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Research Article

Dreaming and awareness during dexmedetomidine- and propofol-induced unresponsiveness

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Background: Experiences during anaesthetic-induced unresponsiveness have previously been investigated by interviews after recovery. To explore whether experiences occur during drug administration, we interviewed participants during target-controlled infusion (TCI) of dexmedetomidine or propofol and after recovery.
Methods: Healthy participants received dexmedetomidine (n=23) or propofol (n=24) in stepwise increments until loss of responsiveness (LOR1). During TCI we attempted to arouse them for interview (return of responsiveness, ROR1). After the interview, if unresponsiveness ensued with the same dose (LOR2), the procedure was repeated (ROR2). Finally, the concentration was increased 1.5-fold to achieve presumable loss of consciousness (LOC), infusion terminated, and the participants interviewed upon recovery (ROR3). An emotional sound stimulus was presented during LORs and LOC, and memory for stimuli was assessed with recognition task after recovery. Interview transcripts were content analysed.
Results: Of participants receiving dexmedetomidine, 18/23 were arousable from LOR1 and LOR2. Of participants receiving propofol, 10/24 were arousable from LOR1 and two of four were arousable from LOR2. Of 93 interviews performed, 84% included experiences from periods of unresponsiveness (dexmedetomidine 90%, propofol 74%). Internally generated experiences (dreaming) were present in 86% of reports from unresponsive periods, while externally generated experiences (awareness) were rare and linked to brief arousals. No within drug differences in the prevalence or content of experiences during infusion *vs* after recovery were observed, but participants receiving dexmedetomidine reported dreaming and awareness more often. Participants receiving dexmedetomidine recognised the emotional sounds better than participants receiving propofol (42% *vs* 15%), but none reported references to sounds spontaneously.

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Conclusion: Anaesthetic-induced unresponsiveness does not induce unconsciousness or necessarily even disconnectedness.
Clinical trial registration: NCT01889004.

Keywords: awareness; consciousness; dexmedetomidine; interview; propofol

Editor's key points

- The frequency and drug dependence of dreaming and awareness during infusion of i.v. anaesthesia have not been carefully studied under controlled conditions.
- Healthy male volunteers rendered unresponsive with target controlled infusion of dexmedetomidine or propofol were awakened and subjected to semi-structured interviews.
- Dreaming during unresponsiveness was frequent with both drugs, while awareness was rare.
- Dexmedetomidine or propofol titrated to induce behavioural unresponsiveness frequently do not abolish conscious experiences or even necessarily induce disconnectedness.

The content of consciousness, i.e. subjective experiences, can be either externally or internally generated. Being able to have externally generated experiences implies that the person is, at least momentarily, in a state of connected consciousness. In contrast, when externally generated contents of consciousness cannot occur, but purely internally generated contents of consciousness are present, the person is in a state of disconnected consciousness. In general anaesthesia, intraoperative awareness with explicit recall implies connectedness to the environment, while internally generated experiences, often conceptualised as dreaming in anaesthesia literature, are typically interpreted to represent a disconnected conscious state.[1,2]

Most studies on subjective experiences under anaesthesia have been conducted in a clinical setting. In previous studies, the incidence of awareness has ranged from 0.007% to 1.0%.[3] Similarly, the incidence of dreaming has varied greatly, from 3.2% to 52.6%[4–9] when patients have been interviewed after recovery from general anaesthesia. After sedation, 19.0% have reported dreaming.[10] However, the length and depth of anaesthesia, the patient's clinical condition, and the combination of anaesthetics and other medications can affect the presence and later recall of experiences.[11] The only single-drug experimental study found that 58.6% of participants reported experiences after spontaneous emergence from unresponsiveness induced by dexmedetomidine or propofol, of which 26.3% included dream-like imagery and 38.6% references to the research setting.[11] However, a common bias to previous studies is that participants have been interviewed after a recovery period. In fact, it has been suggested that dreaming occurs after termination of drug administration before awakening when patients are sedated or in a physiological sleep state.[5,12,13] As it remains unresolved whether the reported experiences originate from the drug administration period or the recovery-phase with only minimal drug concentrations, we conducted interviews by arousing healthy participants from unresponsiveness during target-controlled infusion (TCI), and upon recovery after terminating drug administration. We defined internally generated experiences as dreaming (implying disconnected consciousness), and externally generated experiences as accurate awareness of the research environment (implying connectedness). Based on the suggestion that dreaming occurs during recovery,[5,12,13] we hypothesised dream experiences to be more prevalent in recovery reports than in reports obtained during infusion. To measure awareness of specific stimuli, participants were also presented with emotional sound stimuli during unresponsiveness followed by a recognition task after recovery.

Methods

The protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland, and the Finnish Medicines Agency Fimea, and registered in ClinicalTrials.gov (NCT01889004). Written informed consent was acquired from the participants according to the Declaration of Helsinki. Spectral analysis of the EEG and event related potentials from the same study are reported elsewhere.[14–15]

Participants

Forty-seven non-smoking, 20–30-yr-old, right-handed healthy male subjects (ASA physical status I) with normal hearing participated in this open-label, randomised (permuted blocks) parallel-group (n=23 for dexmedetomidine and n=24 for propofol) study. Participants were recruited from the local universities by advertising in student mailing lists, and they were paid €150 (approved by the Ethics Committee). Only males were considered eligible because of radiation exposure related to a subsequent positron emission tomography study. No statistical power calculation regarding the required number of participants was conducted before the study, but the sample size was based on our previous experience with this design. Participants' mean age was 24 (range 20–30) yrs, mean height was 180 (range 165–198) cm and mean weight 78 (range 53–122) kg. Fulfilment of exclusion criteria (smoking, history of psychiatric disorder, propensity for nausea, substance abuse) was verified by prestudy interview and laboratory screening.

Anaesthetic protocol

The anaesthetic procedure (as described in[14]) was conducted by a resident and an experienced senior an aesthesiologist was always present. Medication and alcohol use were forbidden for 48 h preceding the experiment, and participants fasted overnight. Vital signs were monitored and step-wise increasing concentrations of either dexmedetomidine or propofol were administered using TCI until loss of responsiveness (LORs) was achieved. For dexmedetomidine, the starting target plasma concentration was 1.0 ng ml^{-1}, followed first by a 0.5 ng ml^{-1} target concentration increase and 0.25 ng ml^{-1} increases thereafter. For propofol, the starting target plasma concentration was 1.0 μg ml^{-1}, followed first by a 0.5 μg ml^{-1}

target concentration increase and 0.25 μg ml^{-1} increases thereafter. Each sedation step lasted 7 min. Reported pharmacokinetic parameters for dexmedetomidine[16] and propofol[17] were used, and drug plasma concentrations measured.

At every drug concentration, unresponsiveness was tested with standardised responsiveness test (R-test). R-test was composed of 10 semantically congruent (n=5) or incongruent (n=5) prerecorded sentences; it assessed whether the participant could process complex semantic information and respond according to instructions. The participants were to respond by pressing response handles with either their right or left hand to congruous or incongruous sentences, and LORs was defined as zero responses to the R-test. The Presentation 17.0 stimulus delivery and experimental control software system (Neurobehavioral Systems Inc., Berkeley, CA, USA) was used to present all stimuli.

When the first loss of responsiveness (LOR1) was achieved, pseudo-steady state TCI was continued for ~25 min. Without terminating or changing the drug infusion, an attempt was made to awaken the participant by addressing him twice by name, followed by mild physical stimulation. Awakenings were conducted in an identical manner for all participants. If the participant regained responsiveness (return of responsiveness, ROR1), a semi-structured interview addressing the content of consciousness was conducted (Table 1). If after the interview the participant became unresponsive again with the same constant drug concentration, the procedure was repeated (LOR2/ROR2). After ROR1/ROR2 or an unsuccessful awakening attempt, the drug concentration was increased by 50% to achieve presumable loss of consciousness (LOC). Finally, the drug infusion was terminated and ROR3 was monitored by repeating the R-test. The last interview was conducted immediately after spontaneous ROR3, or in the absence of spontaneous recovery within 30 min, an awakening was performed in a similar manner as previously described. The outline of the study is illustrated in Figure 1.

Stimuli and recognition task

Two minutes before the attempted awakenings from LORs and before terminating the drug infusion in LOC, a 6 s long emotionally unpleasant sound stimulus (LOR1: puppy in distress; LOR2: baby crying; LOC: car horns in traffic jam), selected from the International Affective Digitized Sound library[18] with normative data, was presented via headphones (Fig. 1). Participants were not informed in advance of the presentation of these emotional stimuli, intended to measure awareness of the environment (i.e. connectedness) and learning of emotional material during unresponsiveness. After the final interview, participants performed a recognition task composed of sounds from the same sound library.[18] They heard the target sound and four novel sounds for each sound stimulus presented during the experiment (puppy *vs* four other animal sounds; baby crying *vs* four other human sounds; car horns *vs* four other human artefact sounds). After each stimulus and a response cue, participants indicated whether the stimulus felt familiar or not by pressing the response handles.

Interviews and content analysis

After every successful awakening, participants were presented with a semi-structured interview (Table 1) modified from Brice's questionnaire[19] and our previous study.[11] Participants were familiarised with the questions and the intention of the interview before the experiment. Each participant was interviewed in an open, non-leading manner one to three times, but at least once (i.e. after final awakening; ROR3). The aim of the interviews was to assess the prevalence and content of experiences.

The interviews were recorded digitally and transcribed word by word for systematic content analysis, conducted by two independent judges with the modified SEDA[11] and Orlinsky[20] scales. In the first stage of content analysis (Fig. 2, Table 1), we differentiated unresponsiveness reports (experiences that had most evidently taken place during unresponsiveness) from responsiveness reports (experiences that had clearly taken place before unresponsiveness ensued or after the participant woke up), and from white reports (experiences where no content was recalled while a strong impression of having experienced something was retained). In the second stage, experiences in unresponsiveness reports were categorised as dreaming (internally generated experiences signifying disconnected consciousness), memory incorporation, or awareness of environment or stimuli (externally generated experiences signifying connectedness). In awareness coding, specific attention was paid to possible references to the emotional sound stimuli. Because references related to the research setting were frequently reported in our previous study,[11] we established a separate memory incorporation category for these experiences. Memory incorporation is an experience that realistically depicts objects or persons that have been present, or events that have occurred, during the experimental session, but the timing of which cannot be verified because the reported elements have been present during the experimental session also beyond the confines of the unresponsiveness periods. In the third stage, each type of experience (dreaming, memory incorporation, awareness) was further explored regarding sensory-perceptual modalities, affective states and cognition (stage 3a), and perceptual dynamics and complexity (stage 3b; i.e. whether the experience was an isolated, static and fragmentary percept or temporally progressing, complex, and multisensory). Examples of interview reports and content analysis of transcripts are presented in Supplementary Table S1.

Statistical methods

The content analysis inter-rater agreement was evaluated with percent agreement and Cohen's κ coefficient. Data were mostly analysed using non-parametric methods because of the skewed distributions and the outlying observations. Differences in the number and content of reports between anaesthetics, and within anaesthetics between RORs, were analysed with Mann–Whitney U test, Fisher's exact test, and Kruskal–Wallis test. The probability of recognition rates of emotional sounds was analysed with logistic regression analyses using generalised estimating equations method to account for the dependency between the repeated measurements. Models included the main effects of state, drug, and stimulus and their interactions. Reaction times from response cue to response were analysed with mixed model with random intercepts for participants. Natural log-transformed reaction times were used because of the positively skewed distribution. Mixed models included the main effects of state, drug, and stimulus and their interactions, or state, drug, and correctness of response and their interactions. If the interactions were not significant, then logistic and mixed models were reduced to the main effects model. Results of

Table 1 Interview questions and content analysis scale. Interview questions were presented to each subject in the same way, and depending on the actual report, further details were inquired about the content. All interview transcripts were coded by two independent raters. In case of disagreement, the content of the report was discussed until an agreement was reached or the final decision was made by a third judge. The inter-rater reliability between the two independent judges for the categorisation of the report types was 92.8%, K=0.887 (P<0.001), and for the coding of the unresponsiveness experiences to include dream-like imagery, memory incorporation or awareness of the environment 98.8%, K=0.973 (P<0.001). Modality of experiences scale was applied with an overall reliability of 89.0% (κ could not be computed because of the binary nature of the data), and perceptual complexity and dynamics scale with 88.5%, K=0.758 (P<0.001)

The interview questions	
If the participant answered yes to any question, he was asked to describe the experience in as much detail as possible	
Did you dream during unresponsiveness?	
Did you experience anything related to the research environment during unresponsiveness?	
Did you hear anything during unresponsiveness?	
Did you sense anything (else) during unresponsiveness?	
Do you remember anything else that you have not already mentioned?	
Additional questions asked only after ROR3	
What is the last thing you remember before falling asleep for the first time?	
What is the first thing you remember after awakening?	
Content analysis scale for the classification of the interview reports	
Stage 1. All interviews were coded as follows	
Awakening but no recall	*The subject regains responsiveness but does not recall any experiences.*
Responsiveness report	*The participant reports experiences related to events that have clearly taken place before unresponsiveness ensued (i.e. during infusion or before the experiment was started) or after the participant woke up.*
White report	*The participant reports having had experiences during 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).*
Unresponsiveness report	*The participant reports having had experiences that have most evidently taken place during the period of unresponsiveness.*
Stage 2. Unresponsiveness 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 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 unresponsiveness periods.*
Awareness	*Externally generated experiences which are related to objects/persons that have been present, or events that have occurred, during unresponsiveness, and the occurrence of which the participant could not anticipate, and which thus cannot be memory incorporation (e.g. the emotional sound).*
Stage 3a. Modality of experiences was coded separately for dreaming, memory incorporation, and awareness in unresponsiveness reports	
Sensory-perceptual experiences	*Visual, auditory, gustatory, olfactory, interoceptive (hunger, thirst), kinaesthetic (vestibular, movement), tactile, and temperature and pain experiences.*
Affective states	*Positive and negative moods and emotions.*
Cognition	*Thoughts, memories, inner speech, planning, reflection of content of consciousness.*
Out-of-body experience	*Observing one's body or the research environment from outside one's physical body.*
Sense of presence	*Sensing a presence of another person or being, without any perception of presence.*
Stage 3b. Perceptual complexity and dynamics of experience was coded separately for dreaming, memory incorporation, and awareness in unresponsiveness reports	
Static experience	*An isolated percept, or several connected percepts, are reported typically in a single modality without any change occurring in the percept(s).*
Scenery experience	*A stable scene with connected percepts is reported typically in a single modality. A scene is defined as one perceptual experience encompassing or being a background to another.*
Dynamic experience	*Complex, connected, and typically multisensory percepts, which are located within a scene, with temporal progression occurring either between percepts within a scene or between scenes.*

mixed models are expressed with geometric means [95% confidence interval (CI)]. Significance level was set at P<0.05. Statistical analyses were performed using SAS System version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA), and IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Return of responsiveness and interview reports

The mean (SD) measured drug concentrations were 2.1 (0.7) ng ml^{-1} for dexmedetomidine and 1.7 (0.6) μg ml^{-1} for propofol in LOR1, 1.9 (0.7) ng ml^{-1} and 1.5 (0.7) μg ml^{-1} in LOR2, and 3.1 (0.9) ng ml^{-1} and 2.6 (0.8) μg ml^{-1} in LOC (results for LOR1 and LOC have also been reported in Scheinin and colleagues[14]). Two propofol anaesthesia sessions were terminated prematurely because of apnoea, one during and one after LOR1, thus data from 46 participants are included in ROR1, and from 45 participants in ROR3 analyses.

Successful awakenings during steady infusion were significantly more frequent with participants receiving dexmedetomidine (Table 2). Of the 23 participants receiving dexmedetomidine, 18 (78%) were arousable from LOR1 (i.e. reached ROR1), while only 10 of 24 (43%) participants receiving

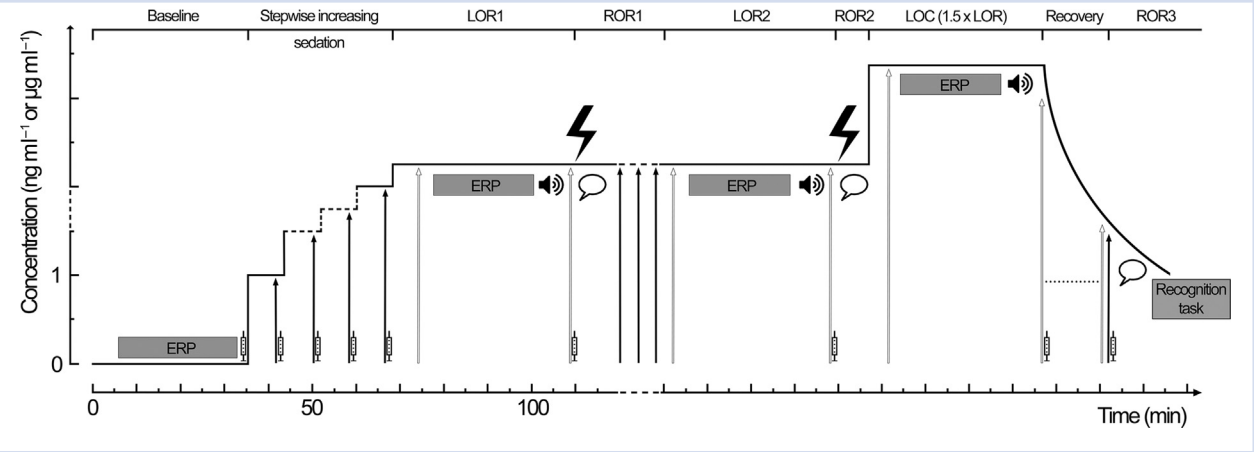

Fig 1. Design of the experiment. Dosing required to achieve loss of responsiveness (LORs) was individually titrated in 7 min steps, and LORs determined by R-test. LORs period lasted ~25 min, and 2 min before an awakening attempt an emotional sound stimulus was presented. If return of responsiveness (ROR1) occurred, the participant was interviewed. If the participant became unresponsive with the same drug concentration, the procedure was repeated (LOR2, ROR2). The target concentration was then increased 50% to induce presumable loss of consciousness (LOC), and participant interviewed upon recovery. The final interview was followed by emotional sound stimulus recognition task. EEG was continuously recorded throughout the experiment (for more details, see Scheinin and colleagues).[14] Event-related potential (ERP) paradigm was conducted at baseline, LORs, and LOC (for more details, see Kallionpää and colleagues).[15] Black arrows, responsiveness in R-test; white arrows, unresponsiveness in R-test; sound symbol, emotionally unpleasant sound stimulus; lightning symbol, awakening attempt; speech bubble, interview; syringe symbol, blood sample.

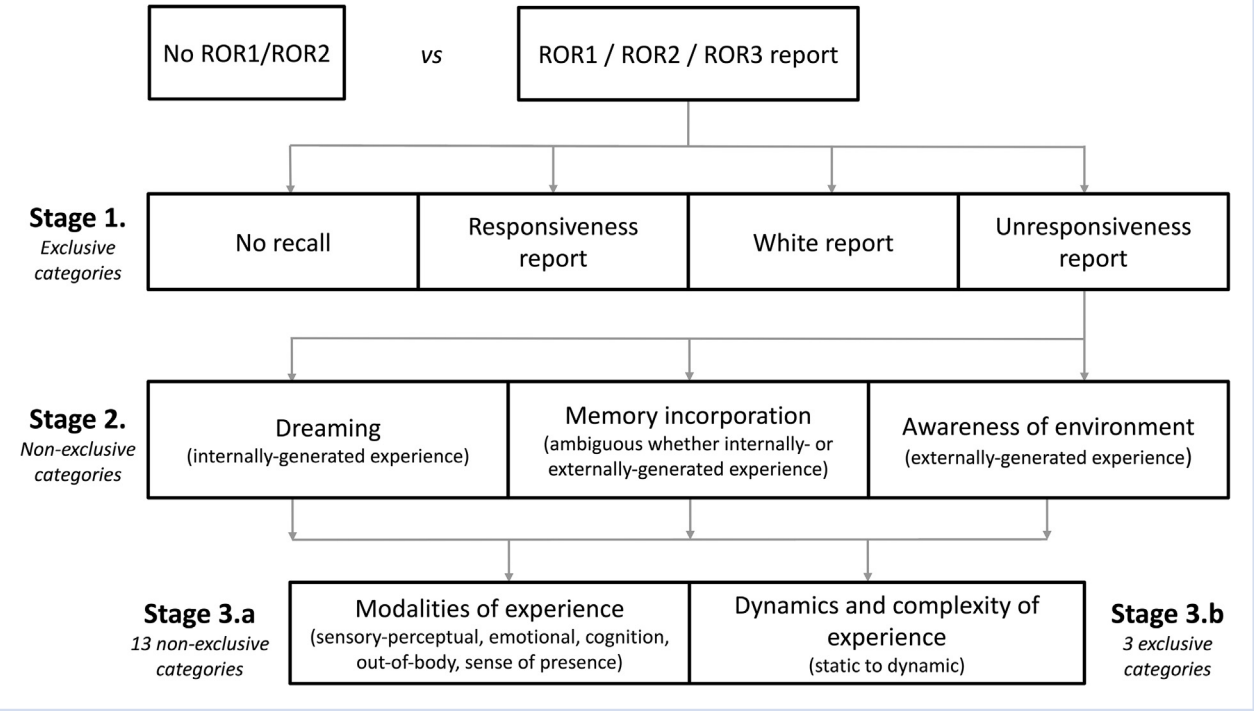

Fig 2. Outline of the interview transcript coding procedure. In Stage 1, the unit of analysis was the whole interview transcript, and in subsequent stages, elements within the single transcript. A single report could contain simultaneously dreaming, memory incorporation and awareness (i.e. in Stage 2 the categories were not exclusive). The same applied to modality of experiences scale (Stage 3a), while with the perceptual complexity and dynamics scale each experience type could be coded only as static, scenery or dynamic experience (i.e. categories were exclusive; Stage 3b). The definitions for each category are given in Table 1.

propofol could be aroused from LOR1 (P=0.02). All 18 participants receiving dexmedetomidine, but only four participants receiving propofol, became unresponsive again when left unstimulated (i.e. reached LOR2; P<0.001). Of these four, only two were arousable (i.e. reached ROR2), whereas all 18 participants receiving dexmedetomidine were again arousable (P<0.001).

Of all 93 interviews performed after the unresponsive periods (n=59 for dexmedetomidine, n=34 for propofol, Table 2), 84% were unresponsiveness reports (i.e. included experiences from the unresponsive period; dexmedetomidine 90%, propofol 74%; Table 3). Participants receiving dexmedetomidine reported experiences from the unresponsive period significantly more often than participants receiving propofol (P<0.001).

Dreaming, memory incorporation, and awareness

Dreaming was present in 93% and 72% of the unresponsiveness reports in the dexmedetomidine and propofol groups, respectively (Table 3). Within drug groups there were no differences in the prevalence of dreaming between awakenings during infusion or after recovery. However, there was a significant difference between drugs: participants receiving dexmedetomidine reported dreaming more often than those receiving propofol (P=0.03; Table 3).

Memory incorporation of the research setting was present in 72% of the unresponsiveness reports in the dexmedetomidine and in 88% in the propofol group, respectively (Table 3). There were no differences between drugs or between RORs within drug groups (Table 3).

Reports containing awareness of the environment (i.e. incorporation of events that the participant could not have anticipated to occur during LORs or LOC) were infrequent and, when checked against case report forms and EEG-recordings, always related to brief arousals from the unresponsive state. None of the participants reported a direct reference to the emotional sound even though the interview included a question whether the participant had heard anything during anaesthesia (although, after being presented with the puppy in distress sound in LOR1, one participant reported being in the forest training his Labrador retriever; Table S1). Awareness of the environment was more common when receiving dexmedetomidine than when receiving propofol (12 reports *vs* one report, P=0.04; Table 3).

In ROR3, the median time from termination of infusion to beginning of the interview was 20.4 min (range 1.5–32.5) in participants receiving dexmedetomidine, and 12.0 min (range 5.5–39.5) in participants receiving propofol. Time from end of infusion to ROR3 interview did not associate with whether the report included dreaming or memory incorporation for either drug.

Modality and perceptual complexity of experiences

There were no differences between drugs in the modalities dreaming and memory incorporation were composed of (i.e. sensory–perceptual experiences, affective states, cognition, out-of-body experience, and sense of presence), or their perceptual dynamics and complexity (i.e. whether the experience was static and simple, or dynamic and complex with temporal progression). Thus, these are reported for both drugs and all RORs combined (Table 4).

Recognition task

The emotional sound stimuli were recognised better by participants receiving dexmedetomidine than by participants receiving propofol (P=0.02 for stimulus by drug interaction in the model from which non-significant interactions were removed). In the dexmedetomidine group, sounds presented during unresponsiveness were recognised as familiar more often than novel sounds. In the participants receiving dexmedetomidine, 41.7% of responses to sounds presented during unresponsiveness were correct and the false alarm rate was 26.8% (OR for the familiar sounds, 1.75; 95% CI 1.10–2.79 after adjustment for state), while in the propofol group these were 15.2% and 21.9% (OR 0.67; 95% CI 0.35–1.28 after adjustment for state). State or drug was not associated with correctness of responses.

There were no significant two- or three-way interactions between state, drug, and correctness of response, or between state, drug, and stimuli, for the response times. Familiar stimuli, with state- and drug-adjusted geometric mean reaction time of 627 ms (95% CI 551–713), elicited a faster response than novel stimuli, with adjusted geometric mean reaction time of 715 ms (95% CI 647–792; state and drug adjusted P=0.02). State, drug, or correctness did not influence reaction times.

Discussion

Conscious experiences can be purely internally generated and disconnected from the environment or externally generated and connected to the environment. Lack of responsiveness does not necessarily inform us whether a person is unconscious, conscious but disconnected, or conscious and connected.[1] We found that most of the awakenings during a constant drug concentration of either propofol or dexmedetomidine, titrated to just exceed the threshold of unresponsiveness, led to reporting experiences that originate from the unresponsive period. The findings were similar when the dose

Table 2 Number of awakenings after periods of unresponsiveness. ROR, return of responsiveness; ~One participant was discontinued during and one after LOR1; ^LOR2 was attempted with 28 participants who achieved ROR1 but six propofol participants did not re-enter unresponsiveness. *Statistically significant difference between drugs, P<0.05

Awakenings	ROR1 n/N (%) after LOR1	ROR2, n/N (%) after LOR2	ROR3, n/N (%) after LOC
Both drugs	28/46~ (60.1)*	20/22^ (90.1)*	45/45~ (100.0)
Dexmedetomidine	18/23 (78.3)	18/18 (100.0)	23/23 (100.0)
Propofol	10/23 (43.5)	2/4 (50.0)	22/22 (100.0)

Table 3 Prevalence of report types, and prevalence of dream-like experiences, memory incorporation, and awareness of the environment (as defined in Table 1) in unresponsiveness reports. *Statistically significant difference between drugs, $P<0.05$. Data are n/N (%)

Report types	ROR1 (after LOR1)	ROR2 (after LOR2)	ROR3 (after LOC)	All RORs combined
No recall				
Both drugs	1/28 (3.6)	4/20 (20.0)	0/45 (0.0)	5/93 (5.4)
Dexmedetomidine	0/18 (0.0)	3/18 (16.7)	0/23 (0.0)	3/59 (5.1)
Propofol	1/10 (10.0)	1/2 (50.0)	0/22 (0.0)	2/34 (5.9)
Responsiveness report				
Both drugs	1/28 (3.6)	0/20 (0.0)	6/45 (13.3)*	7/93 (7.5)*
Dexmedetomidine	0/18 (0.0)	0/18 (0.0)	0/23 (0.0)	0/59 (0.0)
Propofol	1/10 (10.0)	0/2 (0.0)	6/22 (27.3)	7/34 (20.6)
White report				
Both drugs	1/28 (3.6)	1/20 (5.0)	1/45 (2.2)	3/93 (3.2)
Dexmedetomidine	1/18 (5.6)	1/18 (5.6)	1/23 (4.4)	3/59 (5.1)
Propofol	0/10 (0.0)	0/2 (0.0)	0/22 (0.0)	0/34 (0.0)
Unresponsiveness report				
Both drugs	25/28 (89.3)	15/20 (75.0)	38/45 (84.4)*	78/93 (83.9)*
Dexmedetomidine	17/18 (94.4)	14/18 (77.8)	22/23 (95.7)	53/59 (89.8)
Propofol	8/10 (80.0)	1/2 (50.0)	16/22 (72.7)	25/34 (73.5)
Type of experience in the unresponsiveness report				
Dreaming				
Both drugs	22/25 (88.0)*	12/15 (80.0)	33/38 (86.8)	67/78 (85.9)*
Dexmedetomidine	17/17 (100.0)	12/14 (85.7)	20/22 (90.9)	49/53 (92.5)
Propofol	5/8 (62.5)	0/1 (0.0)	13/16 (81.3)	18/25 (72.0)
Memory incorporation				
Both drugs	22/25 (88.0)	8/15 (53.3)	30/38 (78.9)	60/78 (76.9)
Dexmedetomidine	15/17 (88.2)	7/14 (50.0)	16/22 (72.7)	38/53 (71.7)
Propofol	7/8 (87.5)	1/1 (100.0)	14/16 (87.5)	22/25 (88.0)
Awareness				
Both drugs	4/25 (16.0)	4/15 (26.7)	5/38 (13.2)	13/78 (16.7)*
Dexmedetomidine	4/17 (23.5)	4/14 (28.6)	4/22 (18.2)	12/53 (22.6)
Propofol	0/8 (0.0)	0/1 (0.0)	1/16 (6.3)	1/25 (4.0)

Table 4 Modality and perceptual complexity of experiences in unresponsiveness reports. The 13 reports containing references to awareness of the environment included mostly auditory experiences (8/13), three references to sensed presence of someone nearby, and were mostly static (11/13). See Table 1 for definitions

Modality	Percentage of Dream experiences	Percentage of Memory incorporation
Sensory-perceptual		
Visual	89.1	33.0
Auditory	31.1	66.6
Gustatory	9.1	0.0
Olfactory	0.0	0.0
Interoceptive	8.3	1.1
Kinesthetic	27.8	15.5
Tactile	9.1	15.4
Pain, temperature	6.1	17.6
Affective states		
Positive	19.9	5.
Negative	12.4	2.6
Cognition	30.1	14.7
Out-of-body experience	0.0	0.0
Sense of presence	2.5	10.5
Perceptual complexity and dynamics		
Static report	37.5	84.5
Scenery report	34.4	15.5
Dynamic report	28.1	0.0

was increased by 50% and participants interviewed after a brief recovery period. Most of the experiences were either dreaming (internally generated content of consciousness) or memory incorporation of the experimental setting, while the few awareness reports (externally generated content of consciousness) were linked to arousals. These indicate that experiences during unresponsiveness were internally generated and consciousness was therefore disconnected.

Dreaming during anaesthesia has been defined as a recalled experience that takes place between the induction of anaesthesia and the recovery of consciousness upon emergence.[12] Reports of dreaming in patients are relatively common, ranging from 3.2% to 52.6%.[4–9,11] Factors associated with dreaming are youth,[5,7,13,21] good general health,[5,7,13,21] and rapid emergence from anaesthesia[5,7,13]; additionally, propofol anaesthesia has been associated with a higher incidence of dreaming.[5,6,10,13] However, all previous studies addressed the incidence of dreaming in surgical patients or experimental participants after a significant temporal delay, leaving the question open of whether dreaming occurs during drug administration or during emergence.[4–9]

It has been suggested that dreaming is limited to the short period before awakening, when patients are sedated or in a physiological sleep state.[5,13,22] Given this, we expected that dreaming would be more frequently reported after the recovery period. This hypothesis was not confirmed: although dreaming was more frequently reported by participants receiving dexmedetomidine, with both drugs the

participants reported dreaming with similar frequency during TCI (ROR1/ROR2) and after recovery (ROR3). This indicates that dreaming is not limited to the recovery period but is also present during anaesthetic infusion. However, the maximal concentration of propofol in our study was slightly lower than in clinical (surgical) anaesthesia, and that of dexmedetomidine somewhat higher than typically used in intensive care sedation.

The contents of dreams seem to be fairly similar in both general anaesthesia and sedation.[10] In previous studies, dreams reported after anaesthesia are usually pleasant, short, simple, related to everyday life, and unrelated to the operative setting.[10,13,22,23] Our findings partially corroborate previous results as the dream reports were brief, only a quarter of the dream experiences were dynamic, and positive emotional states were slightly more frequent than negative emotional experiences.

When directly questioned about experiences related to the research environment, memory incorporation was frequently reported, most often static auditory experiences. No differences between drugs or between awakenings in rates of memory incorporation were observed. It has been noted that many 'dreams' reported by patients after emergence contain people talking or standing around the patient,[5] which in our study would have been coded as memory incorporation.

Indications of awareness of the environment were infrequent and always related to brief arousals, thus not actually experienced during unresponsiveness. Awareness was more prevalent in participants receiving dexmedetomidine. Spontaneous recall of emotional stimuli did not occur with either drug. Therefore, at first glance and based on the interviews, the participants seemed disconnected. In the recognition task, responses to emotional stimuli presented during unresponsiveness were, however, significantly faster than to novel stimuli in both drug groups. Thus, implicit learning may have occurred. Nevertheless, this is not evidence of connected consciousness given that implicit learning does not require conscious processing. However, it is evidence of external stimuli having been received and processed at some unconscious or preconscious level of processing, without the stimuli reaching the level of connected consciousness. Notably, participants receiving dexmedetomidine recognised familiar stimuli as familiar more often than participants receiving propofol (42% *vs* 15%), which might also imply explicit memory for stimuli, and possibly conscious connectedness that was forgotten as no explicit memory reports of the stimuli were given by any participant.

Dexmedetomidine has been suggested to cause memory impairment dose-dependently because of weakened encoding, but at low doses memory for emotionally arousing stimuli seems to be better preserved than memory for neutral stimuli.[24,25] At anaesthetic concentrations, propofol is known to suppress learning of emotionally charged information.[24] However, another study has demonstrated that sedative doses of propofol do not disrupt the amygdala response to visual emotionally arousing stimuli, although they do suppress the hippocampal response.[26] This indicates that, while the mechanisms for immediate emotional response may remain relatively intact despite sedation, memory for emotionally arousing material is diminished or lost. This may have clinical implications; patients sedated with dexmedetomidine, or patients receiving sedative doses of propofol, could have emotional reactions to arousing or painful stimuli during sedation without later explicit recall. However, post-traumatic symptoms might appear even without explicit recall of traumatic events.[27–29]

The present study has several limitations. Although participants were interviewed immediately after awakening at ROR1, subsequent to 25 min of unresponsiveness, it is possible that some reports coded as unresponsiveness reports actually included experiences from the preceding dose titration period. Further, in reports acquired after recovery at ROR3, it is practically impossible to separate experiences that occurred during LOC with constant drug concentration from those that occurred after terminating the infusion. The reports at ROR2 are thus the most reliable indicators of content of consciousness during unresponsiveness but, notably, data were available from only one propofol participant (four propofol participants lost responsiveness twice, of whom two could be aroused from LOR2, and only one recalled experiences). Nevertheless, the similarity of the prevalence and content of reports across RORs with both drugs suggests that major differences in the presence and content of subjective experiences are not likely to exist, strengthening the conclusion that experiences truly originate from the unresponsive period.

Another problem relates to defining memory incorporation of the research setting. Many participants reported elements related to the research environment, such as hearing speech (probably referring to the event-related potential paradigm) or feeling a touch in the arm (probably referring to blood sampling). We could not time the origin of these types of experiences, given that the elements the interview reports referred to were equally present during wakefulness, sedation, and unresponsiveness. Therefore, we cannot separate whether these memory incorporations were internally or externally generated. We interpret these as unlikely to signify true awareness and connectedness, and comparable with laboratory references of dreams collected in a sleep laboratory setting[30] (i.e. memory incorporations reflect the transference of significant and salient waking events into dreams).

Conclusions

When participants were woken up and interviewed during and after dexmedetomidine or propofol infusion in an experimental setting, experiences were equally frequently reported between awakenings (80–87%) and were most often dreaming (86%) and memory incorporation of the research environment (77%). Both dreaming and awareness were more frequently reported by participants receiving dexmedetomidine. Internally generated disconnected experiences do not only take place during the recovery period but also during target controlled anaesthetic infusion. In contrast, awareness of the research environment (i.e. connectedness) was seldom evident from the interview reports, and always associated with brief arousals. However, response times to familiar stimuli were faster than to novel stimuli in both drug groups, indicating implicit memory formation, and participants receiving dexmedetomidine recognised familiar stimuli better than by chance, indicating partial explicit recall and connectedness. Taken together, anaesthetics titrated to concentrations inducing behavioural unresponsiveness frequently do not abolish conscious experiences, and do not even necessarily induce disconnectedness.

Authors' contributions

Principal investigator: H.S.
Study design: A.M., J.L., K.K., T.V., A.R., H.S., K.V.
Study conduct: R.E.K., A.S., A.M., J.L., K.K., K.V.
Content analysis: L.R., M.K.
Data analysis: L.R., R.E.K, M.K., K.V.
Statistical analyses: T.V., K.V.
Writing the manuscript: L.R., R.E.K., A.M., H.S., K.V.
Revising paper: all authors.

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Declaration of interests

J.L. has received lecture compensation from Orion Pharma and holds Orion Pharma stock. J.L. has attended an educational congress as a guest of Pfizer Pharmaceuticals.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.03.014.

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