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Spectral entropy measurement of patient responsiveness during propofol and remifentanil. A comparison with the bispectral index†

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Background. We compared two spectral entropies, state entropy (SE) and response entropy (RE), based on the irregularity of the EEG, to measure loss of response to verbal command (LOR_{verbal}) and noxious stimulus ($LOR_{noxious}$) with the bispectral index (BIS) during propofol infusion with and without remifentanil.

Methods. Three groups of 20 patients received an effect-site controlled propofol infusion (Ce_{PROP}) starting at 1 $\mu g\ ml^{-1}$ and increased in steps of 0.5 $\mu g\ ml^{-1}$ at 4 min intervals. In addition, a remifentanil infusion was maintained at a group-dependent, fixed effect-site target concentration (Ce_{REMI}) (0, 2 or 4 $ng\ ml^{-1}$). The ability of BIS, SE or RE to predict LOR_{verbal} and $LOR_{noxious}$ were compared with the changes in BIS, SE and RE using logistic regression, prediction probability (P_K), and sensitivity/specificity.

Results. In all groups, BIS, SE and RE decreased with increasing Ce_{PROP}. However, BIS decreased more smoothly than SE and RE at deeper levels of sedation. At LOR_{verbal}, BIS_{50}, SE_{50} and RE_{50} increased with increasing Ce_{REMI}. BIS, SE and RE all detected LOR_{verbal} accurately but BIS performed better at 100% sensitivity. Sensitivity/specificity for detection of LOR_{verbal} decreased for all methods with increasing Ce_{REMI}. $LOR_{noxious}$ was poorly described by all measures.

Conclusion. LOR_{verbal} was detected accurately by BIS, SE and RE except for 100% sensitivity, where BIS performed better. Though BIS, SE and RE were influenced by remifentanil during propofol administration, their ability to detect LOR_{verbal} remained accurate. None of the measures predicted $LOR_{noxious}$.

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The regularity of the background electroencephalograph (EEG) alters with changing levels of consciousness. Recently, different entropy concepts have been applied to describe the amount of order in the EEG.[1–3] One of these, Shannon entropy, has been shown to be a useful measure of anaesthetic drug effect.[3] Shannon entropy measures the predictability of future amplitude values of the EEG based on the probability distribution of amplitude values already observed in the signal. Unfortunately, Shannon entropy as described is not normalized to the total power of the EEG. Therefore, its absolute value may vary between individuals because of inter-individual differences in signal strength, precluding its use clinically. To overcome these shortcomings, 'spectral entropy' has been developed. This is obtained by applying the Shannon entropy concept to the power distribution of the Fourier-transformed signal that has been normalized to unit power. A particularly advantageous feature of spectral entropy is that one can explicitly separate contributions from different frequency ranges; for example, to separate the high-frequency (>32 Hz) from the low-frequency contribution (<32 Hz). This brings two advantages: the high frequencies can be treated with a smaller time window than the lower frequencies to speed up the response, and the separation also gives an indication of whether the contribution comes primarily from the EEG or the electromyograph (EMG). Recently, this technology has become available commercially (M-Entropy, Entropy™ Module; Datex-Ohmeda, Helsinki, Finland). In this device, two spectral entropy indicators are considered, one over the EEG dominant frequency (0.8–32 Hz) called 'state entropy' (SE) and another over the complete range of frequencies (0.8–47 Hz) called 'response entropy' (RE), including

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both EEG and EMG components. The sudden appearance of EMG signal data often indicates that the patient is responding to some external stimulus, such as pain, i.e. nociception, as a result of some surgical event.[4 5] Such a response may occur if the level of analgesia is insufficient and EMG might provide a rapid indication of impending arousal. As SE will be the same as RE when EMG power becomes zero, it is advantageous to normalize both SE and RE. Therefore, SE ranges from 0 to 91 and RE from 0 to 100, lower values indicating deeper levels of the hypnotic component of anaesthesia.

The bispectral index or BIS (Aspect Medical Systems, Newton, MA, USA) is another commercially available univariate parameter, derived from the EEG, to measure the hypnotic component of anaesthesia.[6] In previous work, we have shown that EEG-derived variables can be used to optimize drug delivery. A first step in answering this question was to examine the performance and accuracy of these monitors under various conditions and to compare them with the accuracy and usefulness of the on-line calculated drug effect-site concentration. A secondary question is how opiates affect these performance parameters.[6 7] For spectral entropy, these questions have still to be answered.

This study was conducted to assess the performance accuracy of entropy (SE and RE) in reflecting the hypnotic component of anaesthesia and to measure loss of responses to different stimuli, defined as loss of response to verbal command (LOR_{verbal}) and loss of response to a noxious stimulus ($LOR_{noxious}$) during stepwise increased levels of propofol infusion with and without remifentanil. The performance of SE and RE was compared with that of BIS.

Methods and materials

Clinical protocol

After Institutional Ethics Committee (Gent University Hospital, Gent, Belgium) approval, informed consent was obtained from 60 ASA I patients, aged 18–60 yr, scheduled for day-case gynaecological or urological surgery. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight, neurological disorder, and recent use of psychoactive medication, including alcohol. They were randomly allocated to one of three groups using block randomization (permuted block design, three blocks of 20 patients with a 1:1:1 ratio). In all groups, patients received a 'staircase' computer-controlled infusion of propofol, targeting the effect compartment, as shown in Figure 1. Initially, an effect-site concentration of 1.0 $\mu g\ ml^{-1}$ was targeted, increased every 4 min by 0.5 $\mu g\ ml^{-1}$ until loss of response to all relevant clinical measures of anaesthetic depth was observed. In the 'remi 0 ng ml^{-1}' group, no remifentanil was given. In the 'remi 2 ng ml^{-1}' and 'remi 4 ng ml^{-1}' groups, an effect compartment controlled infusion of remifentanil was started 4 min before the start of propofol.

Propofol and remifentanil were administered via a computer-assisted continuous infusion device to a target effect-site concentration (Rugloop) using a three-compartment model enlarged with an effect-site compartment. For propofol, the pharmacokinetic–dynamic model previously published by Schnider and colleagues[8 9] was used. For remifentanil, the pharmacokinetic-dynamic model previously published by Minto and colleagues[10 11] was used. Ce_{PROP} was computed to yield a time to peak effect[12] of 1.6 min after bolus injection, as also published by Schnider and colleagues[8] and confirmed clinically by Struys and colleagues.[13] For remifentanil, an age-dependent ke0 value of 0.595–0.007×(age–40) min^{-1} was applied.[10 11] Propofol and remifentanil infusions were administered using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brésin, France). Rugloop drives the pump at infusion rates between 0 and 1200 ml h^{-1} via an RS232 interface. Using this infusion technique, we were able to obtain a steady-state condition for both propofol and remifentanil at every target level after 4 min infusion. Steady-state is defined here as the equilibration between the calculated plasma and effect-site concentration of the drug. Remifentanil and propofol were infused via a large vein in the left forearm. Every patient received about 200 ml of crystalloid fluid during the study period. No fluid load was given before induction. No patient received pre-anaesthetic medication. No other drugs were given. All patients maintained spontaneous ventilation via face mask delivering oxygen 6 litres min^{-1}.

Heart rate and non-invasive blood pressure, Sp_{O_2} and capnography were recorded at 1-min intervals using an S/5 Anesthesia Monitor (Datex-Ohmeda). BIS (version 4.0) was derived from the frontal EEG (At-Fpzt) and calculated by the A-2000 BIS® monitor using a BIS-sensor® (Aspect Medical Systems). The smoothing time of the BIS monitor was set at 15 s. The SE (91–0) and RE (100–0) values were calculated using the Entropy Module from the S/5 Anesthesia Monitor (Datex-Ohmeda). Both entropy values were derived from the frontal EEG and EMG using three electrodes. SE is computed over the frequency range from 0.8 to 32 Hz. The time windows for SE are chosen optimally for each particular frequency component and range from 60 s to 15 s. RE is computed over a frequency range from 0.8 to 47 Hz. The time windows for RE are chosen optimally for each frequency, with the longest time window equal to 15.36 s and the shortest time window, applied for frequencies between 32 and 47 Hz, equal to 1.92 s. The description of the full algorithm is reported elsewhere.[14]

Ten seconds before each increase in propofol target concentration (after 4 min infusion at the specific target effect-site concentration), measures of BIS, SE, RE, level of consciousness (using the modified OAA/S score shown in Table 1) and the reaction to a noxious stimulus was recorded. The sequence of testing was always the same: first the electronic indicators, then the OAA/S score. The response to noxious stimulus was recorded last.

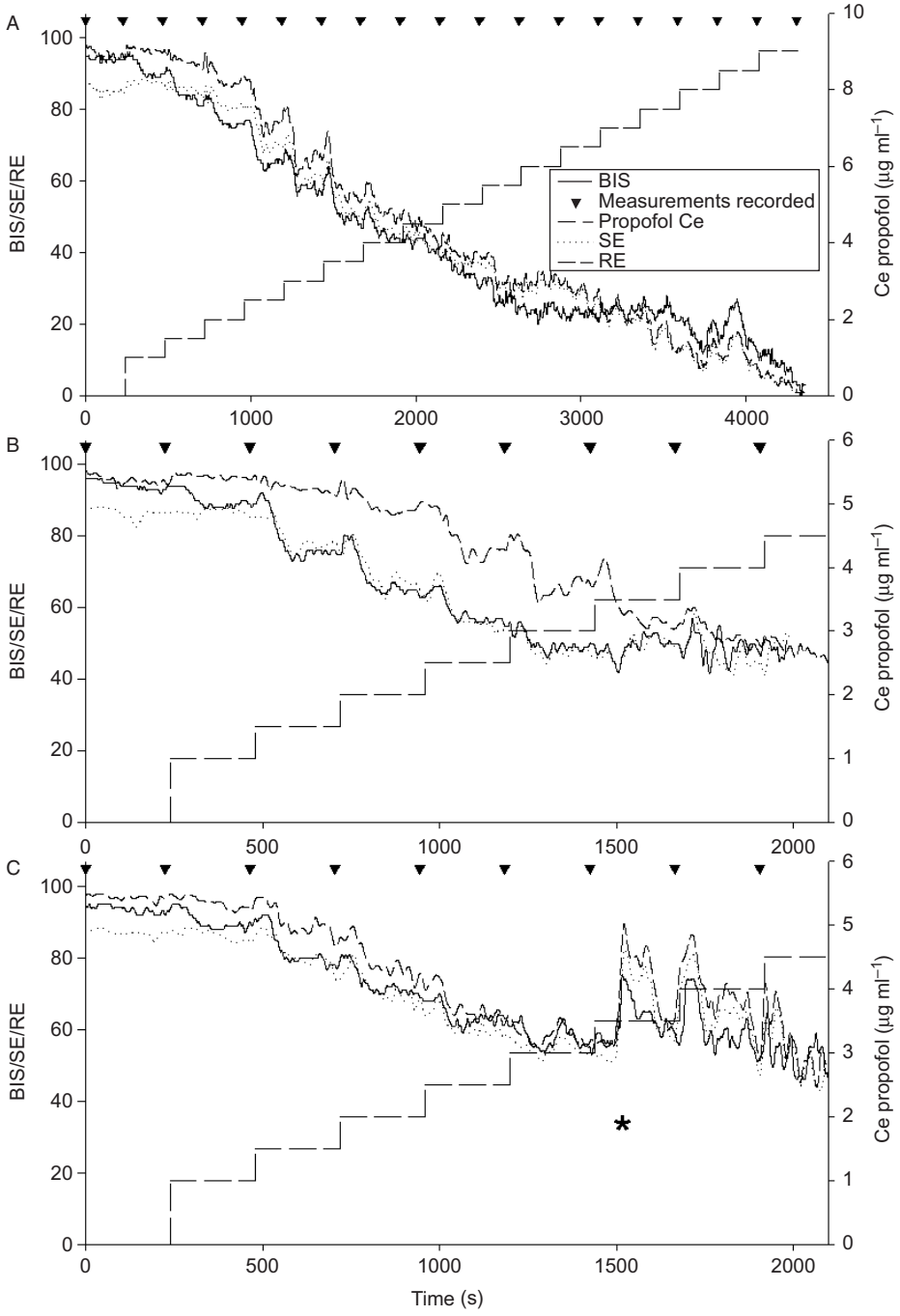

Fig 1 Averaged bispectral index (BIS), state entropy (SE) and response entropy (RE) *vs* time. The triangles indicate time of measurement of the response to verbal command and noxious stimulus. Data from the groups remi 0, 2 and 4 ng ml^{-1} are shown in A, B and C respectively.

Table 1 Responsiveness scores of the modified Observer's Assessment of Alertness/Sedation scale (OAA/S)

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Response only after name is called loudly and/or repeatedly
2	Response only after mild prodding or shaking
1	Response only after painful trapezius squeeze
0	No response after painful trapezius squeeze

The responsiveness component of the OAA/S scale (Table 1) is an assessment procedure involving a presentation of progressively more intense stimulation, ranging from a moderate speaking voice to physical shaking or moderate noxious stimulus (trapezius squeeze) until a response is observed. Patients were considered responsive at an OAA/S level of 5, 4 or 3 and scored as unresponsive at an OAA/S level 2, 1 or 0. Patients were considered to have loss of consciousness (LOC) at the transition between level 3 and level 2. For measuring the reaction to noxious

stimulus, a tetanic electrical stimulus (100 Hz, 50 mA) for 2 s was applied at the volar forearm level.

BIS was also logged automatically. Rugloop digitally recorded all data each 5 s. Afterwards, all data were extracted and time-synchronized using Labgrab® data management software (Demed, Temse, Belgium).

Statistical analysis

The significance level was set at 5% unless otherwise reported. The methods used were similar to those in our previous work.[6 7]

Using logistic regression analysis, the effective concentration or index at which 50% (ED_{50}) and 95% (ED_{95}) of the patients reached LOR_{verbal} and $LOR_{noxious}$ was calculated for BIS, SE and RE. For these, ED_{50} and ED_{95} values were compared between groups using one-way ANOVA statistics. If significant, an unpaired two-sided Student's *t* test with Bonferroni correction was used.

The ability of BIS, SE and RE to detect the level of OAA/S and $LOR_{noxious}$ was evaluated using the prediction probability (P_K), which compares the performance of independent variables having different units of measurements, as developed by Smith and colleagues.[15 16] P_K values range from 0.5 and 1. A P_K of 1 for an independent variable would mean that BIS, SE or RE always increases (decreases) as the level of anaesthesia gets lighter (deeper) according to the gold standard dependent variable. Such a variable would be a good measure of anaesthetic depth. A P_K value of 0.5 would mean that there is no correlation between any change in clinically determined depth of anaesthesia and change in the corresponding values from the monitor. The jack-knife method was used to compute the standard error of the estimate, based on the assumption that all assessments were independent.[15 16] Student's *t* test with Bonferroni's correction was used to evaluate whether the P_K for one variable was different from another. Prediction probability was calculated using a custom spreadsheet macro, P_KMACRO, developed by Smith and colleagues.[15 16] The P_K value was calculated for BIS, SE and RE in each group.

The power for the P_K values was calculated using a *t* statistic defined as the difference considered to be clinically important divided by the standard error of the difference between two independent variables. Assuming a P_K difference of 0.05 as being significant with a standard error of 0.02, then 20 patients should be included in order to find significant differences with $P<0.01$ (Bonferroni's correction for multiple *t* tests). This assumption was based on previous literature.[6 7]

We calculated cut-off (threshold) values for the ability of the BIS, SE and RE to detect LOR_{verbal} and $LOR_{noxious}$ in each group. For these calculations, we used 'positive' to denote a test result that suggested responsiveness and 'negative' to denote a test result that suggested non-responsiveness. We assumed that increases in BIS, SE and RE corresponded to increased likelihood of responsiveness.

Table 2 Demographic data. Mean (SD)

	Group		
	Remi 0 ng ml^{-1}	**Remi 2 ng ml^{-1}**	**Remi 4 ng ml^{-1}**
	(*n*=20)	(*n*=20)	(*n*=19)
Age (yr)	30 (8)	31 (6)	33 (6)
Weight (kg)	67 (11)	66 (18)	69 (11)
Height (cm)	169 (11)	171 (8)	171 (7)
Gender (male/female)	4/16	3/17	6/13

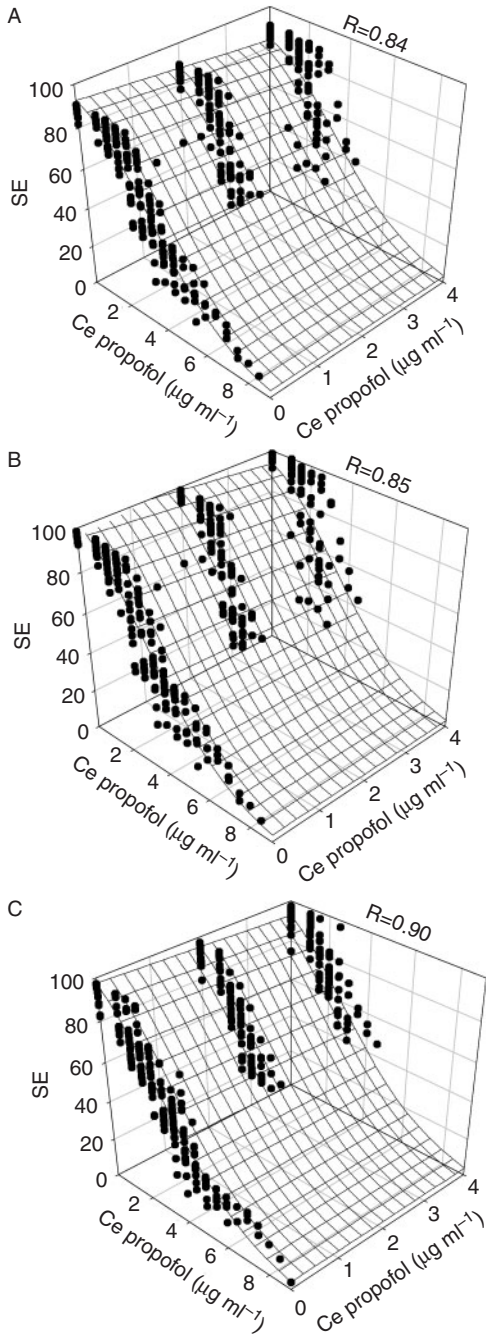

Fig 2 Non-linear regression analysis from raw data for all groups (remifentanil 0, 2 and 4 ng ml^{-1}) at different propofol effect-site concentrations. BIS=bispectral index; RE=response entropy; SE=state entropy.

We computed sensitivity as the proportion of responsive patients with positive test results (value higher than the cut-off value). Similarly, we computed specificity as the proportion of non-responsive patients with negative test results (value lower than the cut-off value). We computed the cut-off values for BIS, SE and RE and its specificity at a level of 100% sensitivity and at which the sum of sensitivity and specificity was highest.

Results

The demographic data for all patients are shown in Table 2. In group remi 4 ng ml^{-1}, one patient had to be excluded *post hoc* because of technical problems. During the administration of stepwise increasing Ce_{PROP}, a clear decrease in the averaged BIS, SE and RE was observed over time (Fig. 1A–C). The late increase in mean BIS, SE and RE (Fig. 1C) was due to there being only two remaining patients at that time, who required a longer time to obtain low values. The correlation coefficient between BIS and the drug effect-site concentrations (r=0.90) was higher than for SE (r=0.84) and RE (r=0.85) (Fig. 2A–C). BIS, SE and RE decreased in all groups with decreasing OAA/S scores (Fig. 3). At LOR_{verbal} and $LOR_{noxious}$, although the median value decreased significantly between

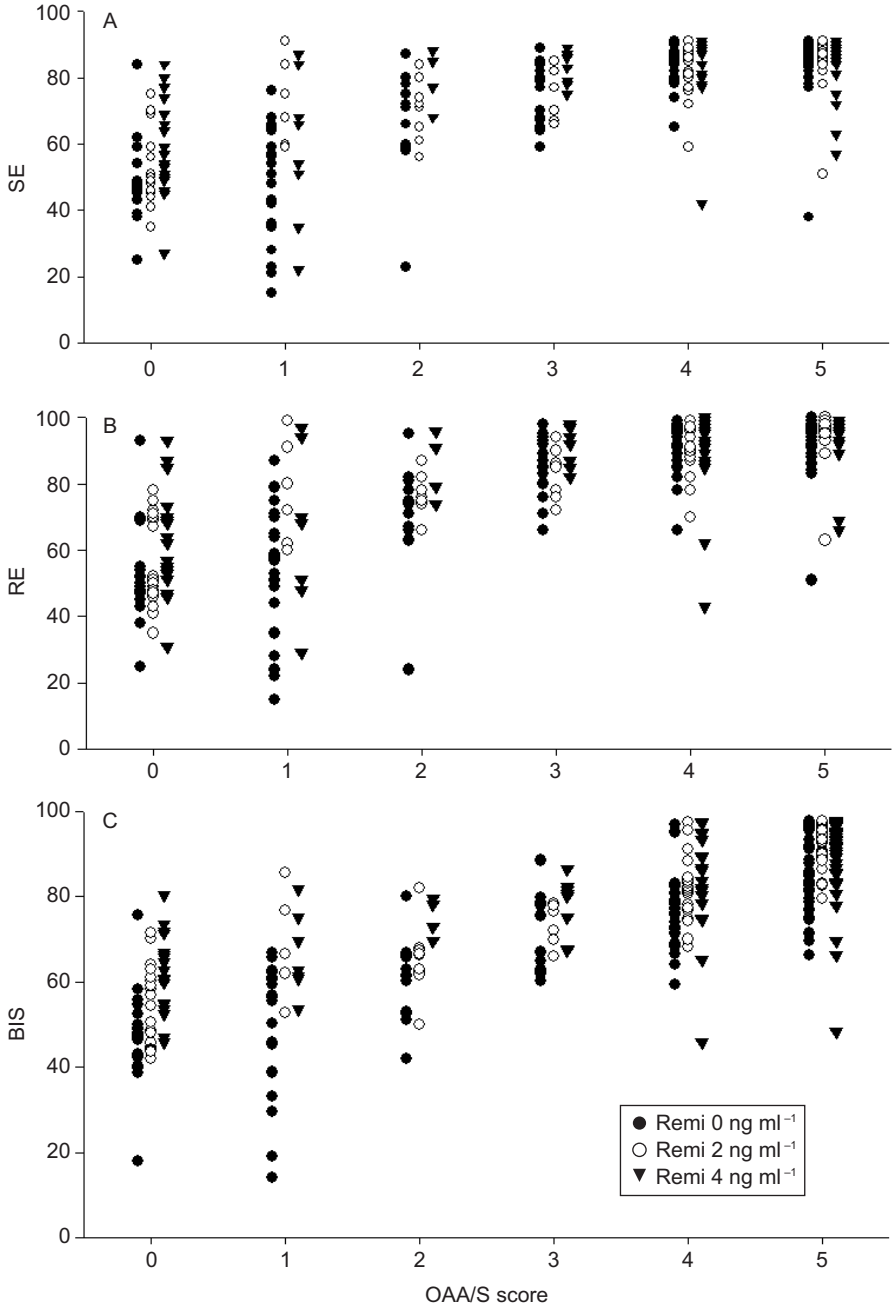

Fig 3 Raw data at every OAA/S score for bispectral index (BIS), response entropy (RE) and state entropy (SE).

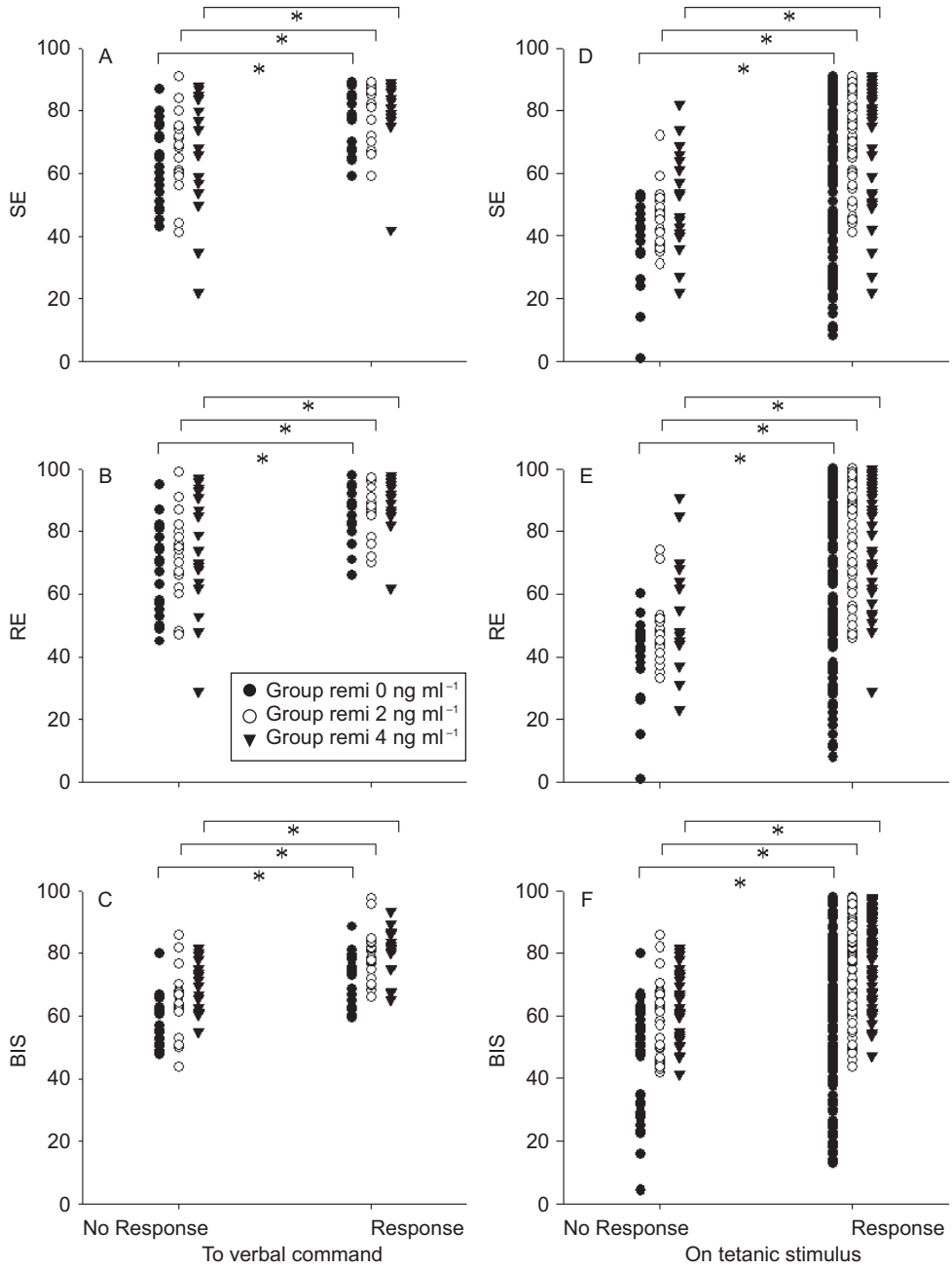

Fig 4 Raw data for (no) response to verbal command (A, B and C) and noxious stimulus (D, E and F) for BIS, response entropy (RE) and state entropy (SE). **P*<0.05 for each group, responsive *vs* non-responsive state.

the response and no-response level for BIS, SE and RE in all groups, a wide range of overlap was observed (Fig. 4A–C).

The effective BIS, SE and RE values at which 50% (ED_{50}) and 95% (ED_{95}) of the patients produced a LOR_{verbal} and $LOR_{noxious}$ were calculated by logistic regression (Table 3). Remifentanil infusion, in a concentration-dependent matter, resulted in higher values for BIS, SE and RE at LOR_{verbal} (Fig. 5A–C).

The P_K values demonstrate an overall similar ability of BIS, SE and RE to predict the level of LOR_{verbal} and $LOR_{noxious}$ (Table 4). The *t* statistic suggests that this study, by including 20 patients in each group, had the power to determine significant differences between BIS, SE and RE to predict OAA/S score >0.058.

The sensitivity/specificity analysis showed that the cut-off values for BIS, SE and RE, at which the sum of the sensitivity and specificity are highest, representing the monitoring value at which the overall 'errors' are minimized, were similar and did not differ between groups (Table 5). At the level of 100% sensitivity, BIS showed significantly better specificity in all groups compared with SE and RE (Table 6).

Table 3 ED_{50} (95% confidence interval)/ED_{95} values of BIS, SE, RE for all groups at LOR_{verbal} and $LOR_{noxious}$. $^{*}P<0.0167$ between all groups; $^{\$}P<0.0167$, remi 0 ng ml^{-1} *vs* remi 2 ng ml^{-1} and remi 0 ng ml^{-1} *vs* remi 4 ng ml^{-1}; $^{\#}P<0.0167$ for remi 0 ng ml^{-1} *vs* remi 2 ng ml^{-1} and remi 2 ng ml^{-1} *vs* remi 4 ng ml^{-1}. BIS=bispectral index; SE=state entropy. RE=response entropy; LOR_{verbal}=loss of response to verbal command; $LOR_{noxious}$=loss of response to electrical tetanic stimulus

	Group		
	Remi 0 ng ml^{-1}	**Remi 2 ng ml^{-1}**	**Remi 4 ng ml^{-1}**
LOR_{verbal}			
BIS	61 (59–62)*/52$^{\#}$	68 (67–70)*/65$^{\#}$	71 (70–73)*/64$^{\#}$
SE	64 (62–66)$^{\$}$/53$^{\#}$	68 (67–69)$^{\$}$/60$^{\#}$	70 (68–72)$^{\$}$/54$^{\#}$
RE	70 (68–72)*/57$^{\$}$	74 (73–75)*/69$^{\$}$	81 (80–83)*/68$^{\$}$
$LOR_{noxious}$			
BIS	32 (31–34)*/17*	53 (52–54)*/45*	61 (60–62)*/50*
SE	37 (34–40)$^{\$}$/22$^{\$}$	50 (49–51)$^{\$}$/39$^{\$}$	53 (51–55)$^{\$}$/32$^{\$}$
RE	39 (36–42)*/22*	53 (52–54)*/41*	59 (57–61)*/34*

Discussion

This study compared the performance of SE and RE with that of BIS. In our previous work, we showed that, during propofol administration, the ability of the BIS to detect OAA/S remained accurate, although it was influenced by remifentanil. Remifentanil decreases the ability of the BIS to detect $LOR_{noxious}$.[7] The hypnotic–anaesthetic component of anaesthesia was measured clinically by using the OAA/S score. We selected the OAA/S score because it provides a good correlation with a clinical reflection of the hypnotic component of anaesthesia and has been tested prospectively.[17]

In all groups, a stepwise increase in Ce_{PROP} resulted in a similar pattern of decrease in BIS, SE and RE. Inter-individual variability means that patients do not have equal Ce_{PROP} at equal time points. Thus, to show similarity, the relationship of BIS, SE and RE with Ce_{PROP} and OAA/S must be studied. The correlation between BIS and the combined drug effect-site concentrations was higher than for SE and RE. This is in agreement with our previous work investigating the performance accuracy of SE and RE *vs* BIS as cerebral measure of anaesthetic drug effect during propofol administration. It was concluded that, although all were within acceptable range, the prediction probability and individualized Spearman rank correlation of BIS, SE and RE with Ce_{PROP} was highest for BIS and lowest for SE.[18] In all groups, BIS, SE and RE decreased with decreasing OAA/S scores. For SE and RE, no clinically significant decrease was observed from OAA/S score 5 to 3, whereas from OAA/S score 3 to 0 there was a steeper (and clinically useful) decline. In contrast, BIS decreased more gradually. In all groups, BIS, SE and RE decreased significantly at LOR_{verbal}.

LOR_{verbal} was reached at higher values of BIS, SE and RE in a concentration-dependent matter when adding remifentanil. This can be concluded from the logistic regression analyses and the extracted ED_{50} and ED_{95}. Although some differences between groups for the ED_{50} did not reach the level of significance, a clear trend could be observed. These observations are in agreement with previous work showing a similar influence of fentanyl[19] and remifentanil at similar concentrations[7,20] on the BIS ED_{50} for loss of consciousness.

Although it has been reported that these shifts in cut-off values for LOR_{verbal} might influence the performance accuracy of depth of hypnotic–anaesthesia measures,[20–22] specific statistical methods, such as prediction probability[15,16] and sensitivity/specificity[23] calculations, are required to prove this statement. The prediction probability, P_K, provides a good alternative for the investigation of the overall relative performance of the different EEG-derived indices in measuring the hypnotic component of anaesthesia and loss of responsiveness to different stimuli.[15,16] Previously, no decrease in P_K for the ability of various EEG derived variables was found when adding clinical dosages of opioids or placebo during propofol administration.[7,24,25] However, no data are available for spectral entropy. In our study, the performance results indicate that BIS, SE and RE are reliable for assessing the level of OAA/S and LOR_{verbal}, and they did not decrease with the addition of remifentanil. When comparing the P_K between BIS, SE and RE within one group, we found that BIS tended to have higher values than SE and RE. However, under the statistical power conditions used in this study, significance was not reached. Therefore, it might be appropriate to study more detailed sensitivity/specificity characteristics.

As the P_K concept was developed to generalize non-parametric ROC curve areas to the polytomous ordinal patient state,[15] we felt it useful to define some specific sensitivity/specificity characteristics for BIS, SE and RE. The most frequently applied point of combined sensitivity/specificity lies at the elbow of the ROC curve, where the sum of sensitivity and specificity is the highest.[26] However, a depth of anaesthesia monitor should have 100% sensitivity (i.e. no false-negatives) if a specific numeric threshold (cut-off value) that can be interpreted as 'not aware' is required.[23] Therefore, as in our previous work with BIS and mid-latency auditory evoked responses,[6,7] we calculated the behaviour of BIS, SE and RE at the two important points of the ROC curves: (i) the highest sum of sensitivity and specificity, and (ii) the level of 100% sensitivity. With the addition of remifentanil, BIS, SE and RE cut-off values at LOR_{verbal} increased in a dose-dependent fashion. However, the changes in the highest sum were minimal and similar between BIS, SE and RE and did not differ between groups. This means that the accuracy of BIS, SE and RE was similar at this level of combined sensitivity/specificity and did not decrease with the addition of remifentanil. In contrast, at the level of 100% sensitivity, BIS showed a significantly better specificity in all groups compared with SE and RE.

We also tested the performance accuracy of BIS, SE and RE in predicting $LOR_{noxious}$ and the influence of remifentanil on it. The supramaximal tetanic stimulus used in this study has been described and used previously.[6,7] The overall

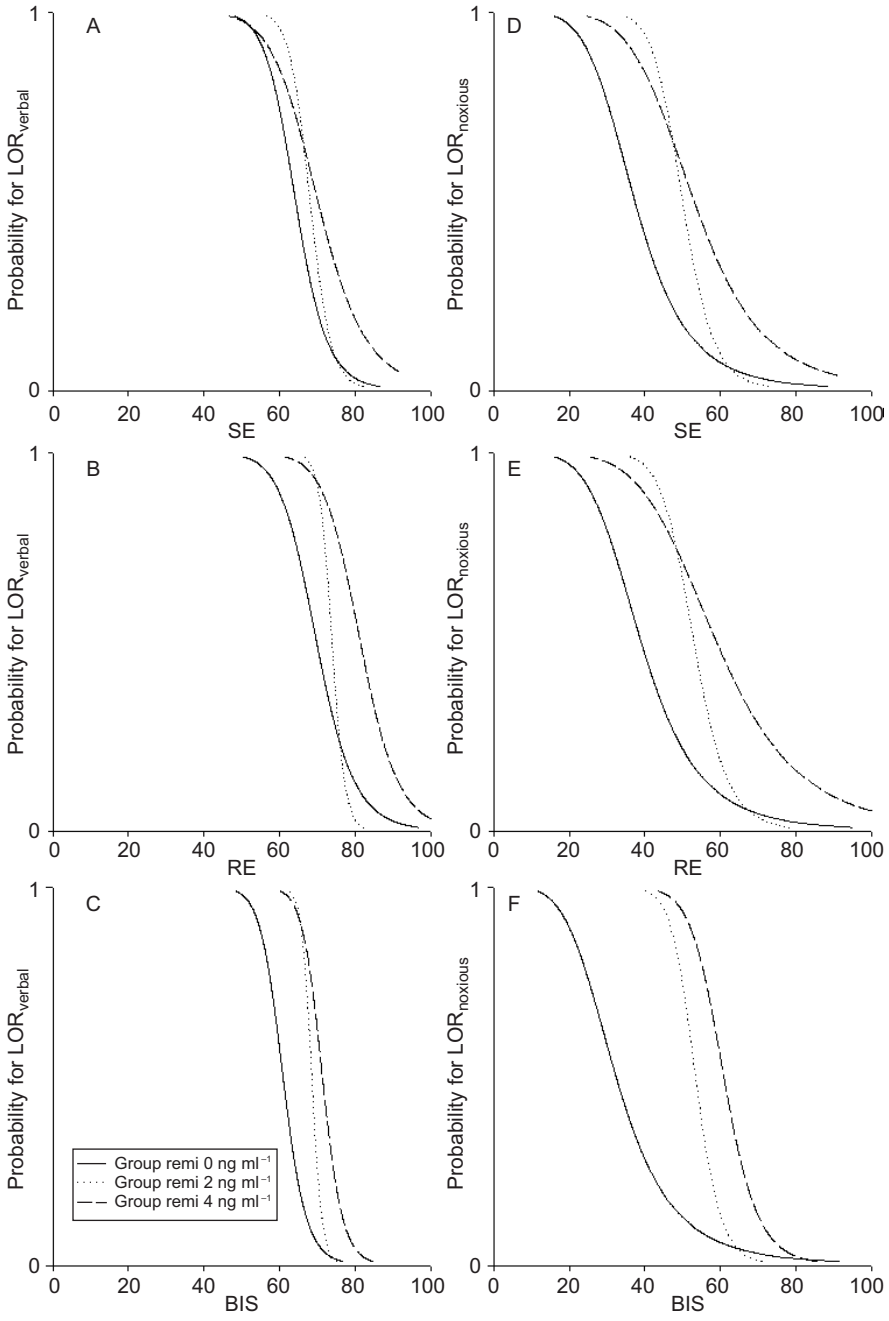

Fig 5 Probability of loss of response to verbal commend (LOR_{verbal}) (A, B, C) and a tetanic electrical stimulus ($LOR_{noxious}$) (D, E, F) as a function of bispectral index (BIS), response entropy (RE) and state entropy (SE).

accuracy for $LOR_{noxious}$ tended to be lower for BIS, SE and RE compared with their hypnotic prediction accuracy. The P_K values were lower, but not statistically significant in our study. Sensitivity/specificity profiles for BIS, SE and RE showed that the cut-off values for $LOR_{noxious}$ at the point of maximum combined sensitivity/specificity increased with the addition of remifentanil. At the level of 100% sensitivity, very low values were required for $LOR_{noxious}$ when no remifentanil was used, resulting in very low specificity. Addition of remifentanil resulted in higher cut-off values at 100% sensitivity because of the analgesic blockade, but with low specificity. Therefore, neither BIS nor spectral entropy can be promoted as monitors of $LOR_{noxious}$.

In conclusion, during propofol anaesthesia with steady-state conditions, we found that the hypnotic component of anaesthesia was more smoothly described by BIS than by spectral entropy when using the OAA/S score. Both BIS and spectral entropy performed accurately in detecting LOR_{verbal}, except at the 100% level of sensitivity, where BIS performed better than entropy. Although BIS and spectral entropy were influenced by remifentanil administration, their ability to predict OAA/S remained accurate.

Table 4 Prediction probability (P_K): mean (standard error) for BIS, SE and RE using LOR_{verbal} and $LOR_{noxious}$. BIS=bispectral index; SE=state entropy; RE=response entropy; LOR_{verbal}=loss of response to verbal command; $LOR_{noxious}$=loss of response to electrical tetanic stimulus

	Group		
	Remi 0 ng ml^{-1}	**Remi 2 ng ml^{-1}**	**Remi 4 ng ml^{-1}**
LOR_{verbal}			
BIS	0.91 (0.01)	0.93 (0.02)	0.89 (0.02)
SE	0.86 (0.02)	0.85 (0.03)	0.81 (0.03)
RE	0.88 (0.02)	0.89 (0.03)	0.83 (0.03)
$LOR_{noxious}$			
BIS	0.69 (0.10)	0.75 (0.08)	0.77 (0.08)
SE	0.65 (0.09)	0.80 (0.07)	0.67 (0.09)
RE	0.67 (0.09)	0.85 (0.06)	0.67 (0.09)

Table 5 Cut-off values for BIS, SE and RE at maximum level of sensitivity+specificity (sensitivity>specificity) for all groups. Results are reported as cut-off value [sensitivity (%) minus specificity (%); sum of sensitivity+specificity (%)]. BIS=bispectral index; SE=state entropy; RE=response entropy; LOR_{verbal}=loss of response to verbal command; $LOR_{noxious}$=loss of response to electrical tetanic stimulus

	Group		
	Remi 0 ng ml^{-1}	**Remi 2 ng ml^{-1}**	**Remi 4 ng ml^{-1}**
LOR_{verbal}			
BIS	63 (93–87; 179)	69 (97–86; 182)	74 (94–83; 177)
SE	73 (92–89; 180)	75 (90–89; 179)	77 (94–79; 174)
RE	79 (92–91; 182)	81 (90–89; 179)	85 (91–79; 170)
$LOR_{noxious}$			
BIS	37 (84–70; 154)	57 (89–85; 174)	64 (87–83; 170)
SE	45 (76–75; 151)	52 (89–85; 174)	65 (83–78; 161)
RE	47 (79–75; 154)	54 (91–90; 181)	68 (82–79; 161)

Table 6 Cut-off values (specificity) at 100% sensitivity. *At 99% sensitivity. BIS=bispectral index; SE=state entropy; RE=response entropy; LOR_{verbal}=loss of response to verbal command; $LOR_{noxious}$=loss of response to electrical tetanic stimulus

	Group		
	Remi 0 ng ml^{-1}	**Remi 2 ng ml^{-1}**	**Remi 4 ng ml^{-1}**
LOR_{verbal}			
BIS	58 (68%)	65 (71%)	64 (48%)
SE	37 (15%)	50 (31%)	41 (10%)
RE	50 (42%)	62 (43%)	61 (31%)
$LOR_{noxious}$			
BIS	12 (5%)	43 (25%)	46 (11%)
SE	7 (5%)	40 (25%)	21 (5%)*
RE	7 (5%)	45 (50%)	28 (5%)

Remifentanil decreases the ability of BIS, SE and RE to detect loss of response to noxious stimulus.

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