Consciousness lost and found: Subjective experiences in an unresponsive state

Valdas Noreika [a,*], Leila Jylhänkangas [a], Levente Móró [a], Katja Valli [a,b], Kimmo Kaskinoro [c], Riku Aantaa [c], Harry Scheinin [d], Antti Revonsuo [a,b]

[a] Centre for Cognitive Neuroscience, Department of Psychology, University of Turku, 20014 Turku, Finland
[b] School of Humanities and Informatics, University of Skövde, Skövde, Sweden
[c] Department of Anesthesia, Intensive Care, Emergency Medicine and Pain Therapy, Turku University Hospital, Turku, Finland
[d] Department of Pharmacology and Clinical Pharmacology, and Turku PET Centre, University of Turku, Turku, Finland

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ABSTRACT

Anesthetic-induced changes in the neural activity of the brain have been recently utilized as a research model to investigate the neural mechanisms of phenomenal consciousness. However, the anesthesiologic definition of consciousness as "responsiveness to the environment" seems to sidestep the possibility that an unresponsive individual may have subjective experiences. The aim of the present study was to analyze subjective reports in sessions where sedation and the loss of responsiveness were induced by dexmedetomidine, propofol, sevoflurane or xenon in a nonsurgical experimental setting. After regaining responsiveness, participants recalled subjective experiences in almost 60% of sessions. During dexmedetomidine sessions, subjective experiences were associated with shallower "depth of sedation" as measured by an electroencephalography-derived anesthesia depth monitor. Results confirm that subjective experiences may occur during clinically defined unresponsiveness, and that studies aiming to investigate phenomenal consciousness under sedative and anesthetic effects should control the subjective state of unresponsive participants with post-recovery interviews.

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1. Introduction

At present, no objective physiologic markers are known that would reveal with perfect accuracy the presence or the absence of consciousness. Therefore, in clinical medicine standardized scales of indirect behavioral criteria are typically used, such as the Glasgow Coma Scale (Teasdale & Jennett, 1974) or, more recently, the Full Outline of Unresponsiveness score (Wijdicks, Bamlet, Maramattom, Manno, & McClelland, 2005). Such scales rely on a patient's behavioral responsiveness to standardized stimuli, e.g., a verbal command to open the eyes, or an application of a noxious stimulus. Typically, when meaningful behavioral responses to stimuli cannot be elicited, the person is defined as "unconscious". Similarly, anesthesiologists use terms such as "loss of consciousness" to describe a state where a meaningful motor response to a verbal command, as well as explicit memory for the external events, is absent. Nevertheless, loss of motor response to a verbal stimulus merely represents disturbed control and interaction of these two brain functions. Typically, the additional criterion for "general anesthesia" is the loss of meaningful response to a painful stimulus, which usually takes place after the loss of responses to verbal stimuli and is therefore a state of deeper unconsciousness than the mere loss of responses to verbal commands.

In principle it is possible that someone who fulfills the criteria of being "unconscious" according to the above definition might still in another sense be "conscious". That is, even a motorically unresponsive person may process information in other brain areas and thus might undergo, e.g., subjective experiences (either internally generated or triggered by external stimuli). The mere occurrence of subjective experiences is often called "phenomenal consciousness" (Block, 1995; Revonsuo, 2006). Phenomenal consciousness does not necessarily include the ability to respond to stimuli or communicate with the environment, as evidenced by the locked-in syndrome in which motor responses are lost but phenomenal consciousness is preserved (Kahane & Savulescu, 2009). Recently, also evidence from functional magnetic resonance imaging (fMRI) experiments with vegetative patients suggests that at least some of the patients undergo both internally generated and stimulus triggered subjective experiences, and are able to carry out mental imagery tasks according to the instructions given to them verbally (Monti et al., 2010; Owen et al., 2006).

In consciousness research, a new concept has been recently introduced to refer to the dissociation between the first and the second type of consciousness (responsiveness vs. phenomenal consciousness). A person who fulfills the criteria of "unconsciousness" based on external responsiveness (e.g., to verbal commands) despite the fact that he or she is phenomenally conscious, is called an "inverse zombie" (Mashour & LaRock, 2008). In anesthesiology, a state of "inversed zombiehood" with preserved phenomenal consciousness

* Corresponding author. Fax: +358 2 3335060.
E-mail addresses: valnor@utu.fi, valnoreika@gmail.com (V. Noreika).

during anesthetically induced unconsciousness has been studied under the labels of "anesthesia awareness" and "anesthesia dreaming" (Errando et al., 2008). The former concept refers to veridical awareness of external stimuli during the unresponsive state, the latter to the occurrence of purely internally generated, stimulus-independent subjective experiences during the unresponsive state.

Studies on surgical patients have shown that anesthesia awareness is a relatively rare, but still occasionally occurring condition with estimated frequencies ranging from 0.023% to 1% of the general anesthesia cases (Errando et al., 2008; Mashour et al., 2009; Ranta, Laurila, Saario, Ali-Melkkilä, & Hynynen, 1998; Sandin, Enlund, Samuelsson, & Lennmarken, 2000), with a common reported incidence being around 0.13% (Sebel et al., 2004; for discussion regarding different incidence estimates, see Sebel, 2009). The occurrence of anesthesia dreaming appears to be a much more common phenomenon, and has been reported in 6–53% of post-anesthesia interviews (Brandner, Blagrove, McCallum, & Bromley, 1997; Errando et al., 2008; Leslie, Skrzypek, Paech, Kurowski, & Whybrow, 2007; Leslie et al., 2005). The exact incidence is, however, very difficult to estimate, because it depends on several intervening factors, such as the length and the depth of anesthesia required for different medical interventions, the way in which the patients are interviewed about their experiences, and the delay between the recovery from anesthesia and the interview. Furthermore, the patients' general medical condition as well as combination of various anesthetic agents and other drugs given during surgery may affect the memory and reduce recall for such experiences.

In the present study our main aim was to specifically estimate the frequency of the occurrence of subjective experiences during sedative "unconsciousness" as defined by the loss of behavioral responsiveness to verbal stimuli. In addition, the following research questions were asked: What kinds of contents of phenomenal consciousness are reported and what is the frequency of their recall? Does the recall frequency of subjective experiences depend on the type of sedative/anesthetic agent used? Does the recall frequency of subjective experiences depend on the "depth of sedation" as measured by an electroencephalography (EEG)-derived anesthesia depth monitor? The study was designed to avoid many of the problems of previous studies. First, we used only young healthy participants without any notable cognitive or memory problems. Second, the setting was completely experimental rather than clinical or surgical. Third, we used single sedative/anesthetic agents rather than drug cocktails. Fourth, no other drugs in addition to the sedative/anesthetic were applied (such as muscle relaxants). Fifth, the behavioral loss of consciousness was carefully tested throughout the sessions, which is not common in clinical settings. Sixth, the "depth of sedation" was conscientiously monitored by an EEG-derived measure. Seventh, after the session the participants were interviewed twice in detail using a structured interview specifically inquiring about their subjective experiences during the state of unresponsiveness. Eighth, the content of the participants' reports and the quality of the subjective experiences was analyzed in detail by methods similar to those used in dream research to study dream reports. Thus, we expected to develop a more systematic and accurate description of dissociation between phenomenal consciousness and behavioral unresponsiveness than many of the previous studies have been able to provide.

2. Materials and methods

2.1. Participants

An open invitation for students to participate in the study, which was designed to explore the neural mechanisms of the loss of responsiveness, was put to several notice boards at the campus area as well as to the intranet pages of the University of Turku. Forty right-handed male volunteers, age 18–30 years, signed an informed consent and were paid for participation in the study. All participants were of a good general health (American Society of Anesthesiologists physical status I). The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and the Finnish Medicines Agency.

2.2. Design and materials

Each participant was sedated by one of the following sedative/anesthetic agents with ten participants per single drug: dexmedetomidine, propofol, sevoflurane and xenon. Dexmedetomidine is a specific alpha2-adrenoceptor agonist, propofol may affect the gamma-amino-butyric-acid (GABA) system, whereas the action of sevoflurane is likely more complex including both enhancement of the GABA system and effects on ion channels. The mechanism of the anesthetic action of xenon is less well known but N-methyl-d-aspartate (NMDA) receptor is likely involved (for review of neuronal mechanisms of general anesthetics, see Franks, 2008). Notably, despite the differences in the binding sites, it is still possible that the lower-level molecular mechanisms are shared between different anesthetic drugs (Hameroff, 2006).

There was only one session for each participant receiving sevoflurane or xenon, whereas participants attending dexmedetomidine or propofol sessions were invited for two separate sessions with a 1 month interval in between. Bispectral index (BIS XP, algorithm version 4.0, smoothing rate 15 s, Aspect Medical Systems), an EEG-derived method for assessment of the "depth of sedation", was recorded throughout the sessions. The BIS monitor provides a numeric value ranging from 0, which equals to isoelectric EEG silence, to 100, which reflects a fully awake and alert state of an adult participant. Skin of the forehead was cleaned with an alcohol swab, and a disposable EEG electrode strip for the BIS recording was positioned on the forehead as recommended by the manufacturers. Unilateral sensors were used and the side of the forehead was randomized across the sessions. GE Datex-Ohmeda S/5 Anaesthesia Monitor and a portable computer running the S/5 Collect software (Datex-Ohmeda S/5 Collect Version 4.0, GE Healthcare) were used for recording the BIS indices at 10 s interval. During all sessions, 10–20 electroencephalography (EEG) recordings were carried out, whereas the second dexmedetomidine and propofol sessions were additionally complemented by positron emission tomography (PET) imaging. EEG and PET data will be reported elsewhere.

The loss of responsiveness (LOR) was induced by stepwise increases in the drug concentration (except for the more abrupt xenon sessions), and was assessed by an absence of response to the repeated verbal command "Open your eyes!" Likewise, regaining of responsiveness (ROR) was defined as the first meaningful response to the same request "Open your eyes!" after the study drug was discontinued. Responsiveness was tested at 5 min intervals at each escalating concentration level (i.e. at 4 and 9 min of each 10 min level) until the loss of responsiveness (LOR) and thereafter at 1 min intervals after study drug discontinuation. As an exception, there were two cycles of the LOR and ROR during the second set of dexmedetomidine sessions in the PET scanner ($N = 9$).

Dexmedetomidine (Precedex 100 µg ml^{-1}, Orion, 02200 Espoo, Finland) was administered intravenously using target controlled infusion (TCI) scheme aiming at escalating pseudo steady-state plasma concentrations at 10 min intervals. A Harvard 22 syringe pump (Harvard Apparatus, South Natick, MA) connected to portable computer running Stanpump software (freely available from the author, Steven L. Shafer, M.D. at http://anesthesia.stanford.edu/pkpd/) and the pharmacokinetic parameters of Talke, Lobo, and Brown (2003) were used. Infusion was started at target

concentration of 1.0 ng ml⁻¹, followed first by 0.5 ng ml⁻¹ target concentration increase and 0.25 ng ml⁻¹ increases thereafter (i.e. 1.0–1.5–1.75–2.0–2.25, etc. ng ml⁻¹) until LOR was achieved.

Propofol (Propofol Lipuro 10 mg ml⁻¹, B. Braun Melsungen AG, Pfieffewiesen, D-34212 Melsungen, Germany) was administrated intravenously with the same infusion system and scheme as dexmedetomidine, using the pharmacokinetic model developed by Marsh, White, Morton, and Kenny (1991). Infusion was started at plasma target concentration of 1.0 µg ml⁻¹, followed first by 0.5 µg ml⁻¹ target concentration increase and 0.25 µg ml⁻¹ increases thereafter (i.e. 1.0–1.5–1.75–2.0–2.25, etc. µg ml⁻¹) until LOR was achieved.

During the second propofol and dexmedetomidine session, the computer controlled drug infusion was repeated for each participant by aiming at their individually determined drug concentrations of .50%, 75% and 100% of the LOC concentration. Responsiveness was tested once during each concentration level, i.e., 8 min after the infusion was started or increased. If the drug concentration defined in the first session of the study was not sufficient to produce LOR in the second session, the drug infusion was continued and an additional 25% target concentration increment was added to the rate.

Sevoflurane (Abbott, Scandinavia AB, Solna, Sweden) was administered by inhalation using a tight facemask and a calibrated sevoflurane vaporizer with on-line end-tidal sevoflurane measurement (Datex-Ohmeda S/5 Anaesthesia Monitor, Collect Version 4.0, GE Healthcare). Participants were sedated with escalating end-tidal concentrations started at 0.5% and followed by 0.25% increases (i.e. 0.5–0.75–1.0–1.25, etc. % end-tidal) at 10 min intervals until LOR was achieved (Eger & Bahlman, 1971).

Given that one minimum alveolar concentration (MAC) for xenon is about 65% of the end-tidal concentration, denitrogenation of participants was performed by asking them to breathe 100% oxygen through a tight 5-cm H_2O continuous positive airway pressure mask for 1 h. After the denitrogenation period, participants were told to hold their breath to avoid any breathing of room air while the pressure mask was changed to a tightly fitting regular face mask connected to the closed loop anesthesia ventilator (PhysioFlex, Dräger, Lübeck, Germany). Thereafter, sedation was induced by changing the inhaled oxygen concentration from 100% to 21%, this way increasing the xenon concentration in the gas mixture. Xenon concentration increase was facilitated by flushing the breathing system with a mixture of xenon 75% and oxygen 25%, while participants continued breathing spontaneously via the face mask.

On the average, 3.7 (range 2–6) concentration steps were needed for dexmedetomidine, 4.8 (3–9) for propofol and 2.6 (2–5) for sevoflurane to reach the loss of responsiveness. The mean (SD) target concentrations needed for loss of responsiveness were 1.93 (0.37) ng ml⁻¹ for dexmedetomidine and 2.23 (0.62) µg ml⁻¹ for propofol. The mean end-tidal sevoflurane concentration was 0.9% (0.24), and the mean end-tidal xenon concentration was 55.7% (6.46). Compared to the previously reported age rated MAC-incision values, sevoflurane concentration was 47% of 1 MAC (Lerou, 2004) and xenon concentration was 55.7% of 1 MAC (Nakata et al., 2001).

After the eventual ROR and 5 min of EEG recording in a resting state, reports of subjective experiences were collected in a structured interview (see Table 1). Specific interview guidelines were given to participants in advance, informing what questions will be asked after ROR. Interviews were repeated 10–30 min after the first interview, when participants had fully recovered.

For a general overview of the experimental protocol, see Fig. 1. Due to participant withdrawal and technical reasons, two sessions were not completed, and thus 58 sessions were conducted as a total.

2.3. Data analyses

To evaluate the frequency and quality of subjective experiences during induced unresponsiveness, the Subjective Experiences During Anesthesia Coding System (SEDA-Coding) was devised. It was constructed on the basis of different complexity of subjective experiences, including: (1) micro-level experiences (sensory, affective, and thought-like experiences), (2) macro-level experiences (dream-like, lab-related, out-of-body experiences, and changed experience of the passage of time), and (3) white reports (that is, the participant remembered having had experiences during unresponsiveness or thought he may have had some, but could not recall any specific content). The unit of content analysis was a single report, combined of the first and the second interviews, which were transcribed word by word. Two independent judges were instructed to evaluate which of the reported subjective experiences may have happened during a period from LOR to ROR. In this step, reported experiences that clearly took place outside the unresponsiveness phase, e.g., they were related to the factual events taking place during the induction or recovery phases, such as "after I woke up I noticed that I felt anxious because of the mask. It was very hard to breath and I wished to get rid of it" (participant S102), were excluded from further analysis. Experiences that were reported as if they could have occurred during a state of unresponsiveness and did not refer to the factual events outside the unresponsiveness phase were further classified according to the SEDA-Coding categories. After the two judges had completed the analysis individually, the identified categories were compared and inter-judge agreement was evaluated. In case of disagreement, the two judges discussed the unclear parts of the report until agreement was achieved. Full instructions for the use of the SEDA-Coding and its category definitions are presented in Supplementary material available on-line.

All statistical analyses were performed with the SPSS 15.0 for Windows™ software. Inter-rater agreement was evaluated with Cohen's Kappa coefficient. Kappa values <.4 indicate weak agreement, values .4–.75 fair to good agreement, whereas values >.75 indicate strong agreement (Fleiss, 1981). Content analyses with categorical data were carried out with Fisher's exact test. To fulfill the assumption of independent observation, only one and always the first attended session was used from each participant for the statistical analysis of SEDA-Coding categories ($N = 40$), i.e., the second attended dexmedetomidine and propofol sessions were excluded from inferential analysis.

To compare "depth of sedation" that was required to induce and maintain unresponsiveness in dexmedetomidine, propofol and sevoflurane groups, BIS values averaged within each experimental phase (expressed as a mean, M) were analyzed using one-way between-participants analysis of variance (ANOVA) and independent samples t-test. The induction phase was defined as a period from the last meaningful response to the command "Open your eyes!" to the LOR, which lasted on average 4.9 min ($SD = 0.32$) during the first and 12.98 min ($SD = 0.83$) during the second dexmedetomidine sessions, 5.08 min ($SD = 0.23$) during the first and 14.43 min ($SD = 1.92$) during the second propofol sessions, and 5.48 min ($SD = 0.63$) during sevoflurane sessions. The unresponsiveness phase was defined as a period from the first LOR to the first ROR, which was on average 9.32 min ($SD = 7.05$) during the first and 10.41 min ($SD = 1.53$) during the second dexmedetomidine sessions, 6.73 min ($SD = 3.02$) during the first and 12.59 min ($SD = 4.04$) during the second propofol sessions, and 8.85 min ($SD = 3.19$) during sevoflurane sessions. The recovery phase was defined as the first 2 min following ROR. Due to a very brief duration of xenon sessions, BIS analysis could not be used for this group. For within-participant comparison between two dexmedetomidine sessions, a paired samples t-test was used. Differences

Table 1
Guidelines for the structured interview after awakening from loss of responsiveness.

1. General questions	(1) Tell me everything that was going on in your mind starting from anesthesia induction to the awakening from anesthesia
	(2) If you had some experiences related to the laboratory surroundings or the experiment, describe them as precisely as possible
2. Specific questions	(3) If you had some moods or feelings, specify them
	(4) If you had visual experiences, list the figures, objects and characters you have seen
	(5) If you had some experiences of your own body or self, describe them
	(6) If some changes happened in your experiences, for example one object or feeling was replaced by another, describe them
	(7) Tell me if you remember something else that is not reported yet
3. Additional questions	Free questions depending on the report
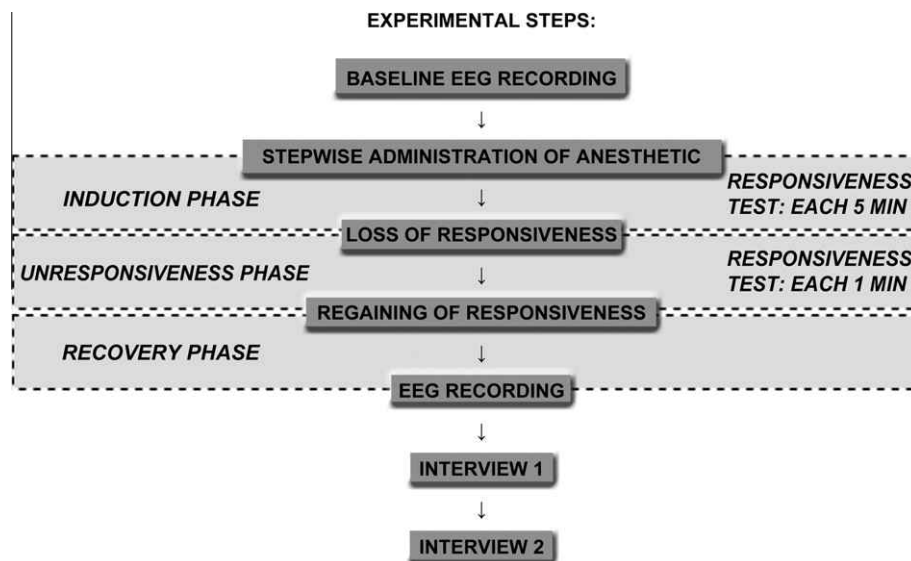
Fig. 1. The main steps and phases of the experimental procedure.

were considered statistically significant if $p < .05$, and two-tailed hypotheses were always used. When applicable, the magnitude of the effect was estimated with Cohen's d.

3. Results

3.1. Incidence of subjective experiences

After ROR, subjective experiences were reported in 62.5% of sessions when unresponsiveness was induced for the first time ($N = 40$), in 50% of sessions when unresponsiveness was induced for the second time ($N = 18$), and taken together, in 58.6% of all sessions ($N = 58$) (see Table 2). During the first sessions, the difference between the frequency of reports with subjective experiences across all four anesthetic groups was not significant ($N = 40$, $p = .057$, Fisher's exact test). When drugs were compared individually, dexmedetomidine sessions showed higher incidence of reports containing subjective experiences than propofol sessions ($N = 20$, $p = .02$, Fisher's exact test).

3.2. Content of subjective experiences

Two independent judges content-analyzed subjective reports according to the SEDA-Coding categories. The inter-rater reliability between judges, as measured with Cohen's Kappa coefficient, varied from .469 (76.5%) to 1.00 (100%). Mean for all judgments considered together was .74 (91.6%), approaching a strong inter-judge agreement (see Table S1 in Supplementary material). All categories of the SEDA-Coding received scoring points, except for olfactory sensations (see Table 3). Post-recovery interviews contained

diverse experiences that varied from one report to another (see Table 4). All four sedative/anesthetic agents induced comparable proportions of different experiences, and the only significant difference between the drugs was related to the frequency of laboratory-related experiences ($N = 40$, $p < .05$, Fisher's exact test). In particular, administration of sevoflurane induced more experiences related to the operating room and hospital than did administration of dexmedetomidine ($N = 20$, $p < .01$, Fisher's exact test).

3.3. Subjective experiences and the "depth of sedation"

During the unresponsiveness phase of sevoflurane and the first dexmedetomidine and propofol sessions, BIS values averaged to 61.9 ($SD = 11.43$, range = 41–83). There was a statistically significant difference between anesthetic agents regarding the "depth of sedation" that was required to maintain unresponsiveness ($F_{2,27} = 5.79$, $p < .01$). More precisely, sedation was "deeper", as expressed by the lower BIS values, during propofol ($M = 60.54$, $SD = 7.95$) than during sevoflurane ($M = 70.00$, $SD = 6.11$) sessions ($t(18) = 2.99$, $p < .01$, $d = 1.41$). Sedation was also deeper in dexmedetomidine ($M = 55.10$, $SD = 13.93$) than in sevoflurane ($M = 70.00$, $SD = 6.11$) sessions ($t(18) = 2.94$, $p < .01$, $d = 1.39$). Even though subjective experiences were more common after dexmedetomidine induced unresponsiveness than propofol unresponsiveness, there was no difference between these two groups regarding the "depth of sedation" as assessed by the BIS monitor during the actual loss of responsiveness ($t(18) = 1.07$, $p = .298$).

When dexmedetomidine data from both sessions were compared, five participants were found to report subjective experiences in one, but not in another session. Considering these

Table 2
Incidence of reported subjective experiences after recovery from sedative/anesthetic-induced unresponsiveness.

Sedative/anesthetic drug	First session N	Experiences N (%)	Second session N	Experiences N (%)	All sessions N	Experiences N (%)
Dexmedetomidine	10	9 (90)	9	5 (55.6)	19	14 (73.7)
Propofol	10	3 (30)	9	4 (44.4)	19	7 (36.8)
Sevoflurane	10	6 (60)	–	–	10	6 (60)
Xenon	10	7 (70)	–	–	10	7 (70)
Total	40	25 (62.5)	18	9 (50)	58	34 (58.6)

Table 3
Frequencies of specific subjective experiences during sedation as scored by the SEDA-Coding.

Subjective content	Sedative/anesthetic drug			
	Dexmedetomidine N = 10 (=19)	Propofol N = 10 (=19)	Sevoflurane N = 10	Xenon N = 10
Micro-level experiences				
Visual	7 (11)	3 (5)	4	5
Auditory	2 (3)	3 (5)	4	5
Sensorimotor	3 (6)	1 (4)	3	3
Olfactory	–	–	–	–
Gustatory	(1)	–	–	–
Positive affective state	1 (4)	2 (4)	1	4
Negative affective state	1 (1)	–	1	4
Thought-like	3 (3)	1 (1)	–	4
Macro-level experiences				
Dream-like	2 (3)	2 (2)	–	3
Laboratory-related	2 (3)	2 (4)	6	4
Out of body	1 (2)	–	–	–
Changed time	1 (2)	–	–	1
White reports	1 (1)	(1)	–	–

Table 4
Examples of subjective experiences during sedation.

Drug and participant code	SEDA-Coding categories	Summary of verbal report
D102	Visual, sensorimotor, out of body	Had several quick visual experiences. In one vision the participant was "playing football". "Suddenly [after the football dream] we were pirates, and at some point we went to swim", "when the drug started to work, my head came out of my body"
P104	Visual, auditory, dream-like, positive affective state	Had a fragmentary dream about "a trip in Eastern Europe", "this was a quite pleasant experience and I was not afraid", "I felt that even if I was having that dream I still heard that you were here"
S109	Visual, positive affective state, lab-related	"I had a dream in which one of the nurses here got suspended from her work, which was not a bad thing after all", and then "I saw a beautiful beach"
X105	Auditory, lab-related, positive and negative affective state	"I had a dream in which my friend's roommate, who studies medicine, was sitting next to me here in the laboratory, telling me that we have to go to the city". "At some point I was a bit anxious, but after that I felt extraordinarily good"

participants, reported experiences were associated with higher BIS values during unresponsiveness phase ($M = 58.60$, $SD = 15.63$) compared to the same phase of sessions that did not produce reports of subjective experiences ($M = 47.01$, $SD = 12.80$) ($t(4) = 4.58$, $p = .01$, $d = 2.05$).

Regarding the "depth of sedation" during the induction phase of dexmedetomidine sessions, there was no difference between the presence and absence of subjective experiences ($t(4) = -.87$, $p > .05$). Likewise, the "sedation depth" did not differ between the presence and absence of subjective experiences during the recovery phase ($t(4) = 1.14$, $p > .05$). Concerning the propofol sessions, there were three participants who reported subjective experiences in one, but not another session. Contrary to the dexmedetomidine findings, propofol sessions with subjective experiences showed a tendency towards lower BIS values during unresponsiveness phase ($M = 55.16$ vs. $M = 60.64$); yet, due to a small sample, inferential statistics were not carried out.

4. Discussion

Results of the present study show that unresponsiveness to verbal stimuli caused by different sedative/anesthetic agents is frequently accompanied by subjective experiences, ranging from simple sensations to complex dream-like stories. This finding extends observation of the presence of subjective experiences in otherwise unresponsive vegetative patients (Monti et al., 2010; Owen et al., 2006) to anesthetic-induced loss of responsiveness in healthy participants, which has important implications for consciousness research.

Consciousness is often seen as a dependent variable that can be manipulated by sedative/anesthetic agents affecting distinct brain functions at different levels of drug concentration. For instance, Antognini and Carstens (2002) describe a model where explicit memory is suppressed in response to a relatively low anesthetic dosage (see also Alkire et al., 2008), a slightly increased anesthetic

concentration induces unconsciousness, whereas much higher concentration levels are required for immobility. If so, paradigms combining slow increase of sedative/anesthetic dosage with simultaneous monitoring of brain functioning should enable a contrast between the neural activity immediately before and after the loss of consciousness. Such studies could eventually identify which neural mechanisms underlie consciousness and its loss. In fact, it has been even proposed that research of the neural mechanisms of unconsciousness under anesthetic effects may eventually reveal which neurobiological processes generate waking consciousness (Flohr, Glade, & Motzko, 2000; Hameroff, 2006; Mashour, 2006). Yet, our findings demonstrate a large inconsistency between anesthesiologic definition of consciousness as the presence of instantaneous responsiveness, and consciousness as the presence of subjective experience, which is a widely accepted definition in psychology and cognitive neuroscience (see also Alkire, Hudetz, & Tononi, 2008). In most of the previous anesthesiology studies that have explored neural mechanisms of unconsciousness, the "unconscious end point" was defined as the moment at which a sufficient concentration of an anesthetic has been administered to suppress a motor reaction to a rousing shake or to a verbal command (e.g., Alkire & Miller, 2006; Lee, Mashour, Seunghwan, Noh, & Choi, 2009). In the present study, estimation of the loss of consciousness as responsiveness was similarly limited to the assessment of the effects of verbal commands to participants' motor responses. Consequently, it remains possible that identified patterns of neural activity are related to the loss of responsiveness rather than the suppression of phenomenal consciousness itself.

Our conclusion that phenomenal consciousness is compatible with clinically defined unresponsiveness could be questioned by arguing that subjective experiences are not generated during the actual loss of responsiveness. For instance, Leslie et al. (2007) reported that anesthesia dreaming is unrelated to depth of anesthesia and probably occurs during the recovery phase. Similarly, Samuelsson, Brudin, and Sandin (2008) showed that the occurrence of dreaming is not associated with BIS values during the surgery. Yet, deeper surgical levels of anesthesia were maintained in these studies, and several agents were typically used in combination for anesthesia. Our study shows that the frequency of reported subjective experiences may be associated with the "depth of sedation" as measured by the BIS values, at least during dexmedetomidine administration. Among participants who reported subjective experiences in one but not in another dexmedetomidine session, the reported sensations and dreams were associated with sessions where BIS values were higher during the actual loss of responsiveness. Contrary, there were no differences in the "depth" of dexmedetomidine sedation regarding the presence or absence of subjective experiences during the induction or recovery phases. This suggests that reported subjective experiences could have been generated during the actual loss of responsiveness rather than before it or after its return. Nevertheless, dexmedetomidine findings came from a small subsample of participants and require further replication. In addition, findings concerning the depth of dexmedetomidine sedation cannot be generalized to all anesthetic drugs. It is obvious that different sedative/anesthetic agents affect different neuronal pathways in their action to produce unresponsiveness (Franks, 2008; Hudetz, 2006). In particular, dexmedetomidine is a sedative unlike the other anesthetic drugs that were used in the present study: molecularly, it acts as an agonist of alpha-2 adrenergic receptors, and behaviorally, it induces a state of deep sedation that can be terminated with intense stimulation, which resembles physiological non-rapid eye movement (NREM) sleep. Specifically, dexmedetomidine activates endogenous NREM sleep-promoting pathways as reflected by increased c-Fos expression in the ventrolateral preoptic nucleus, and decreased expression in the locus coeruleus and tuberomammillary nucleus

(Nelson et al., 2003). At the EEG level of description, dexmedetomidine induces spindle activity that is almost indistinguishable from spindle activity recorded during NREM sleep (Huupponen et al., 2008). Interestingly, dreams reported after awakening from the early night NREM sleep are very brief and static (Noreika, Valli, Lahtela, & Revonsuo, 2009), closely resembling subjective experiences observed after dexmedetomidine sedation in the present study.

Specificity of distinct drugs was also confirmed in the present study by the analyses of the BIS values and the content of subjective reports. Loss of responsiveness was induced at higher BIS values during sevoflurane sessions when compared to propofol and dexmedetomidine sessions (for more details about the relationship between the BIS values and responsiveness, see a separate report by Kaskinoro et al. (2011)). The occurrence of subjective experiences was higher among participants attending dexmedetomidine sessions than propofol sessions. We did not, however, replicate findings of Kasuya et al. (2009) who showed that BIS values are significantly lower during dexmedetomidine than propofol-induced unresponsiveness as measured by scores 2, 3 and 4 of the Observer's Assessment of Alertness/Sedation Scale (Chernik et al., 1990). Nevertheless, the same direction of drug effect on BIS values during unresponsiveness phase was observed in the present study (propofol: $M = 60.5$, dexmedetomidine: $M = 55.1$). One important methodological difference between the two studies is that much deeper levels of unresponsiveness were probed by Kasuya et al. (2009). Regarding laboratory-related experiences, they were more frequently reported in the sevoflurane sessions than in the dexmedetomidine sessions. Moreover, propofol sessions containing subjective experiences tended to have lower BIS values during the loss of responsiveness than propofol sessions without such experiences, which contradicted findings of the dexmedetomidine sessions. Individual drug differences suggest that in studies exploring cognitive and neural mechanisms of phenomenal consciousness and responsiveness, different sedative/anesthetic agents should be administered and analyzed individually.

In the present study, subjective experiences were reported in 58.6% of sessions, which is in line with the 53% reported in a study on the incidence of intraoperative dreaming (Errando et al., 2008). Yet, most of the clinical studies report a considerably lower incidence of anesthesia dreaming, such as 6% (Leslie et al., 2005) or 22% (Brandner et al., 1997) of all anesthesia sessions. Even though there was a delay of several minutes between ROR and the first interview in the present study, which might have reduced recall of anesthesia dreaming (Leslie, 2010), several other factors might relate to the relatively high incidence of subjective experiences: the sessions did not reach surgical depth of anesthesia, a single sedative/anesthetic agent was always used, and the participants, young healthy students, were informed in advance about the post-anesthesia interviews. Such purely experimental setup differs from clinical studies probably involving more anxious and less prepared surgical patients, deeper anesthesia levels and the frequent use of a combination of memory-affecting drugs in clinical studies. As the lack of any recollection of subjective experiences is a necessary but not sufficient condition for showing that phenomenal consciousness is absent (Revonsuo, 2006), it is conceptually possible that sedated or anesthetized patients always dream but usually cannot recall it. Thus, further studies are needed to explore and control memory processes during the formation and reporting of subjective experiences under the effect of sedative and anesthetic agents.

There are several limitations in the present study that should be considered in future research. In most of the sessions the LOR was induced stepwise, and due to EEG recordings there was some delay between the ROR and the interview. In some of the sessions there were several repetitions of the LOR and ROR. Ideally, subjective

experiences would be collected after a single, abruptly induced and short period of unresponsiveness, which would strengthen our suggestion that reported sensations were experienced during the actual loss of responsiveness rather than during its induction or brief recovery episodes. Finally, despite the identical guidelines given to the participants in advance, their reactions differed from each other when the interviews took place, and not all of them were well oriented and remembered that they will be interviewed immediately after recovering from unresponsiveness. On the other hand, as the interview guidelines were given in advance, this may have increased the demand characteristics of the interview, and some participants may have been willing to report the kind of experiences they assumed the interviewer wished to hear (Farthing, 1992). Despite of these shortcomings, the SEDA-Coding proved to be a suitable and reliable method for identifying and classifying the frequency and quality of subjective experiences during drug-induced unresponsiveness. Still, surgical anesthesia is generally deeper than that induced in the present study, and our results are limited to relatively low dosage of anesthetic drugs. We expect that the use of the SEDA-Coding in a clinical rather than an experimental setting would probably result in lower frequencies of subjective experiences than in the present study. Recently, Mashour et al. (2010) introduced a new classification instrument for intraoperative awareness events with six categories ranging from "Class 0: no awareness" to "Class 5: paralysis and pain". Compared to the SEDA-Coding, which was developed in order to classify all types of experiences occurring during sedation and anesthesia, the new instrument developed by Mashour et al. (2010) is focused on awareness related experiences and it leaves out some other types of experiences, e.g., visual sensations or changed experience of time, which are more common for anesthesia dreaming. Given that these instruments target somewhat different aspects of subjective experiences occurring during anesthesia and they both show comparable inter-rater reliability between judges, it would be preferable to use both instruments in the experimental studies aiming to investigate phenomenal consciousness during sedation and anesthesia.

To conclude, the questions of how frequently and when subjective experiences occur under drug-induced LOR should not be answered primarily with observation based methods. On the contrary, to investigate the neural mechanisms of phenomenal consciousness, its concept should be operationalized in such a way that the possibility of internally generated and stimulus-independent experiences is recognized. For this, a postoperative interview should be conducted shortly after a participant emerges from anesthetic-induced unresponsiveness. Arguably, if one aims to explore the neural correlates of phenomenal consciousness, it would be fruitful to contrast the neural activity during anesthesia dreaming vs. the neural activity during dreamless anesthesia, rather than comparing brain processes before and after the LOR. The first successful attempt towards such contrast was recently reported by Leslie et al. (2009), who compared the spontaneous EEG, recorded during propofol and desflurane anesthesia, of dreamers ($N = 34$) and non-dreamers ($N = 116$). Several minutes before the awakening the dreamers showed less pronounced spindle activity (10.7 Hz) and higher power of faster frequencies (30 Hz). Both of these patterns resembled EEG signal of rapid eye movement (REM) sleep (Leslie et al., 2009), which is the most dreamful stage of natural sleep (Nielsen, 2000). Mashour (2010) suggested that the emergence from anesthesia might reflect the "covert REM sleep", which has been proposed by Nielsen (2000) and aims to unify theories regarding the neural mechanisms of REM and NREM sleep dreams. If that is true, we might be entering an exciting new endeavor towards integration of anesthesia, sleep and consciousness research.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bandc.2011.09.002.

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