyric acid (GABA) activity enhance inhibition and suppress the activity of vigilance maintaining systems (Alkire et al., 2008; Mashour, 2014). Dexmedetomidine is an alpha-2 adrenergic agonist that activates the ventrolateral preoptic nucleus, the main sleep-promoting system in the brain, and induces a sedative state neurophysiologically similar to non-rapid eye movement (NREM) sleep by leading to the release of inhibitory neurotransmitters GABA and galanin (Mashour, 2016; Nelson et al., 2003). Propofol also activates the release of inhibitory neurotransmitter GABA to cause its hypnotic effects (Brohan & Goudra, 2017; Chidambaram et al., 2015; Franks, 2008). Sevoflurane is a volatile agent that is thought to facilitate the inhibitory GABA and glycine receptors (Brohan & Goudra, 2017; Franks, 2008; Moppett, 2015). In contrast, NMDA-receptor antagonist ketamine decreases excitation and activates vigilance suppressing systems (Alkire et al., 2008; Mashour, 2014). Ketamine has hypnotic, analgesic and amnesic effects, and in addition to NMDA receptors, it affects opioid receptors, dopamine D2 and serotonin binding sites (Kapur & Seaman, 2002; Kohrs & Durieux, 1998; Långsjö et al., 2005).

Unintended intraoperative awareness during general anesthesia implies connected consciousness (Schwender et al., 1998). There are certain factors that predispose to possible awareness during surgery which can be patient-related, surgery-related or iatrogenic,

such as underdosing (Aranake et al., 2013; Ghoneim & Block, 1992, 1997). The incidence of unintended intraoperative awareness has been estimated to range from 0.006 to 0.16% (Pandit et al., 2013; Sandin et al., 2000). Intraoperative awareness is clinically relevant as there is no definite method to detect it, and it can lead to long-term psychological distress, such as posttraumatic stress disorder (PTSD). According to previous studies, the incidence of PTSD after intraoperative awareness varies from 14.2 to 71.4% (Cyr et al., 2021; Leslie et al., 2010; Whitlock et al., 2015).

In anesthesia literature, dreaming during anesthesia typically refers to any experience (excluding awareness) that the person experienced between the onset of anesthesia and the first moment of regaining awareness of the environment (Hobbs et al., 1988). Dreaming, a form of disconnected consciousness, has been reported in post-anesthesia interviews by 13.7 to 52.6% of patients (Casella et al., 2017; Errando et al., 2008; Grace, 2003; Leslie et al., 2005, 2007, 2009; Leslie & Skrzypek, 2007; Yoshida et al., 2021), and a relatively similar incidence (13.7–39.8%) has been observed after responsive sedation (Casella et al., 2017; Eer et al., 2009; Kim et al., 2011; Stait et al., 2008, Xu et al., 2013). Notably, when ketamine has been used as the only anesthetic in procedural sedation or emergency surgery, 55.3% of patients have reported dreaming during the operation when interviewed approximately 24 h after recovery (Villegas et al., 2019). Factors associated with the incidence of dreaming include patients' age, the choice of anesthetic agent, the depth of anesthesia, and time-lag between anesthesia and the interview (Leslie & Skrzypek, 2007).

In patient studies the time-lag between the end of anesthesia and the interview may often have been substantial as the interviews cannot have been carried out until the patient has sufficiently recovered. It has therefore been suspected that dreaming during surgical anesthesia does not occur during the actual administration phase, but during the recovery period when anesthesia transforms to natural sleep (Leslie et al., 2007). As dream reports most likely capture only those experiences which have been present just prior to the awakening (Leslie & Skrzypek, 2007; Windt, 2015), delayed interviews, especially in a surgical but also in an experimental setting, are susceptible to amnesia. However, in an experimental study where healthy participants were roused during constant infusion of dexmedetomidine or propofol, and also interviewed after recovery from deeper unresponsive sedation, participants reported dream-like experiences equally often during the constant infusion and after recovery period (Radek et al., 2018). This indicates that dreaming also occurs during the drug administration phase.

There are only few controlled experimental studies on the effects of a single anesthetic drug on prevalence and content of subjective experiences. It seems that experimental setting, as compared to surgical, is generally more likely to yield a higher incidence of recall of subjective experiences, possibly due to a more moderate dose of anesthetics and conducting interviews soon after spontaneous or forced awakenings. In an experimental study by Noreika et al. (2011), participants who were rendered unresponsive with dexmedetomidine, propofol, sevoflurane or xenon reported experiences in 58.6% of awakenings after spontaneously regaining responsiveness. However, in a study by Sarasso et al. (2015) where delayed retrospective reports were collected after spontaneous awakenings from unresponsive sedation induced with propofol, xenon or ketamine, participants who received propofol or xenon did not report experiences at all whereas participants who received ketamine all reported long vivid dreams. Radek et al. (2018) utilized forced serial awakenings during constant-dose dexmedetomidine and propofol unresponsive sedation, and 83.9% of reports collected after the awakenings included experiences from the unresponsiveness period. Most of these were dream-like experiences (85.9%) or included memory incorporation of the experimental setting (76.9%) while awareness reports, indicating connected consciousness, were rare (16.7%) and always linked to brief spontaneous arousals.

Previous studies have found that the contents of dreams reported after surgical anesthesia seem to resemble dreaming during physiological NREM sleep (Leslie & Skrzypek, 2007), although comparisons have not been conducted by collecting reports from the same subjects both after anesthetic administration and physiological sleep. The dreams reported after anesthesia or sedation induced by different anesthetics have generally been found to be short, pleasant and often related to everyday events (Aceto et al., 2007; Casella et al., 2017; Eer et al., 2009; Kim et al., 2011; Leslie & Skrzypek, 2007; Leslie et al., 2009; Stait et al., 2008; Xu et al., 2013). Ketamine also tends to more often induce pleasant than frightening dreams which are, in contrast to dreams reported with other anesthetics, often long and vivid (Collier, 1972; Sarasso et al., 2015; Villegas et al., 2019). In the studies by Noreika et al. (2011) and Radek et al. (2018) which addressed experiences during unresponsiveness induced with a single-drug in an experimental setting, the contents of interview reports were categorized using the Subjective Experiences during Anesthesia coding system (SEDA) or a modified version of SEDA. Noreika et al. (2011) concluded that the subjective experiences ranged from simple sensations to complex dream-like stories and Radek et al. (2018) noted that dream-like experiences were brief, often lacking temporal progression of the narrative, and emotionally slightly more positive than negative. When the contents of subjective experiences between drugs have been compared, Noreika et al. (2011) found that experiences related to the research setting and hospital were more frequent when participants received sevoflurane than dexmedetomidine, whereas Radek et al. (2018) did not find any differences in the contents of reports between dexmedetomidine and propofol.

1.3. The aims of the present study

In this study, we investigated the prevalence and quality of subjective experiences during responsive and unresponsive sedation induced by equisedative doses of dexmedetomidine, propofol, sevoflurane or S-ketamine, administered to healthy participants. We explored the differences in the presence and contents of subjective experiences between the four different anesthetic agents, and were specifically interested in whether signs of connectedness (i.e., awareness of the research environment, for example, stimuli presented during anesthetic administration) or disconnectedness (i.e., dream-like hallucinatory experiences and memory incorporation of the research setting) differed between drugs. We further addressed whether being responsive versus unresponsive during the last minutes of sedation affected the recall rates or contents of the experiences.

2. Material and methods

This study was part of a larger project “The Neural Mechanisms of Anesthesia and Human Consciousness” that investigated cerebral metabolic rate of glucose, electroencephalographic (EEG) markers and subjective experiences in responsive and unresponsive participants exposed to equisedative doses of four different anesthetics. The functional imaging results and metabolic effects from the same study have been previously published (Laaksonen et al., 2018; Nummela et al., 2021). The study 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). The experiment was conducted in the Turku PET Centre, Finland, in a nonsurgical setting during one session. A written informed consent was acquired from all the participants according to the Declaration of Helsinki.

2.1. Participants

The participant inclusion criteria were: male, age between 18 and 30 years, good physical health (American Society of Anesthesiologists status class I), and normal results in physical examination, laboratory tests and drug screening. Given the exposure to radioactive fluorodeoxyglucose tracer [^{18}F]FDG due to PET scanning, only male participants were recruited. All participants were right-handed, had normal hearing, and were fluent in Finnish. Altogether, 366 participants were assessed for eligibility. Of them, 151 did not fulfill the inclusion criteria, 35 declined participation, and 180 were recruited for the experiment. Due to the exploratory nature of the study, a formal power analysis was not considered applicable.

The design was a controlled, parallel-group experiment. Participants were randomized with balanced permuted block sizes of 16 to receive one of the four anesthetic agents (dexmedetomidine, propofol, sevoflurane or S-ketamine) or saline placebo. Further 15 participants withdrew after randomisation, and four experimental sessions were prematurely terminated due to excessive motor anxiety. Data from one participant could not be included in any analyses due to infusion pump programming error which resulted in lower than intended anesthetic dose. Altogether 160 successful sessions were conducted ($n = 40$ in dexmedetomidine, propofol and sevoflurane groups, and $n = 20$ in S-ketamine and saline placebo groups). Each participant was compensated with 340 euros after completing the study.

The 20 participants receiving saline placebo were excluded from the current analysis. Additionally, seven participants receiving anesthetics were discarded from analyses due to missing responsiveness ($n = 4$) or interview data ($n = 3$). Thus, the final number of participants in the current study was 133, distributed followingly in the drug groups: dexmedetomidine $n = 40$, propofol $n = 39$, sevoflurane $n = 35$, and S-ketamine $n = 19$. The average age of the participants was 24.1 years ($SD = 2.9$), height 180.3 cm ($SD = 6.5$), and weight 78.3 kg ($SD = 10.4$), and there were no statistically significant differences in these participant characteristics between drug groups.

2.2. Materials and procedure

The detailed anesthetic and PET data acquisition protocol have been previously published (Laaksonen et al., 2018) and are therefore only summarized here while the methods most relevant for the present study are described in more detail. The participants were forbidden to use any medication or alcohol for 48 h, and fasted overnight prior to the experimental session. The anesthetic agents used were dexmedetomidine (Dexdor 100 $\mu\text{g ml}^{-1}$; Orion Pharma, Espoo, Finland), propofol (Propolipid 10 mg ml^{-1} ; Fresenius Kabi, Uppsala, Sweden), sevoflurane (Sevorane 100%; Abbvie, Espoo, Finland), and S-ketamine (Ketanest-S 25 mg ml^{-1} ; Pfizer, Helsinki, Finland). The participants were cannulated for administration of intravenous anesthetic, fluids, and radiotracer, and to obtain blood samples during the session. Blood pressure was measured at the beginning and end of drug administration to avoid possible cuff pain. EEG was recorded continuously and participants' end-tidal carbon dioxide and peripheral oxygen saturation with pletysmography were monitored throughout the session.

The target controlled infusion for intravenous agents was started with a Harvard 22 syringe pump (Harvard Apparatus, South Natick, MA, USA) connected to a portable computer running Stanpump software (www.opentci.org/code/stanpump) with previously reported pharmacokinetic parameters (Domino et al., 1984; Marsh et al., 1991; Talke et al., 2003). For sevoflurane, inhalation with fresh gas flow set at 6 L min^{-1} was started through a tight facemask. 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 h).

Within the drug groups, the anesthetic dose was set to obtain a sample where 50% of participants would be rendered unresponsive and 50% would sustain responsiveness, determined as the 50% effective concentration for loss of responsiveness (LOR) to verbal command (i.e., EC_{50} for LOR) or minimum alveolar concentration (MAC) for LOR (i.e., MAC_{LOR}) for sevoflurane. EC_{50} for LOR (1.5 ng ml^{-1} for dexmedetomidine, 1.7 $\mu\text{g ml}^{-1}$ for propofol, and 0.75 $\mu\text{g ml}^{-1}$ 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 level of sedation allowed all participants to sustain spontaneous breathing.

To assess participants' behavioural state during the anesthetic administration, responsiveness testing (R-test) was performed at 2.5 min intervals starting from the beginning of the steady-state anesthesia and ending with the termination of the drug infusion. 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 participants' wrists with velcro and when the participants squeezed their fingers in response to stimuli, a time-locked trigger was saved to the digital EEG tracing.

Drug administration was terminated after 60 min, and the participants were roused by addressing them by name and shaking them

Table 1

The interview questions.

Did you dream during the anesthetic administration?
Did you experience anything related to the research environment during the anesthetic administration?
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?

gently by the shoulder. If awakening was successful, they were interviewed about their experiences using a semi-structured interview modified from Brice's questionnaire and our previous studies (Brice et al., 1970; Noreika et al., 2011; Radek et al., 2018) (see Table 1.). If the participants answered yes to any interview question, they were asked to describe the experience in as much detail as possible, and additional individually tailored questions were presented based on the answers. The interviews were digitally recorded and later transcribed (for examples of interview transcripts, see [Supplementary Material](#)). After the interview, the participants were transported to PET scanner for imaging which lasted for 30 min.

2.3. Data analyses

The interview transcripts were systemically content analyzed by two independent raters using a slightly modified version of previously published scale (Radek et al., 2018). First, the obtained reports were categorized as 1) no recall reports, 2) white reports, and 3) content reports (see Table 2. for the content analysis procedure and definitions). The content reports were further categorized based on whether they included 1) dream-like fully hallucinatory experiences, 2) memory incorporation of the research environment, or 3) awareness of the environment, or a combination of these. Reports of dream-like hallucinatory experiences and memory incorporation were conceptualized as signs as disconnected consciousness whereas reports including awareness of the research environment, such as explicit recall of events that occurred during the anesthetic administration, as connected consciousness. The perceptual complexity and modality of experiences were separately analysed for dream-like, memory incorporation and awareness reports. The inter-rater reliability was calculated at each step, and the judges settled the disagreements by discussion.

Table 3. presents examples of experiences the participants reported after sedation and illustrates how the reports were coded for content.

To investigate the effect of responsiveness on recall of experiences, the participants were divided into two groups depending on whether they had shown signs of responsiveness during the last 2.5 min of the anesthetic administration. Participants who were not responsive in the penultimate and the last R-test were classified as unresponsive (UR) whereas participants who were responsive in

Table 2

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

Step 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 did not recall any experiences.
White report	The participant reported having had experiences during anesthetic administration but had no recall of explicit content (i.e., failed to recall any aspects of content while retaining a strong impression of having experienced something).
Content report	The participant reported having had experiences that had most evidently taken place during the period of anesthetic administration.
Step 2. Content reports were further coded to include any or several of the following features	
Dreaming	Purely internally-generated hallucinatory experiences, that is, reports of contents of consciousness that are not directly related to or do 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, and which have been present also beyond the confines of the administration period.
Awareness of environment	Externally-generated experiences which are related to objects/persons that have been present, or events that have occurred, during anesthetic administration, but which have been not been present beyond the confines of the administration period, and which thus cannot be memory incorporation.
Step 3. Dreaming, memory incorporation and awareness of environment experiences were separately categorized by perceptual complexity and dynamics of the experiences.	
Static	An isolated, fragmentary percept or several unconnected or interconnected percepts, with typically only one sensory modality present, with no temporal progression or narrative structure
Dynamic	An experience where some change, movement, 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), and the experience involves temporal progression and/or narrative structure.
Step 4. Dreaming, memory incorporation and awareness of environment experiences were separately categorized by modalities of the experiences.	
Sensations and perceptions	Visual, auditory, interoceptive, tactile, noci- and thermoceptive, kinesthetic, olfactory and gustatory experiences.
Affective states	Positive or negative emotions, feelings or moods.
Cognition	Inner speech, thinking, remembering, planning or reflection.
Out-of-body experience	Observing one's body and/or the experimental situation from outside of one's physical body.
Sense of presence	Feeling a sense of presence of another person or being, without perception of the person or being.

Table 3
Summarized examples of reported subjective experiences and content analysis.

Drug	Type of content report	Complexity	Modalities	Summary of the report
Dex	Dream, memory incorporation	Dynamic dream, static memory incorporation	Visual, positive emotion	The participant reported having experienced several brief dream fragments, one of them including skirts, but he best remembered a short "quite pleasant" hospital-related dream where "there was a labyrinth in a hospital" and "real drugs, real doctors and a hamster dressed in gold came out from the labyrinth".
Pro	Dream	Static	Visual, kinesthetic, negative emotion	The participant described "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 reported that "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.
S-Ket	Dream, memory incorporation	Dynamic dream, static memory incorporation	Visual, cognition	The participant reported "a wild experience" where "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 on what was happening in my head and wondering who I am, 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 and people around him".
S-Ket	Awareness of the research setting	Static	Auditory	The participant reported hearing the requests to press handles during sedation: "there were demands that roused me, demands that suddenly I had to respond to in some way and I heard them all clearly and I could respond to them" and "they felt little external to the dream". He did press the handles when the R-test was presented. Additionally, he recalled hearing "murmuring" at some point. (There was a continuous silent beeping sound during the first 10 min of the session from an unknown origin).

either of the last two R-tests were classified as showing signs of responsiveness (SoR),¹ respectively. Notably, the participants could have been responsive or unresponsive in any of the other preceding R-tests during the session, but a 2.5 min cut-off was used in classifying responsiveness as we assumed that if the participants reported experiences in the interview, the experiences probably originated from the latter part of the anesthetic infusion rather than beginning of the drug administration. Yet, the exact timing of the reported experiences cannot be determined with certainty.

2.4. Statistical methods

Statistical analyses were performed with IBM SPSS version 25 for WindowsTM software (IBM Corp, Armonk, NY, USA). The data were mostly analyzed with nonparametric methods due to modest sample size and skewed distributions, tested with Kolmogorov-Smirnov normality test. The inter-rater reliability of content analysis between the two independent judges was measured with Cohen's Kappa coefficient (κ). The differences between drugs in the prevalence of awakenings, report types, perceptual complexity, and modalities were analyzed with Kruskal-Wallis test (H), Mann-Whitney U test (U), Pearson 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, and as a post hoc test for Chi square test, the column proportions were compared using z -test. For Kruskal-Wallis and Mann-Whitney tests, eta squared (η^2) was used as a measure of effect size, whereas Cramer's V and phi coefficient (ϕ) were used as an estimate of strength of association for Chi square test, and Cohen's h as an effect size measure for z -test. Bonferroni correction was used for p values when multiple comparisons were conducted, and alpha level of 0.05 was considered statistically significant.

3. Results

3.1. Interviews and inter-rater reliability

Of the 133 participants, 98 (73.7%) were rousable at the end of the anesthetic administration and able to provide an interview report. There was a significant association between the anesthetic agent and rousability for the interview in participants categorized as unresponsive based on the two last R-tests (see Table 4). The post hoc z -tests showed that a greater proportion of UR participants were

¹ If participants did not have results from the penultimate R-test (three participants), they were categorized based on the antepenultimate and the last R-test. In addition, in participants who did not have results from the last R-test (three participants) categorization was based on the penultimate R-test. Note also that in Laaksonen et al. (2018) responsiveness of participants was categorized at the time of [¹⁸F]FDG-injection (beginning of steady-state anesthesia) for optimization of the PET analyses while in the present study responsiveness categorization was based on the last two R-tests for optimization of interview analyses. Therefore, the reported percentages of responsive and unresponsive participants are different in the present article from those reported in Laaksonen et al.

Table 4

Rousability for interview, prevalence of report types, and type of experience in content reports in each drug group.

	Dexmedetomidine n/N (%)	Propofol n/N (%)	Sevoflurane n/N (%)	S-ketamine n/N (%)	Total n/N (%)	Statistical significance
Rousability	38/40 (95.0)	35/39 (89.7)	16/35 (45.7)	9/19 (47.4)	98/133 (73.7)	$\chi^2(3, N = 99) = 38.23, p < .001$, Cramer's $V = 0.621^*$
Report type						$FET p < .001$, Cramer's $V = 0.349$
No recall	6/38 (15.8)	21/35 (60.0)	7/16 (43.8)	3/9 (33.3)	37/98 (37.8)	
White report	5/38 (13.2)	3/35 (8.6)	5/16 (31.2)	2/9 (22.2)	15/98 (15.3)	
Content report	27/38 (71.1)	11/35 (31.4)	4/16 (25.0)	4/9 (44.4)	46/98 (46.9)	
Type of experience in the content report						
Dreaming	26/27 (96.3)	11/11 (100)	4/4 (100)	4/4 (100)	45/46 (97.8)	ns
Memory incorporation	10/27 (37.0)	0/11 (0.0)	2/4 (50.0)	3/4 (75.0)	15/46 (32.6)	$FET p = .010$, Cramer's $V = 0.452$
Awareness	0/27 (0.0)	0/11 (0.0)	0/4 (0.0)	1/4 (25.0)	1/46 (2.2)	ns

*One participant receiving S-ketamine who provided a delayed report but was not immediately rousable is counted as unresponsive in statistical analysis on rousability (see also Table 6.).

**The only awareness experience was reported in a delayed interview after PET imaging by a participant receiving S-ketamine and categorized as SoR.

rousable for the interview in the dexmedetomidine group than in the sevoflurane ($p < .001, h = 1.327$) and S-ketamine groups ($p < .001, h = 1.787$). Also a greater proportion of UR participants in the propofol group were rousable for the interview than in the sevoflurane ($p = .002, h = 1.035$) and S-ketamine groups ($p < .001, h = 1.494$).

Notably, although we aimed to interview all participants immediately after the termination of the anesthetic administration, three participants who received S-ketamine produced delayed reports, that is, reported experiences during or after the PET imaging (between 5 and 35 min after termination of anesthetic infusion). One of these participants did not wake up immediately after termination of anesthetic infusion but later recalled experiences. Another participant was immediately rousable, and first reported that he did not experience anything but later recalled experiences, and a third participant, also immediately rousable, first gave a white report, but later recalled the contents of the experience. These delayed reports were included in the content analysis given the otherwise low number of successful interviews in the S-ketamine group.

Two independent judges content analyzed the reports with substantial agreement. The overall inter-rater agreement was $\kappa = 0.88, p < .001, 95\% \text{ CI}[0.86, 0.90]$. The reliability for categorizations of the report type (no recall, white report, content report) was $\kappa = 0.94, p < .001, \text{ CI}[0.91, 0.99]$, for the content reports to include dreaming, memory incorporation or awareness of the environment $\kappa = 0.90, p < .001, \text{ CI}[0.82, 0.97]$, for the perceptual complexity $\kappa = 0.74, p < .001, \text{ CI}[0.65, 0.83]$, and for the modality of experiences $\kappa = 0.72, p < .001, \text{ CI}[0.66, 0.79]$.

3.2. Subjective experiences in content reports

Altogether, 46.9% of 98 interviews led to content reports, whereas in 37.8% of awakenings no recall was reported, and 15.3% of awakenings resulted in white reports (see Table 4.). There was a significant association between the anesthetic agent and report type (see Table 4.) and subsequent bivariate comparisons revealed that participants receiving dexmedetomidine produced more content reports than participants receiving propofol ($p = .006, \phi = -0.396$) or sevoflurane ($p = .016, \phi = -0.425$). No differences were found between drugs in reporting dreaming, but there was an association between drug and reporting memory incorporations (see Table 4.). However, no statistically significant differences were found in bivariate comparisons after Bonferroni correction. For prevalence of report types, and frequency of content reports indicating disconnectedness (i.e., dreaming or memory incorporation) and connectedness (i.e., awareness) per drug group, see Table 4.

3.3. Perceptual complexity and the modality of experiences

Perceptual complexity and modality of experiences were analyzed separately for dreaming, memory incorporation and awareness reports. The complexity of the dream-like experiences associated with the used anesthetic agent (see Table 5.). Dunn's pairwise tests indicated that there was a significant difference between dexmedetomidine ($n = 26$) and S-ketamine ($n = 4$), $p = .036$: participants receiving S-ketamine had more dynamic dream-like experiences than those who received dexmedetomidine. As to the complexity of perceptual content in the memory incorporations, there were no statistically significant differences between anesthetic agents.

To compare modalities of dream and memory incorporation experiences between drugs, the modalities were grouped into three sum variables: sensations and perceptions (visual, auditory, interoception, gustatory, pain and temperature, kinesthesia and balance, olfactory and tactile), affective states (positive and negative emotions) and cognition (thoughts and memories). There were no statistically significant differences between anesthetic agents in the modalities of experiences in dreams, but the anesthetic agent had a large effect on the prevalence of sensations and perceptions in the memory incorporation experiences. Dunn's pairwise tests indicated

Table 5
The frequencies of perceptual complexity and modality of experiences in content reports.

	Dexmedeto- midine n/N (%)	Propofol n/N (%)	Sevoflurane n/N (%)	S-ketamine n/N (%)	Statistical significance
Dream-like experiences					
Perceptual complexity					
No perceptual content	2/26 (7.7)	0/11 (0.0)	1/4 (25.0)	0/4 (0.0)	$H(3, 45) = 8.03, p = .039, \eta^2 = 0.12$
Static report	18/26 (69.2)	7/11 (63.6)	1/4 (25.0)	0/4 (0.0)	
Dynamic report	6/26 (23.1)	4/11 (36.4)	2/4 (50.0)	4/4 (100)	
Sensory-perceptual experiences					
Visual	24/26 (92.3)	10/11 (90.9)	3/4 (75.0)	4/4 (100)	ns
Auditory	3/26 (11.5)	3/11 (27.3)	2/4 (50.0)	3/4 (75.0)	
Interoceptive	0/26 (0.0)	1/11 (9.1)	0/4 (0.0)	0/4 (0.0)	
Tactile	0/26 (0.0)	2/11 (18.2)	0/4 (0.0)	0/4 (0.0)	
Pain and temperature	1/26 (3.8)	0/11 (0.0)	0/4 (0.0)	0/4 (0.0)	
Kinesthetic	1/26 (3.8)	2/11 (18.2)	1/4 (25.0)	2/4 (50.0)	
Olfactory	0/26 (0.0)	0/11 (0.0)	0/4 (0.0)	0/4 (0.0)	
Gustatory	0/26 (0.0)	0/11 (0.0)	0/4 (0.0)	0/4 (0.0)	
Affective states					
Positive	14/26 (53.8)	7/11 (63.6)	3/4 (75.0)	2/4 (50.0)	ns
Negative	3/26 (11.5)	1/11 (9.1)	0/4 (0.0)	0/4 (0.0)	
Cognition					
Cognition	3/26 (11.5)	0/11 (0.0)	0/4 (0.0)	1/4 (25.0)	ns
Out-of-body	0/26 (0.0)	0/11 (0.0)	0/4 (0.0)	0/4 (0.0)	
Sense of presence	0/26 (0.0)	0/11 (0.0)	0/4 (0.0)	0/4 (0.0)	
Memory incorporation					
Perceptual complexity					
No perceptual content	0/10 (0.0)	0/11 (0.0)	0/2 (0.0)	0/3 (0.0)	ns
Static report	9/10 (90.0)	0/11 (0.0)	2/2 (100)	2/3 (66.7)	
Dynamic report	1/10 (10.0)	0/11 (0.0)	0/2 (0.0)	1/3 (33.3)	
Sensory-perceptual experiences					
Visual	10/10 (100)	0/11 (0.0)	2/2 (100)	2/3 (66.7)	$H(2, 15) = 7.27, p = .040, \eta^2 = 0.44$
Auditory	0/10 (0.0)	0/11 (0.0)	0/2 (0.0)	3/3 (100)	
Interoceptive	0/10 (0.0)	0/11 (0.0)	0/2 (0.0)	0/3 (0.0)	
Tactile	0/10 (0.0)	0/11 (0.0)	0/2 (0.0)	0/3 (0.0)	
Pain and temperature	0/10 (0.0)	0/11 (0.0)	0/2 (0.0)	0/3 (0.0)	
Kinesthetic	0/10 (0.0)	0/11 (0.0)	0/2 (0.0)	1/3 (33.3)	
Olfactory	0/10 (0.0)	0/11 (0.0)	1/2 (50.0)	0/3 (0.0)	
Gustatory	0/10 (0.0)	0/11 (0.0)	0/2 (0.0)	0/3 (0.0)	
Affective states					
Positive	0/10 (0.0)	0/11 (0.0)	0/2 (0.0)	0/3 (0.0)	ns
Negative	0/10 (0.0)	0/11 (0.0)	0/2 (0.0)	0/3 (0.0)	
Cognition					
Cognition	2/10 (20.0)	0/11 (0.0)	0/2 (0.0)	0/3 (0.0)	ns
Out-of-body	0/10 (0.0)	0/11 (0.0)	0/2 (0.0)	0/3 (0.0)	
Sense of presence	0/10 (0.0)	0/11 (0.0)	0/2 (0.0)	0/3 (0.0)	

that there was a significant difference between dexmedetomidine ($n = 10$) and S-ketamine ($n = 3$), $p = .036$: participants receiving S-ketamine reported memory incorporations which more often included multisensory experiences.

3.4. Responsiveness and subjective experiences

The participants' responsiveness to R-tests fluctuated during the 40 min constant-dose anesthesia period, and they tended to become less responsive towards the end of the 40 min constant-dose period. The mean percentage of responses during the whole experiment was 42.3% ($SD = 17.49$) among participants receiving dexmedetomidine, 54.0% ($SD = 28.34$) among those receiving propofol, 33.9% ($SD = 21.66$) in the sevoflurane group and 62.3% ($SD = 23.97$) in the S-ketamine group. Of the 133 participants, 99 (74.4%) were categorized as unresponsive (UR) based on the last and penultimate R-test whereas 34 (25.6%) were categorized as showing signs of responsiveness (SoR). The number participants categorized as UR or SoR in different drug groups is presented in Table 6.

There were no statistically significant differences between UR and SoR groups in the prevalence of different report types. Nineteen participants (57.6%) categorized as SoR and 27 participants (41.5%) categorized as UR gave a content report. There were also no statistically significant differences between the UR and SoR groups in the type of reported experiences in the content reports. In UR group, 27 content reports (100%) included dream-like experiences, 11 reports (40.7%) included memory incorporation, and none included awareness. In SoR group, 18 content reports (94.7%) included dream-like experiences, four reports (21.1%) included memory incorporation, and one (5.3%) included awareness.

4. Discussion

The aim of this study was to compare similarities and differences in the presence and quality of subjective experiences during

Table 6

The number of participants categorized as SoR and UR, and number of interviews obtained from each group.

	Dexmedetomidine n/N (%)	Propofol n/N (%)	Sevoflurane n/N (%)	S-ketamine n/N (%)	Total n/N (%)
UR	31/40 (77.5)	26/39 (66.7)	30/35 (85.7)	12/19 (63.2)	99/133 (74.4)
Interview	29/31 (93.5)	22/26 (84.6)	11/30 (36.7)	3/12 (25.0)	65/100 (65.0)
No interview	2/31 (6.5)	4/26 (15.4)	19/30 (63.3)	9/12 (75.0)	34/100 (34.0)
SoR	9/40 (22.5)	13/39 (33.3)	5/35 (14.3)	7/19 (36.8)	34/133 (25.6)
Interview	9/9 (100)	13/13 (100)	5/5 (100.0)	6/7 (85.7)	33/34 (97.1)
No interview	0/9 (0.0)	0/13 (0.0)	0/5 (0.0)	1/7 (14.3)	1/34 (2.9)

responsive and unresponsive sedation induced with dexmedetomidine, propofol, sevoflurane or S-ketamine to investigate whether different anesthetic drugs modulate consciousness, connectedness and responsiveness in different ways. We were specifically interested in whether reports indicative of disconnectedness (i.e., dreaming or memory incorporation of the research setting) or connectedness (i.e., awareness of the environment) vary between drugs with different mechanisms of action. We also assessed whether being responsive or unresponsive during the last minutes of the anesthetic administration affected the recall or content of reported experiences.

Responsiveness was modulated by the anesthetic agent, and unresponsive participants who received dexmedetomidine or propofol were more often rousable compared to unresponsive participants who received sevoflurane or S-ketamine. Almost half of the 98 participants who were successfully interviewed reported experiences from the time of anesthetic administration, and most often experiences were reported by participants administered dexmedetomidine. However, there were no differences between the drug groups in the prevalence of reports indicating disconnectedness or connectedness, and we found no differences in the prevalence of disconnected or connected experiences between participants categorized as unresponsive and participants showing signs of responsiveness just prior to the interview.

4.1. Connected and disconnected consciousness during clinical anesthesia and experimental sedation

Previous studies conducted in the clinical setting have found that dreaming is reported by even up to 52.6% of patients after general anesthesia (Cascella et al., 2017; Errando et al., 2008; Leslie et al., 2007; Leslie & Skrzypek, 2007; Leslie et al., 2009; Villegas et al., 2019; Yoshida et al., 2021), and by up to 56.8% of patients after responsive sedation, especially when administered ketamine (Cascella et al., 2017; Eer et al., 2009; Kim et al., 2011; Stait et al., 2008; Villegas et al., 2019; Xu et al., 2013). The results of the present study thus fit within the range of previous findings. However, in our study the assessment of experiences was conducted immediately after termination of anesthetic infusion and in healthy participants receiving a single drug while in clinical studies the patients were interviewed after lengthier recovery period, and the patients also received higher doses of anesthetics, often in combination with various other medications. The longer the delay between the interview and the original experience, the more likely is amnesia and other memory biases (Sandman, 2017; Sikka, 2019; Windt, 2015). Further, the amnestic properties of anesthetic agents, the higher anesthetic doses, and the multimodal pharmacologic interventions in the clinical setting may have a significant effect on the presence and content of experiences and the retrospective recall rate.

Compared to the two previous studies utilizing an experimental setting and single-drug exposure, the recall rates in the current study are lower. Noreika et al. (2011) evidenced an occurrence of subjective experiences in 58.6% of interviews conducted after recovery from unresponsiveness, while Radek et al. (2018) reported an even higher incidence of recall (83.9%) of subjective experiences. The differences in study designs might partially explain these differences. In the current study, an equisedative fixed concentration of EC₅₀ or MAC₅₀ for loss of responsiveness was targeted and the aim was that half of the participants would remain responsive, while in both previous studies loss of responsiveness was induced in all participants by individually titrated stepwise increases in the drug concentration. Furthermore while Noreika et al. (2011) interviewed participants once after brief recovery period, Radek et al. (2018) interviewed the same participants several times in a serial awakening paradigm with awakenings during constant-dose anesthesia as well as after a recovery period. The participants who were interviewed multiple times thus got practice in responding to the same interview questions repeatedly. In addition, Radek et al. (2018) emphasized the interview questions in pre-anesthesia preparations more than Noreika et al. (2011) or than what was done in the current study. These factors might have resulted in higher number of reported experiences in the Radek et al. study, given that encouraging and instructing participants to pay attention to internal experiences, and the expectation and practice of reporting the experiences, have been shown to increase dream recall (Halliday, 1992; Redfering & Keller, 1974; Schredl et al., 2003).

In line with the previous findings, the participants who received dexmedetomidine tended to report experiences more often than participants who received GABAergic anesthetics propofol or sevoflurane (71.1% vs 31.4% vs 25.0% out of given reports, respectively). Also previous experimental single-drug studies have shown that the occurrence of experiences is higher in unresponsive participants who have been administered dexmedetomidine (73.7–89.8%) compared to participants administered propofol (36.8–73.5%) (Noreika et al., 2011; Radek et al., 2018). S-ketamine, however, seems to present a special case. In previous studies interviews after spontaneous return of responsiveness or a longer delay have shown that ketamine administration very often leads to reports of vivid dreaming, audiovisual hallucinations, perceptual perturbations, and even partially preserved awareness of the environment (Sarasso et al., 2015; Villegas et al., 2019). In the present study, more than half of the participants receiving S-ketamine were

not rousable immediately after administration (10/19) and while almost half (4/9) of the rousable S-ketamine participants reported experiences, majority of these (3/4) were conveyed after short recovery period. Additionally, participants receiving S-ketamine often explained that they wanted to tell more about their experiences but were not able to verbally express their experiences in a coherent fashion or the experiences were too extreme to be described in words, that is, ineffable. Some participants also experienced motor speech difficulties (dysarthria) which prevented them from expressing themselves clearly. We therefore suspect that the administration of ketamine typically prevents immediate interviews, although vivid and complex experiences are often present and can be reported after sufficient recovery.

The dreams during unresponsive and responsive sedation were classified as static more often than dynamic, except when administered S-ketamine. Visual content was most common (75.0–100% of dream reports, depending on the anesthetic used), followed by auditory (11.5–75.0%) and kinesthetic experiences (3.8–50.0%) and the affective tone was more often pleasant (50.0–75.0%) than unpleasant (0–11.5%). These findings are compatible with previous studies which have described dreaming during anesthesia and sedation as simple in nature, emotionally more positive than negative, and containing visual and auditory as well as sensorimotor experiences (Leslie & Skrzypek, 2007; Noreika et al., 2011; Radek et al., 2018; Yoshida et al., 2021). Notably, all dream reports in the S-ketamine group were classified as dynamic and containing multimodal experiences which complies with the previous ketamine studies showing that vivid dreams, floating sensations, and audiovisual perturbations are typical experiences reported after ketamine administration (Collier, 1972; Marland et al., 2013; Sarasso et al., 2015; Vlisides et al., 2018). Additionally, memory incorporations were also frequently reported in conjunction with S-ketamine administration which may be related to the dissociative nature of this anesthetic. Hallucinations and perceptual distortions of the surroundings have been described by healthy participants on emergence from unresponsiveness induced with ketamine (Sarasso et al., 2015). The participants receiving S-ketamine had also more auditory sensations in their memory incorporations than the participants receiving other anesthetics. These observations may suggest that the experiences of participants receiving S-ketamine, although detached, could have been more often connected to the environment and they might have heard the auditory stimuli presented during the experimental session more often than participants receiving dexmedetomidine or GABAergic anesthetics. Relatively high incidence of hearing voices or sounds related to the procedure has been reported by patients who were anesthetized or sedated with ketamine (Villegas et al., 2019). Yet, in our study these kind of elements representing the research environment were not evident enough in the reports to be categorized as awareness of the environment, and would have been considered to be memory incorporation of the research setting. Notably, the only awareness experience indicating connected consciousness was reported in delayed fashion by a participant who received S-ketamine and was categorized as showing signs of responsiveness at the end of the anesthetic administration.

4.2. Responsiveness with different anesthetic agents

Of the 133 participants, 34 (25.6%) were considered responsive and 99 (74.4%) unresponsive in this study based on the last minutes of anesthetic administration before the interview. Unresponsive participants who received dexmedetomidine or propofol were more often rousable compared to unresponsive participants who received sevoflurane or S-ketamine. With dexmedetomidine, the finding is not surprising, given it is a sedative mimicking NREM sleep that enables rousable or semi-rousable sedation (Brown et al., 2011) and has also in our previous study been reported to lead to higher number of arousals from an unresponsive state (Kallionpää et al., 2018; Radek et al., 2018; Scheinin et al., 2018). While propofol also allows for relatively fast recovery after sedation or anesthesia due to its metabolic properties, sevoflurane-maintained anesthesia has in several studies reported to lead to similar or faster awakening than propofol-maintained anesthesia (Ghatge et al., 2003) which does not explain why participants were more often rousable with propofol than with sevoflurane in the current study. However, we apparently failed to achieve the goal of administering equisedative doses of anesthetics during the experiment, as participants receiving sevoflurane were less responsive than participants receiving other anesthetics at the beginning of steady-dose sedation (Laaksonen et al., 2018), responded to fewer R-tests during the experiment and were more often categorized as UR in the last R-tests. This therefore explains why participants administered sevoflurane were not as rousable as participants receiving propofol or dexmedetomidine.

Surprisingly, showing signs of responsiveness during the end of anesthetic infusion did not lead to reporting experiences or specific types of experiences more often. Being more responsive to the environment did not increase the prevalence of recall, and in both unresponsive and responsive participants almost all subjective experiences were categorized as dreaming, that is, hallucinatory content of consciousness. This implies that even though a patient in a clinical setting remains responsive during sedation, hallucinatory disconnected contents of consciousness may be frequently experienced.

4.3. Strengths and limitations

The strength of this study includes the usage of targeted equisedative doses of four different anesthetics which allowed the responsiveness of the participants to vary naturally and also enabled comparisons between anesthetic agents with different molecular mechanisms of action. Additionally, responsiveness was systematically tested to investigate its effect on reporting experiences and we conducted the interviews immediately after the anesthetic infusion was terminated and content analyzed the interview reports carefully, searching for indications of disconnected and connected consciousness.

A major limitation in the study of consciousness is that we cannot infer the presence or absence of consciousness from behavioral unresponsiveness. Thus, we know nothing about the presence of conscious experiences in those participants who could not be roused for interview. Further, we cannot independently verify that the 'no recall' reports in those who could be roused would truly reflect the total absence of subjective experiences. The latter, of course, does not only apply to research conducted with anesthetics, but to all

research that addresses experiences retrospectively. Yet, anesthetics add an additional complication: the amnesic effects of the anesthetic agents may have caused a significant memory bias. It is possible that most of the participants had subjective experiences at some point during the 40-minute steady-state anesthesia but could no longer recall them in the retrospective interview. Thus, while the presence of recall suggests preserved (disconnected) consciousness, the absence of recall or responsiveness does not provide any absolute proof of unconsciousness. Furthermore, white reports were quite frequently given, demonstrating the challenges related to remembering and reporting experiences especially after anesthesia (notably, white reports are also frequently obtained from early night NREM sleep awakenings; Noreika et al., 2009).

Another limitation of this study is that it is not definite whether some of the memory incorporation reports might have actually been masked awareness experiences or, as we interpret them, just memories originating from before the anesthetic infusion. Exposure to a novel environment, such as sleeping in a sleep laboratory, affects dreams strongly as laboratory elements are frequently incorporated into subsequent dream content (Schredl, 2008). We therefore assume (similarly to Radek et al., 2018) that incorporation experiences reflect events from the pre-anesthesia period, originating from memory sources related to novel stimuli, and are thus indicative of disconnected consciousness rather than real awareness. With this methodological choice, we did not, at least, leniently assign an awareness status to experiences which did not clearly represent connectedness. In future studies, a specific stimulus presented only during anesthesia that can distinguish memory incorporation from true awareness should be used to address this issue, and such studies should also systematically assess the probability of explicit or implicit memory formation during responsive and unresponsive sedation, given memories formed during clinical anesthesia and surgery (whether spontaneously recalled or not) are probably the most important driving factor for subsequent psychological disturbances, such as PTSD symptoms, in surgery patients (Wang, 2000; Whitlock et al., 2015).

Moreover, although we aimed to use only immediately acquired interviews in the analyses, we also included three delayed interviews obtained during or after PET imaging from participants receiving S-ketamine. Without this inclusion, our sample of interview reports from S-ketamine participants would have been too small to subject the reports to any content analytic or statistical procedures. Regardless, this presents a methodological bias in the current study: with all other anesthetics, immediate interviews were used and delayed interviews were not conducted, and therefore, the interview reports are not directly comparable between S-ketamine and other agents used. This may compromise our findings with S-ketamine, and therefore these results should be interpreted with caution, even though they are compatible with previously reported findings.

A further limitation of the current study relates to categorizing the participants into UR and SoR groups. Responsiveness fluctuated in most participants during the 40-minute steady-state anesthesia and very few remained either completely responsive or unresponsive throughout the administration period. In practice, almost all UR participants were responsive at some point during the administration and vice versa. Therefore, the decision to divide participants depending on their responsiveness in the last two R-tests of the session was made, based on the assumption that if the participants reported any recall in the interview, the experiences were likely to be those most recently encoded into memory. Yet, we cannot rule out the possibility that some contents may have originated from an earlier time point in the study period, and we have no means to verify the exact time point when the reported experiences occurred.

Additionally, yet another limitation is that the experiment was conducted only with male participants. Due to ethical guidelines concerning recruiting fertile females to studies using radioactive substances, we were not able to include any females in this experiment. Previous studies on sex differences in the recall of experiences after anesthesia and sedation have yielded contradictory results, ranging from higher recall rate in females to higher recall rate in males to no sex difference in recall rates (Grace, 2003; Leslie et al., 2005, 2007; Xu et al., 2013). We therefore believe that future investigations on this topic of potential sex differences are warranted.

Finally, the overall findings of this study should be interpreted with caution. Despite involving 140 study participants, the number of interview reports per drug group was relatively low (especially in sevoflurane and S-ketamine groups), and reports containing specific type of content infrequent, which complicates comparisons between the drugs. Also, this was an experimental study with healthy participants, only one anesthetic agent was used per participant, and anesthetic doses were lower than those used in clinical situations. The incidences reported here thus apply only to experimental conditions and should be considered indicative. We therefore stress that these results cannot be directly generalized to apply to surgical anesthesia. Future patient studies are needed to determine to what extent these results apply to clinically relevant anesthetic states.

5. Conclusion

Unresponsive and responsive sedative states are often followed by reports of subjective experiences which vary from simple static images to dynamic multimodal dreaming and most of the experiences can be considered as stimulus-unrelated mentation indicative of disconnected consciousness. The probability of reporting experiences varied between drugs, and the highest prevalence of experiences was reported when dexmedetomidine was administered. Participants receiving S-ketamine tended to report more often memory incorporations and experiences related to awareness of the environment, suggesting that S-ketamine may cause a “borderline” state when a person is neither completely disconnected nor fully connected. Our results show that different anesthetic agents may have distinct effects on the prevalence and complexity of the experiences, although in the present sample the differences between drugs were minimal. Most importantly, however, we demonstrate that unresponsiveness during administration of four distinct anesthetic drugs in an experimental setting does not denote unconsciousness.

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CRediT authorship contribution statement

Linda Radek: Formal analysis, Methodology, Writing – original draft. **Lauri Koskinen:** Formal analysis, Investigation, Methodology, Writing – original draft. **Nils Sandman:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing. **Lauri Laaksonen:** Investigation, Writing – review & editing. **Roosa E. Kallionpää:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **Annalotta Scheinin:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Ville Rajala:** Data curation, Investigation, Writing – review & editing. **Anu Maksimow:** Investigation, Supervision, Writing – review & editing. **Timo Laitio:** Investigation, Supervision, Writing – review & editing. **Antti Revonsuo:** Conceptualization, Funding acquisition, Writing – review & editing. **Harry Scheinin:** Conceptualization, Funding acquisition, Methodology, Project administration, Writing – review & editing. **Katja Valli:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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