



# IV

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# Increase in high frequency EEG activity explains the poor performance of EEG spectral entropy monitor during S-ketamine anesthesia

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## Abstract

**Objective:** To study the effects of S-ketamine on the EEG and to investigate whether spectral entropy of the EEG can be used to assess the depth of hypnosis during S-ketamine anesthesia.

**Methods:** The effects of sub-anesthetic (159 (21); mean (SD) ng/ml) and anesthetic (1959 (442) ng/ml) serum concentrations of S-ketamine on state entropy (SE), response entropy (RE) and classical EEG spectral power variables (recorded using the Entropy™ Module, GE Healthcare, Helsinki, Finland) were studied in 8 healthy males. These EEG data were compared with EEG recordings from 6 matching subjects anesthetized with propofol.

**Results:** The entropy values decreased from the baseline SE 85 (3) and RE 96 (3) to SE 55 (18) and RE 72 (17) during S-ketamine anesthesia but both inter- and intra-individual variation of entropy indices was wide and their specificity to indicate unconsciousness was poor. Propofol induced more pronounced increase in delta power ( $P < 0.02$ ) than S-ketamine, whereas anesthetic S-ketamine induced more high frequency EEG activity in the gamma band ( $P < 0.001$ ). Relative power of 20–70 Hz EEG activity was associated with high SE ( $P = 0.02$ ) and RE ( $P = 0.03$ ) values during S-ketamine anesthesia.

**Conclusions:** These differences in low and high frequency EEG power bands probably explain why entropy monitor, while adequate for propofol, is not suitable for assessing the depth of S-ketamine anesthesia.

**Significance:** The entropy monitor is not adequate for monitoring S-ketamine-induced hypnosis.

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**Keywords:** Monitoring; Depth of anesthesia; S-Ketamine; EEG; Spectral entropy

## 1. Introduction

Assessment of the depth of anesthesia has proven to be one of the major challenges in anesthesiology. New devices and mathematical algorithms based on processed electroencephalography (EEG) have been developed to quantify the changes in the EEG induced by anesthesia, and to

present the content of a complex signal as a simple numerical index. The purpose of these anesthetic state monitors is to measure the effect of the administered anesthetic drug on brain function and to decrease the incidence of awareness during anesthesia (Ekman et al., 2004; Myles et al., 2004), and to prevent delay in recovery after anesthesia by optimizing anesthetic dosing (Gan et al., 1997; Recart et al., 2003). The entropy monitor (GE Healthcare, Helsinki, Finland; later: entropy) has been introduced as an effective tool for measuring the hypnotic component of anesthesia. Entropy has been validated for

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monitoring the level of hypnosis during propofol, thio-pental, sevoflurane, desflurane and isoflurane anesthesia (Ellerkmann et al., 2004; Schmidt et al., 2004; Vanluchene et al., 2004; Vakkuri et al., 2004, 2005), and it has been shown that entropy monitoring reliably differentiates consciousness from unconsciousness.

Ketamine, a non-competitive NMDA-antagonist, produces so-called dissociative anesthesia, which comprises of analgesia, amnesia and catalepsy. Commonly used racemic ketamine is a mixture of two optical enantiomers, R (–) and S (+) ketamine, but recently also pure S (+) ketamine has been introduced for clinical use. The analgesic and anesthetic potency of S-ketamine is greater than that of racemic ketamine. Additionally, S-ketamine has other beneficial properties over R-ketamine or racemic ketamine such as more rapid emergence from anesthesia (Himmelseher and Pfenninger, 1998). Ketamine stimulates the cardiovascular system, preserves protective reflexes such as coughing, and has only little effect on breathing. Therefore, it has been considered particularly suitable for anesthetizing critically ill or seriously injured patients.

Quantitative analysis of EEG power spectrum allows precise measurement of EEG frequency content and, in general, anesthesia-induced transition from consciousness to unconsciousness is associated with decreases in the amount of high frequency alpha and beta activity and simultaneous increases in the slow-wave delta or theta activity (Gugino et al., 2001; Sleigh and Galletly, 1997). Propofol is a typical example of an anesthetic agent that suppresses cortical activity. At anesthetic doses, propofol increases the total power of the EEG and the amount of low-frequency delta activity, at the same time decreasing the amount of high-frequency activity (Fiset et al., 1999). In previous studies, racemic ketamine has been shown to induce an increase in EEG fast activity (20–50 Hz), which may be related to the CNS stimulating effects of the drug (Ferrer-Allado et al., 1973; Hering et al., 1994; Schultz et al., 1990; Schwartz et al., 1974). EEG changes after administration of the S-enantiomer of ketamine have been found to be partly similar to the effects caused by racemic ketamine: increase in theta amplitude and decrease in alpha amplitude (Engelhardt et al., 1994), but no high frequency activity has been reported during S-ketamine anesthesia.

It has been suggested that the commercially available depth of anesthesia monitor, the bispectral index (BIS, Aspect Medical Systems, Newton, MA) (Hirota et al., 1999; Vereecke et al., 2003; Wu et al., 2001), and recently also the entropy monitor (Hans et al., 2005) cannot reliably assess the hypnotic component of anesthesia when using racemic ketamine alone or in combination with some other anesthetic agents. However, no explanation for the poor performance of these monitoring devices during racemic ketamine administration has been reported. Moreover, to our knowledge, there are no previous data available on the use of EEG spectral entropy for monitoring the level of hypnosis during single agent S-ketamine anesthesia, and

also human EEG data during S-ketamine anesthesia are very scarce.

This study investigated the applicability of the entropy monitor (state entropy (SE) and response entropy (RE) indices) for measuring the level of hypnosis during single agent S-ketamine anesthesia. Since, the entropy monitor has been validated for assessing the level of hypnosis during propofol anesthesia (Schmidt et al., 2004; Vakkuri et al., 2004; Vanluchene et al., 2004), propofol-induced changes in the EEG were used as a reference. The EEG spectral power variables measured during S-ketamine and propofol anesthesia were compared to explore the reason for poor performance of the entropy monitor during S-ketamine anesthesia.

## 2. Methods

The present EEG data were collected in a positron emission tomography (PET) study assessing the effects of sub-anesthetic and anesthetic S-ketamine on cerebral blood flow and metabolism (Långsjö et al., 2005). The study protocol was approved by the Ethical Committee of the Hospital District of Southwest Finland (Turku, Finland). After giving written informed consent, 8 healthy (American Society of Anesthesiologists [ASA] physical status I) male volunteers aged 20–27 years were enrolled. All had normal brain MRI scans and confirmed having no history of drug allergies or ongoing medications. Subjects restrained from using alcohol or any medication for 48 h, and fasted from the midnight prior to the beginning of the study.

The details of the general study design and anesthesia have been previously described (Långsjö et al., 2005). Briefly, an intra-arterial catheter was inserted into radial artery and two intravenous catheters were inserted to forearm veins for monitoring, blood sampling and drug and fluid administration. The subjects received no premedication. S-ketamine was administered as a continuous target controlled intravenous infusion using a Harvard 22 syringe pump (Harvard Apparatus, South Natick, MA) connected to a portable computer running the Stanpump software (Shafer et al., 1988; available at <http://anesthesia.stanford.edu/pkpd>). At sub-anesthetic S-ketamine level, the measured mean serum concentration level was 159 (21) ng/ml (target 150 ng/ml) [mean (SD): hereinafter presented similarly] and at anesthetic level 1959 (442) ng/ml (target 1500–2000 ng/ml) (Långsjö et al., 2005).

Loss of consciousness (LOC) was clinically determined as no response to a verbal request to squeeze hand twice and loss of eyelid reflex. After LOC, rocuronium 0.6–1 mg/kg (Esmeron 10 mg/ml, Organon Ab, Helsinki, Finland) was administered for neuromuscular blockade and an endotracheal tube was inserted for mechanical ventilation. The ventilation was set to air–oxygen mixture (FiO<sub>2</sub> 0.30) and respiratory volume was adjusted to keep the end-tidal carbon dioxide level at the individual baseline (end-tidal

carbon dioxide measured at awake state, approximately 5%). Neuromuscular blockade was monitored with the NMT module of the Datex-Ohmeda S/5 Anesthesia Monitor (GE Healthcare, Helsinki, Finland) and maintained with subsequent 5–30 mg incremental boluses of rocuronium when the first one or two twitches in a train-of-four response were observed.

### 2.1. Entropy and EEG during S-ketamine administration

Entropy is based on time-frequency balanced spectral entropy (Viertiö-Oja et al., 2004). State entropy (SE) is computed over the frequency range from 0.8 to 32 Hz and it includes most of the EEG power reflecting primarily the activity level of the cortical neurons (Vakkuri et al., 2004). Response entropy (RE) is derived over the frequency range 0.8–47 Hz and it includes more electromyography (EMG) activity recorded at the forehead than SE and therefore, reacts fast to patient regaining muscle tone, an indicator of lightening anesthesia (Viertiö-Oja et al., 2004).

The EEG electrode strip (Entropy Sensor, GE Healthcare, Helsinki, Finland) for entropy measurement and EEG recording was positioned on the forehead, after cleaning the skin of the forehead with 70% isopropanol, as recommended by the manufacturer. The entropy measurement was started at awake level immediately after the subject was connected to monitors and continued until the end of anesthesia. Digital EEG with 400 Hz sampling rate (passband 0.5–118 Hz), SE and RE were continuously recorded throughout anesthesia using a portable computer with the S/5 Collect software (GE Datex-Ohmeda S/5 Collect Version 4.0, GE Healthcare, Helsinki, Finland) interfaced to the anesthesia monitor.

Entropy values and the EEG spectral power were analyzed at 3 stages in the S-ketamine group:

- *Awake* approximately 30 min, started 15 min after the beginning of the recording and lasted until the start of S-ketamine infusion at sub-anesthetic dose.
- *Sub-anesthetic level* started after 15 min stabilization time from the beginning of S-ketamine infusion at sub-anesthetic dose and lasted for approximately 30 min until the start of rising S-ketamine dose to the anesthetic level.
- *Anesthetic level* started approximately 1–1.5 h after S-ketamine infusion had been increased to anesthetic level and lasted for 60 min.

EEG data were processed with Matlab 6.5 (The Mathworks, Inc., Natick, MA). The raw EEG signal was inspected visually in 5 s epochs and artifact-contaminated EEG epochs were manually excluded. Due to large amount of eye movements and muscle artifacts, when awake and at sub-anesthetic level, the number of artifact-free epochs was lower awake [13 (7)] and the sub-anesthetic [21 (31)], than during the anesthetic level [235 (185)] when the subjects were paralyzed. Absolute power spectra ( $\mu\text{V}^2/\text{Hz}$ ) of each

artifact-free 5 s epoch were obtained with the psd-function of Matlab utilizing fast Fourier transformation with Hanning-windowing. Power spectra from individual epochs were averaged to obtain final power spectra for each level of the S-ketamine group. Absolute band powers ( $\mu\text{V}^2$ ) were calculated from the power spectra in the following frequency bands: delta (1.0–3.2 Hz), theta (3.4–8.0 Hz), alpha (8.2–13.0 Hz), beta (13.2–30.0 Hz), gamma (30.2–70.0 Hz), wide high frequency (20.2–70.0 Hz), total (1.0–70.0 Hz) and additional narrow bands slow theta (3.4–5.0 Hz), fast theta (5.2–8.0 Hz), slow beta (13.2–20.0 Hz), fast beta (20.2–30.0 Hz) and EMG (105–145 Hz). Relative power (%) for each band (delta–gamma) was calculated by dividing power in each frequency band by total power. Power line interference was digitally filtered from the spectral analysis.

### 2.2. Statistical analyses

In the S-ketamine group SE, RE and EEG power spectrum variables were analyzed with repeated measures analysis of variance (RM ANOVA) having the drug concentration as a within-factor. The following frequency band powers were log-transformed before analyses to meet the assumption of normality: delta, alpha, beta, gamma, fast beta, beta% and fast beta%. Linear contrasts within the same model were used to analyze differences between the S-ketamine levels. Pearson's correlation coefficients between SE, RE and EEG power spectral variables were also calculated. Intra-individual and inter-individual coefficients of variation (CV%) for SE and RE during anesthetic S-ketamine were calculated using the formula:  $\text{SD}/\text{mean} \times 100\%$ . Mann–Whitney *U*-test was used to test for differences between S-ketamine and propofol anesthesia. A two-tailed *P*-value of less than 0.05 was considered statistically significant. Statistical analyses were conducted with SAS (version 8.2, SAS Institute Inc., Cary, NC). Data are presented as mean (SD) if not otherwise stated.

### 2.3. Performance analyses of the Entropy variables

Prediction probability ( $P_K$ ), sensitivity and specificity were calculated to evaluate the performance of entropy variables SE and RE for discriminating conscious and unconscious states during S-ketamine anesthesia. Data from 40 min time window starting 20 min before LOC of S-ketamine recordings were used in the performance analyses. Time window was same as in a previous study (Vakkuri et al., 2004). Prediction probability estimates the performance of the anesthetic depth indicator independently of the choice of the cut-off point (Smith et al., 1996). It gives the probability that the indicator values of two randomly selected data points predict correctly, which of the data points corresponds to a lighter (or deeper) level of hypnosis. A value of  $P_K=0.5$  means that the indicator predicts the observed anesthetic depth not better than a 50:50 chance,

and a value of  $P_K=1$  means that the indicator predicts the observed anesthetic depth always correctly. Custom spreadsheet macro,  $P_K$ MACRO, was used to estimate  $P_K$  and its standard error with the jackknife method (Smith et al., 1996). Sensitivity was defined as the proportion of entropy values measured during the conscious state indicating consciousness. Specificity was defined as the proportion of entropy values indicating unconsciousness during the unconscious state. Sensitivity and specificity were derived with two different cut-off points. First, entropy performance was tested with the same cut-off points, 80 for SE and 87 for RE, as in an earlier study (Vakkuri et al., 2004) with sevoflurane, propofol and thiopental. Second, cut-off points tuned to maximize the sum of sensitivity and specificity in Receiver Operating Characteristic -curve of the S-ketamine data were selected for choosing the optimal threshold value for entropy performance as previously described (Vanluchene et al., 2004). Positive predictive value (indicating consciousness above cut-off values) and negative predictive value (indicating unconsciousness below cut-off values) were calculated using the cut-off values that maximize the sum of sensitivity and specificity. Additionally, specificity was derived with the cut-off value resulting in 100% sensitivity that has been stated as an essential feature of an anesthetic depth monitor (Drummond, 2000). Sensitivity, specificity, and predictive values were calculated with Matlab 6.5.

#### 2.4. Comparisons between S-ketamine and propofol anesthesia

For drug comparisons at the deep anesthetic level, the propofol EEG data was obtained from our previous study assessing the effects of surgical levels of sevoflurane and propofol anesthesia on cerebral blood flow and EEG in healthy subjects (Kaisti et al., 2002). Eight healthy (ASA physical status I) male volunteers were anesthetized with propofol. Inclusion and exclusion criteria for the volunteers in propofol anesthesia group were identical to the criteria used in the S-ketamine study. The EEG data of two subjects in the propofol group were lost due to magnetic tape storage failure. Thus, the EEG comparison material is obtained from the remaining 6 subjects (age: 20–30 years). The details of the propofol anesthesia and study design have been previously described (Kaisti et al., 2002). Anesthesia was induced with intravenous target-controlled infusion of propofol (Diprivan 20 mg/mL; AstraZeneca Oy, Masala, Finland) with the plasma concentration set at 6  $\mu$ g/ml (measured 7.6 (1.9)  $\mu$ g/ml) and rocuronium was used for muscle relaxation.

Digital EEG equipment (EasyEEG System; Cadwell, Kennebec, WA), Ag–AgCl electrodes, and the International 10–20 Electrode Placement System were used as previously described (Kaisti et al., 2002). The EEG data for comparison was recorded from F3–C3 derivation, and the digital sampling frequency was 200 Hz and the passband

0.1–50 Hz. Off-line calculation of spectral entropy values comparable to RE and SE was performed as previously described (Maksimow et al., 2005). EEG spectral power variables were calculated with Matlab 6.5 from a 2 min epoch during steady-state propofol anesthesia (prior to appearance of burst suppression). For comparison between the S-ketamine and propofol anesthesia, power spectra were additionally calculated in S-ketamine and propofol groups within 1.0–48 Hz frequency. The other frequency bands were as mentioned above, the gamma frequency band was limited to 30.2–48 Hz range due to narrow passband of the EasyEEG equipment.

### 3. Results

#### 3.1. Entropy and EEG during S-ketamine administration

State entropy was 85.3 (3.4) at baseline, 86.1 (2.1) at sub-anesthetic level and decreased to 54.6 (18.0) at anesthetic level (overall  $P=0.007$ ,  $P=0.005$  anesthetic vs. awake,  $P=0.004$  anesthetic vs. sub-anesthetic level) and RE decreased, similarly, from 95.7 (2.7) and 96.9 (2.0) to 72.0 (16.7) (overall  $P=0.015$ ,  $P=0.016$  anesthetic vs. awake,  $P=0.01$  anesthetic vs. sub-anesthetic level). The inter-individual and intra-individual variation was high at the anesthetic level. Within the anesthetic level mean CV% was 32.74 for SE and 26.61 for RE and individual ranges varied between 2.15–34.40 for SE and 3.69–27.85 for RE. One subject presented SE values from 14 up to 87 and another subject had constantly high SE ranging from 81 to 89 at the anesthetic level of S-ketamine. RE varied in these same subjects during S-ketamine anesthesia from 27 to 98 and from 88 to 100, respectively.

No significant changes were detected in the EEG power spectra between the baseline and the sub-anesthetic level (Table 1). When comparing the anesthetic S-ketamine level to the awake state, there were clear increases in the powers of theta ( $P=0.014$ ), slow theta ( $P=0.036$ ) and fast theta ( $P=0.017$ ) frequency bands. Comparing anesthetic and sub-anesthetic levels, increases in the powers of theta ( $P=0.020$ ), fast theta ( $P=0.020$ ), alpha ( $P=0.015$ ), and slow beta ( $P=0.030$ ) bands were found. Total power tended to increase during anesthetic S-ketamine but did not reach statistical significance ( $P=0.070$ ). Furthermore, visual analysis of the EEG signal revealed abundant fast gamma spindles during S-ketamine anesthesia in all subjects (Fig. 1). There were no gamma spindles during propofol anesthesia.

Within level analysis at the anesthetic S-ketamine level revealed negative association among RE and delta power ( $r=-0.76$ ,  $P=0.03$ ) and RE and delta% ( $r=-0.81$ ,  $P=0.015$ ), whereas high SE was associated with high fast beta% ( $r=0.76$ ,  $P=0.03$ ). In addition, the combined relative band powers within 20–70 Hz frequency range were analyzed at anesthetic S-ketamine level. Within this

Table 1  
Summary of absolute and relative EEG band powers and EMG at different levels of S-ketamine anesthesia

Processed EEG variable	No drug Mean $\pm$ SD	Sub-anesthetic S-ketamine Mean $\pm$ SD	Anesthetic S-ketamine Mean $\pm$ SD	Overall ANOVA <i>P</i>
Total power ( $\mu\text{V}^2$ )	18.25 $\pm$ 7.36	19.74 $\pm$ 7.96	52.75 $\pm$ 29.78	0.070
Delta ( $\mu\text{V}^2$ )	5.99 $\pm$ 2.02	5.71 $\pm$ 2.70	16.44 $\pm$ 23.56	0.309
Theta ( $\mu\text{V}^2$ )	3.36 $\pm$ 0.97	4.70 $\pm$ 2.21	16.31 $\pm$ 8.88*,**	0.019
Alpha ( $\mu\text{V}^2$ )	3.71 $\pm$ 2.84	2.06 $\pm$ 1.09	5.26 $\pm$ 3.81**	0.001
Beta ( $\mu\text{V}^2$ )	2.53 $\pm$ 0.94	2.68 $\pm$ 1.31	5.78 $\pm$ 5.99	0.356
Gamma ( $\mu\text{V}^2$ )	2.65 $\pm$ 1.28	4.59 $\pm$ 3.68	8.92 $\pm$ 9.53	0.199
Slow theta ( $\mu\text{V}^2$ )	1.35 $\pm$ 0.37	1.74 $\pm$ 0.56	3.51 $\pm$ 1.76*	0.047
Fast theta ( $\mu\text{V}^2$ )	2.01 $\pm$ 0.63	2.96 $\pm$ 1.67	12.80 $\pm$ 7.83*,**	0.023
Slow beta ( $\mu\text{V}^2$ )	1.13 $\pm$ 0.40	1.01 $\pm$ 0.34	2.19 $\pm$ 0.79**	<0.001
Fast beta ( $\mu\text{V}^2$ )	1.41 $\pm$ 0.58	1.67 $\pm$ 1.10	3.60 $\pm$ 5.55	0.838
Delta%	33.75 $\pm$ 4.84	30.21 $\pm$ 12.27	24.10 $\pm$ 18.74	0.197
Theta%	19.58 $\pm$ 5.29	23.81 $\pm$ 5.45	35.11 $\pm$ 15.93	0.133
Alpha%	17.82 $\pm$ 7.75	10.75 $\pm$ 4.99	11.46 $\pm$ 6.20	0.162
Beta%	14.32 $\pm$ 2.68	13.80 $\pm$ 4.36	12.83 $\pm$ 14.16	0.304
Gamma%	14.53 $\pm$ 3.24	21.45 $\pm$ 9.26	16.51 $\pm$ 12.11	0.098
Slow theta%	8.08 $\pm$ 2.59	9.13 $\pm$ 1.70	7.06 $\pm$ 2.21	0.140
Fast theta%	11.51 $\pm$ 3.17	14.68 $\pm$ 4.35	28.05 $\pm$ 14.95	0.060
Slow beta%	6.33 $\pm$ 0.63	5.24 $\pm$ 0.59	5.07 $\pm$ 2.73	0.046
Fast beta%	8.00 $\pm$ 2.39	8.56 $\pm$ 4.59	7.76 $\pm$ 12.95	0.218
EMG ( $\mu\text{V}^2$ )	0.96 $\pm$ 0.58	1.46 $\pm$ 1.54	0.04 $\pm$ 0.01*	0.012

Statistically significant differences between anesthetic S-ketamine and baseline (\* $P$  < 0.05) and between anesthetic and sub-anesthetic S-ketamine (\*\* $P$  < 0.05) marked. Values are given as group mean  $\pm$  SD.

frequency range, high relative power was associated with high values of both the SE ( $r=0.80$ ,  $P=0.016$ ) and the RE ( $r=0.77$ ,  $P=0.027$ ) (Fig. 2).

### 3.2. Performance analyses of the entropy variables

Mean (standard error) values for prediction probability ( $P_K$ ) were 0.931 (0.006) for SE and 0.891 (0.008) for RE. The mean (SD) sensitivity values 95.2% (5.7%) for SE and 99.3% (0.8%) for RE and specificity values 78.4% (26.1%) for SE and 65.1% (30.6%) for RE were obtained with the cut-off values 80 (SE) and 87 (RE). The sum of sensitivity and specificity was maximized with the cut-off value of 80 for SE and of 92 for RE. Corresponding sensitivity and specificity for RE were 97.0% (3.2%) and 73.1% (23.9%). Positive predictive value for SE was 82.9% (16.2%) and for RE 78.7 (15.2%) and negative predictive values were 94.9% (4.6%) for SE and 96.4% (3.0%) for RE. Hundred percentage sensitivity was obtained with a cut-off value of 56 for SE and 77 for RE. With these cut-offs, specificity was 58.0% (31.9%) for SE and 56.0% (31.5%) for RE.

### 3.3. Comparisons between S-ketamine and propofol anesthesia

The power spectrum of EEG differed during propofol anesthesia from that induced by anesthetic dose of S-ketamine. In the propofol group, SE was 39.4 (10.3) and RE 42.9 (4.1) during steady-state propofol anesthesia and mean CV% was 9.05 for SE and 10.37 for RE. The most significant finding in S-ketamine power profile was

the increase in high frequency (gamma) EEG activity within the frequency range of 30.2–48 Hz that was totally absent in the propofol EEG power spectrum ( $P=0.005$ , Table 2, Fig. 2). Also relative power within the 30.2–48 Hz frequency band was much lower in the propofol reference group (0.8%) compared to S-ketamine anesthesia (13.6%,  $P=0.0007$ ) while propofol anesthesia was associated with significantly more activity in the delta band ( $P=0.019$ ). Analysis of the EEG power spectrum revealed differences in absolute delta, alpha and gamma powers and in relative delta, theta and gamma powers between S-ketamine and propofol (Table 2). There were some significant changes also in additional narrow band powers between these groups.

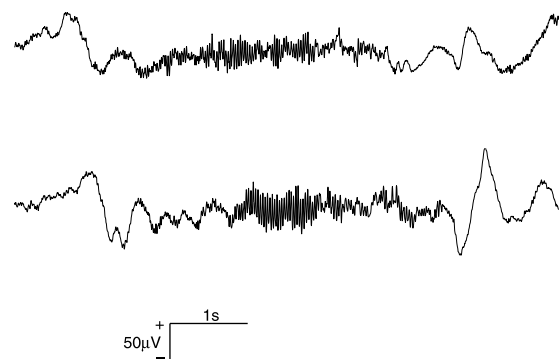


Fig. 1. Examples of typical EEG gamma spindles, which were abundantly seen during S-ketamine anesthesia in all subjects.

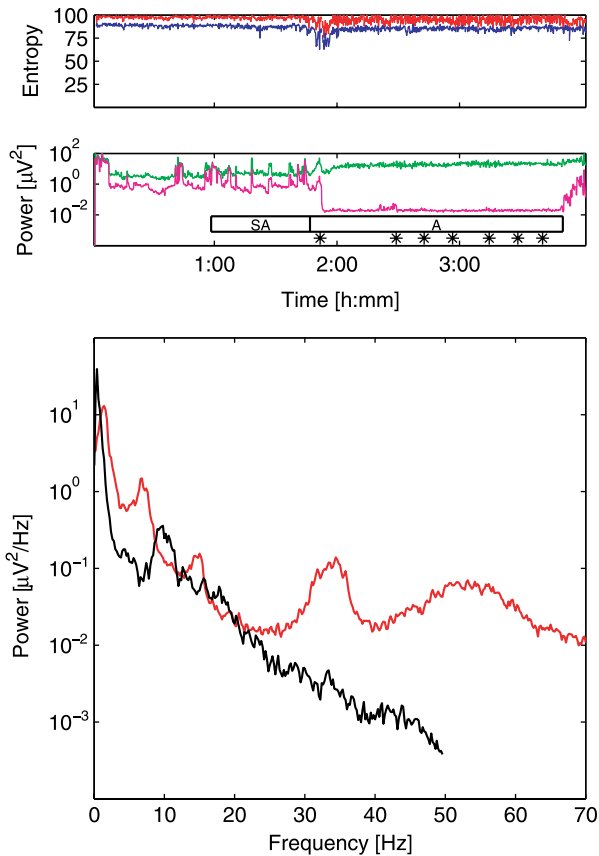


Fig. 2. TOP: An example of response entropy (RE) and state entropy (SE) from the whole recording period of one subject in S-ketamine group. RE (red) is above SE (blue). X-axis presents time in hours. MIDDLE: The EEG band powers from the frequency bands 20–70 Hz (green) and 105–145 Hz (purple) from the same period. When neuromuscular blockade was administered (\*), band power 105–145 Hz dropped remarkably, while band power 20–70 Hz remained high, indicating the presence of EEG gamma activity. Sub-anesthetic S-ketamine, SA; anesthetic ketamine, A. BOTTOM: EEG power spectra from the S-ketamine (red) and propofol (black) anesthesia. Presented spectra are averaged over individual 5 s epoch spectra. Number of individual spectra is 104 in S-ketamine and 24 in propofol anesthesia. Note the high relative power above 20 Hz during S-ketamine anesthesia.

## 4. Discussion

### 4.1. Entropy and EEG during S-ketamine administration

According to the present results, entropy anesthesia monitor is not valid for measuring the level of hypnosis during S-ketamine single-agent anesthesia. Furthermore, entropy did not reliably discriminate between consciousness and unconsciousness when S-ketamine was used. Based on the clinical data reported by the manufacturer of the entropy index monitor, the entropy variables SE and RE should be within the range of 40–60 at appropriate depth of surgical anesthesia. In the present study, the mean SE decreased to 55 during clinically adequate (Långsjö et al., 2005) S-ketamine anesthesia. However, due to high intra- and

inter-individual variability at deep, steady state anesthesia, we must conclude that the Entropy does not give a reliable estimate of anesthetic depth when S-ketamine is used.

Previous studies have implicated that the main EEG characteristics of racemic ketamine are low-amplitude fast-activity (Albanese et al., 1997), a pronounced increase in relative theta power, and a decrease in relative alpha power (Kochs et al., 1996; Plourde et al., 1997; Sloan, 1998). S-ketamine-induced changes presented in this study are in this respect consistent with previous reports on racemic ketamine alone (or in combination anesthesia) (Sakai et al., 1999; Wu et al., 2001), indicating that the effects of the racemic mixture and the S-enantiomer of ketamine on these processed EEG variables are similar. However, perhaps the most interesting finding was the increase in absolute gamma power and the presence of abundant gamma spindles in EEG signal in all subjects during S-ketamine anesthesia. High frequency gamma activity is an unusual feature in EEG during general anesthesia. It has been reported previously with racemic ketamine (Albanese et al., 1997), but not with S-ketamine (Engelhardt et al., 1994).

Increase in activity within 20–48 Hz frequency range with no significant increase in delta power was characteristic of S-ketamine anesthesia and totally different from propofol anesthesia, during which entropy performs well. Significant increase in the amount of EEG activity in wide high frequency range (20–70 Hz) was associated with high SE and RE values. These effects of S-ketamine on the EEG power spectrum may explain why the entropy monitor fails to assess the true hypnotic depth with this anesthetic drug. Entropy monitor probably interprets this increase in high frequency EEG activity as an increase in EMG activity and, thus, lighter anesthesia.

### 4.2. Performance analyses of the entropy variables

Prediction probability is calculated to test the accuracy of the chosen indicator to distinguish between the different states of anesthesia. It has been established as the method of choice for studying the performance of the depth of anesthesia monitoring devices. However, as the  $P_K$  is calculated without any cut-off value, it merely indicates whether the two data sets, e.g. indicator values during consciousness or unconsciousness are overlapping or not. Our study design contributes to the high values in sensitivity and  $P_K$ . The transition from consciousness to unconsciousness was easily detected, and the SE and RE values were slightly lower after LOC than during consciousness. Although  $P_K$  values were satisfactory, they were considerably lower than in an earlier study (Vakkuri et al., 2004). Sensitivity values were good for both SE and RE indicating that Entropy gives appropriate values during sub-anesthetic level of S-ketamine anesthesia when the subjects are conscious. However, specificities were poor regardless of the cut-off point suggesting that entropy falsely gives high values during S-ketamine anesthesia adequate for surgery.

Table 2

Summary of absolute and relative EEG band powers within frequency range from 1 to 48 Hz and comparisons between S-ketamine and propofol anesthesia

Processed EEG variable	Anesthetic S-ketamine Mean $\pm$ SD	Anesthetic propofol Mean $\pm$ SD	Mann–Whitney <i>U</i> -test <i>P</i>
Total power ( $\mu\text{V}^2$ )	51.02 $\pm$ 28.94	96.74 $\pm$ 76.34	0.345
Delta ( $\mu\text{V}^2$ )	16.44 $\pm$ 23.56	61.50 $\pm$ 54.56	0.019*
Theta ( $\mu\text{V}^2$ )	16.31 $\pm$ 8.88	9.35 $\pm$ 5.77	0.108
Alpha ( $\mu\text{V}^2$ )	5.26 $\pm$ 3.81	16.37 $\pm$ 11.86	0.013*
Beta ( $\mu\text{V}^2$ )	5.78 $\pm$ 5.99	8.92 $\pm$ 6.67	0.573
Gamma ( $\mu\text{V}^2$ )	7.23 $\pm$ 9.05	0.61 $\pm$ 0.33	0.005**
Slow theta ( $\mu\text{V}^2$ )	3.51 $\pm$ 1.76	3.66 $\pm$ 2.13	1.0
Fast theta ( $\mu\text{V}^2$ )	12.8 $\pm$ 7.83	5.69 $\pm$ 3.74	0.029*
Slow beta ( $\mu\text{V}^2$ )	2.19 $\pm$ 0.79	6.61 $\pm$ 5.07	0.181
Fast beta ( $\mu\text{V}^2$ )	3.60 $\pm$ 5.55	2.30 $\pm$ 1.63	0.852
Delta%	24.95 $\pm$ 19.41	59.55 $\pm$ 9.67	0.020*
Theta%	36.31 $\pm$ 16.26	11.91 $\pm$ 5.00	0.005**
Alpha%	11.88 $\pm$ 6.40	18.14 $\pm$ 4.97	0.108
Beta%	13.23 $\pm$ 14.38	9.61 $\pm$ 1.64	1.0
Gamma%	13.63 $\pm$ 11.88	0.79 $\pm$ 0.33	<0.001**
Slow theta%	7.30 $\pm$ 2.23	4.80 $\pm$ 1.93	0.029*
Fast theta%	29.02 $\pm$ 15.28	7.11 $\pm$ 3.24	0.001**
Slow beta%	5.26 $\pm$ 2.84	7.02 $\pm$ 1.03	0.491
Fast beta%	7.97 $\pm$ 13.17	2.59 $\pm$ 0.83	0.492

Differences between anesthetic S-ketamine and propofol (\* $P < 0.05$ , \*\* $P < 0.01$ ). Values are given as group mean  $\pm$  SD.

Furthermore, at the level of 100% sensitivity, SE and RE showed very poor specificity values. The cut-off point maximizing the sum of sensitivity and specificity of SE was the same as used in the earlier study (Vakkuri et al., 2004) with sevoflurane, propofol and thiopental. However, cut-off point for RE was higher (92) for S-ketamine than in the earlier study (Vakkuri et al., 2004), suggesting that EEG power spectrum in S-ketamine anesthesia differs in the high frequency range. This was also evident in the power spectral analysis. Towards the end of S-ketamine anesthesia the amount of high frequency EEG-activity increased and higher entropy values were detected.

#### 4.3. Comparisons between S-ketamine and propofol anesthesia

It has been shown that many of the commonly used anesthetic agents, such as propofol, induce a global increase in absolute power across the low frequency range of 1.5–25 Hz at loss of consciousness, then slow-wave delta and theta activity during maintenance and a decrease in gamma range during maintenance (Fiset et al., 1999; Gugino et al., 2001; John et al., 2001). In contrast to propofol, EEG power spectrum during S-ketamine anesthesia included remarkably more power in high frequency beta and gamma range, and also the relative power of gamma band increased simultaneously with only a slight, non-significant increase in slow wave delta activity. Spectral entropy describes the number of dominant EEG frequencies and their relation to other frequencies in the particular frequency range. As Fig. 2 shows, S-ketamine produces more peaks to the power spectrum than propofol, and with propofol peaks are more

prominent when compared to other frequencies of the spectrum. Therefore it is obvious, that higher spectral entropy values are obtained during S-ketamine anesthesia.

In order to provide comparable reference material for investigating the poor performance of the entropy monitor during S-ketamine anesthesia, we utilized EEG recordings of a similar group of young, healthy volunteers anesthetized with propofol as a reference. One flaw concerning this control material was that the EEG was recorded using another EEG equipment, which limited the EEG frequency range up to 50 Hz in the group comparisons. To exclude the potential effects of 50 Hz artifacts, we restricted the power spectrum analysis to frequencies up to 48 Hz. However, as the RE is derived over the frequency range 0.8–47 and the upper limit of SE analysis is no more than 32 Hz, the comparisons between S-ketamine and propofol anesthesia within the chosen frequency range can be considered adequate. Another design issue was that in the S-ketamine group the EEG recording was done using only one frontopolar-anterior temporal derivation. In addition, the propofol control material was recorded from F3 to C3 derivation, which differs slightly from the derivation used in the S-ketamine group. However, commercial anesthetic depth monitors, like entropy and BIS, use only this frontal derivation, and we wanted to compare the classical quantitative EEG variables from the same derivation with entropy indices in the S-ketamine group.

In this study, we demonstrate that the entropy monitor fails to give a reliable estimate of the level of hypnosis during single agent S-ketamine anesthesia. Anesthetic concentration of S-ketamine increased the amount of high



frequency EEG activity above 20 Hz while inducing much less low frequency activity than propofol, and we conclude that these are the reasons why this monitor of anesthetic depth cannot be used to guide S-ketamine dosing.

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