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The Patient State Index as an indicator of the level of hypnosis under general anaesthesia

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Background. This retrospective study describes the performance of the Patient State Index (PSI), under standard clinical practice conditions. The PSI is comprised of quantitative features of the EEG (QEEG) that display clear differences between hypnotic states, but consistency across anaesthetic agents within the state.

Methods. The PSI was constructed from a systematic investigation of a database containing QEEG extracted from the analyses of continuous 19 channel EEG recordings obtained in 176 surgical patients. Induction was accomplished with etomidate, propofol, or thiopental. Anaesthesia was maintained by isoflurane, desflurane, or sevoflurane, total i.v. anaesthesia using propofol, or nitrous oxide/narcotics. It was hypothesized that a multivariate algorithm based on such measures of brain state, would vary significantly with changes in hypnotic state.

Results. Highly significant differences were found between mean PSI values obtained during the different anaesthetic states selected for study. The relationship between level of awareness and PSI value at different stages of anaesthetic delivery was also evaluated. Regression analysis for prediction of arousal level using PSI was found to be highly significant for the combination of all anaesthetics, and for the individual anaesthetics.

Conclusions. The PSI, based upon derived features of brain electrical activity in the anterior/posterior dimension, significantly co-varies with changes in state under general anaesthesia and can significantly predict the level of arousal in varying stages of anaesthetic delivery.

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Historically, attempts to monitor anaesthetic depth using traditional clinical measures have been considered inadequate. A more objective assessment of the depth of anaesthesia has been obtained by using quantitative analysis of the electroencephalogram (QEEG).[1–4] QEEG features have been incorporated into special purpose monitors, such as the Bispectral Index™ (BIS™),[5 6] which has been shown to correlate with the state of hypnosis.[7–10] A number of algorithms incorporate other electrophysiological measures, including entropy,[11] EEG complexity,[12] and an index derived from the auditory evoked potential.[13]

The Patient State Index (PSI) was constructed from a retrospective exploration of the multivariate changes in brain electrical activity observed from loss to return of consciousness. It was hypothesized that an algorithm accounting for the maximum electrophysiological variance of this process, minimizing redundancy and maximizing sensitivity to changes in state, could be used to construct an index sensitive to changes in hypnotic state. In an earlier publication,[14] we described preliminary findings. This paper describes this process and demonstrates the relationship between different states of hypnosis and the PSI value.

Table 1 Type of anaesthesia, duration of surgery, and duration of anaesthesia. *Duration of surgery defined as time between incision and last stitch

Anaesthesia	*n*	Duration of surgery* (min) Mean (SD)	Duration of anaesthesia (min) Mean (SD)
TIVA	49	87.24 (52.80)	124.46 (60.20)
GAS	68	108.18 (65.73)	139.67 (71.26)
N/N	59	55.95 (44.02)	92.42 (42.10)

Methods

Patients

Institutional review board approval and written consent were obtained in all cases. 176 patients, ASA I–III were enrolled in the study from two sites, Brigham and Women's Hospital, Boston, Massachusetts and University Hospital Charité, Humboldt University of Berlin. Patients undergoing cardiac, carotid, joint replacement, or cranial surgery were excluded from the study. Exclusion criteria also included a history of head injury with loss of consciousness, a history of drug or alcohol dependence, previous bad/idiosyncratic reactions to anaesthesia, known neurological or psychiatric disorder, or current use of psychotropic medication.

Anaesthetic procedures

One of three anaesthetic regimens was administered at the discretion of the anaesthetist: (i) propofol total i.v. anaesthesia (TIVA); (ii) inhalation anaesthesia with isoflurane, sevoflurane, or desflurane (GAS); or (iii) nitrous oxide/narcotic (N/N), occasionally supplemented with propofol. All patients received either midazolam or fentanyl 30 min before induction of anaesthesia. At the start of induction, each patient was instructed to count backwards. The method of induction was at the discretion of the anaesthetist and included either etomidate, thiopental, gas or other agents. When patients stopped counting, the eyelash reflex was checked repeatedly until absent. The patient then received either a non-depolarizing neuromuscular blocking drug, or succinylcholine, in clinically determined amounts, in order to facilitate tracheal intubation. For the propofol and potent inhalation anaesthetic maintenance techniques, the anaesthetist chose whether to administer supplemental nitrous oxide and, for the propofol technique only, fentanyl.

EEG data acquisition

Nineteen electrodes were fixed to the scalp with paste, at positions corresponding to the International 10/20 Electrode Placement System.[15] In addition, the following electrodes were used: mastoid electrodes, electro-oculogram electrodes diagonally above and below the orbit of the eye, for detection of eye movement artifact, a ground electrode placed upon the cheek, and an ECG lead on the chest. Recordings were monopolar, referenced to linked earlobes. Amplifiers had a band pass from 0.5 to 70 Hz (3 dB points), with a 60 Hz notch filter. All impedances were kept below 5000 ohms, checked regularly throughout the surgical procedure. The A/D converter sampled at 200 Hz per channel, with 12-bit resolution. The data were reduced to 100 Hz before analysis, using Fant's resampling algorithm, which minimizes aliasing.[16] All recordings were collected using Spectrum 32 EEG Acquisition Systems (Cadwell Laboratories, Kennewick, WA).

Experienced technicians, augmented by an automatic EEG artifact detection algorithm, edited EEG data visually. At each anaesthetic state (defined below), an artifact-free sample was selected for quantitative analysis, containing from 24 to 48 segments each 2.5 s in duration, with the exception of induction in which only the last 12 segments (30 s) before loss of consciousness were used because induction often occurred quickly and its duration varied widely.

For purposes of this study, the time intervals selected reflected stable periods with sufficient data for estimation of the brain state under the selected conditions. While this may result in less sensitivity of the PSI measure and longer response time to events, it was considered to represent a conservative approach. The implementation of the PSI in the Patient State Analyzer is based on continuous updating of the index every 1.25 s.

EEG data analysis

As duration of the surgical procedures varied from patient to patient (see Table 1), a standardized set of anaesthetic states was identified in each case. These states included data from: (1) pre-operative state, day before surgery, with no pre-operative medication; (2) baseline, recorded outside the operating room after delivery of pre-operative sedation (note: this state was taken as baseline in this study since the prior state was only obtained in a subset of patients); (3) induction, recorded from the pre-operatively sedated patient on the operating table during induction, while the patient counted backwards just before cessation of counting; (4) loss of consciousness, recorded immediately after cessation of counting, loss of eyelash reflex and loss of response to painful stimuli; (5) maintenance, averaged across an uneventful period of anaesthesia during surgery, at approximately the mid-point of anaesthetic delivery; (6) spontaneous somatic events, recorded during maintenance of anaesthesia just before a reported unexpected somatic event (e.g. eyes opened, arm or leg movement, head movement); (7) emergence, recorded approximately 10 min before eye opening (emergence –2) and approximately 5 min before eye opening after the maintenance anaesthetic had been discontinued (emergence –1); and (8) return of consciousness, recorded immediately after the patient

opened their eyes, in response to a loud verbal command using the patient's name, and showed aversion to a noxious stimulus.

The artefact-free EEG from each of these states was converted from the time to the frequency domain using a fast Fourier transform. For every electrode and separately for each of the states, data were averaged across artefact-free segments to yield measures of absolute and relative power in the conventional wide frequency bands between 0.5 and 50 Hz (low delta (0.5–1.5 Hz); delta (1.5–3.5 Hz); theta (3.5–7.5 Hz); alpha (7.5–12.5 Hz); beta (12.5–25 Hz); and gamma (25 and 50 Hz) bands), and total power in the spectrum. Intra-hemispheric relationships including power gradients and synchrony, were also computed for all electrode pairs. Bispectral features were also computed for all pairs of 6 Hz wide bands, between 1 and 50 Hz, within each electrode site, for coherence and power.

Following neurometric QEEG procedures,[17 18] all features were transformed to obtain normal distributions and standardized to yield Z-scores, relative to each subject's individual response to anaesthetic and the variance of the baseline (BL) state of the total anaesthetic database of 176 cases. The use of such self-norming takes into account individual variability of the EEG to anaesthetic agents.[19] Using a proprietary multivariate discriminant algorithm based on these self-normed indicators of specific states, PSI values were computed for each of the selected states.

EEG data was collected utilizing circuitry optimized to exclude electrical contamination from the environment. Data from the subset of electrode sites used in calculating the PSI were selected from this full set of data. These sites include two anterior (FPI and FPZ′), a midline central (Cz) and a midline posterior (Pz) scalp locations, spanning anterior to posterior dimensions. All other data were maintained in a 'consciousness' database for further study. The selected sites represent a minimal set of electrodes identified as necessary to reflect the significant changes that occur with loss and return of consciousness, with attention also to the gradient shifts between frontal and posterior regions. As, ultimately, the PSI was to reside in a clinical instrument for monitoring level of arousal, it was important that the required electrode sites could be easily incorporated into a clinical appliance for use in the operating room environment.

Computation of the PSI

Following the frequency analysis of the artefact-free EEG signals a subset of features found to account for most statistical variance related to hypnotic state are derived for input to a multivariate discriminant algorithm (proprietary). These features include: absolute power gradient between frontopolar and vertex regions in the gamma band; absolute power changes between midline frontal and central regions in the beta band and between midline frontal and parietal regions in the alpha band; total spectral power in the frontopolar region; mean frequency of the total spectrum in midline frontal region; absolute power in the delta band at the vertex; and posterior relative power in the slow delta range.

Every element in the set of selected features is transformed to a standard score (Z-score) relative to its distribution in a specific reference state and expressed as the probability of deviation from that state. The current values of these standardized scores are the inputs to the calculation of the PSI value. The PSI is the ratio of the probability that the observation belongs to the reference state *vs* the sum of the probabilities that the observation belongs to either the reference state or to a different level of arousal. Thus, the PSI value can range from 0 to 100. A recent publication by Drover and colleagues[20] provides additional details of this computation.

Arousal scores

In order to estimate the statistical relationship between PSI and arousal level, arousal scores were assigned retrospectively to each selected stage using the Observer's Assessment of Alertness/Sedation Scale (OAA/S, rated 0–5). (In the OAA/S scoring, 5=responds readily to name spoken in normal tone, 4=lethargic response to name spoken in normal tone, 3=lethargic response to name spoken loudly and repeatedly, 2=responds only to name spoken loudly after a mild painful stimulus (train of four), 1=responds only to name spoken loudly after a moderately painful stimulus (50 Hz electrical stimulation), 0=no response to verbal or painful stimulus. Same scale used in our previously published study by Gugino and colleagues.[21]) This was done using a conservative estimate of responsiveness agreed upon by the attending anaesthesiologists responsible for these cases as follows: awake sedated was assigned a 4.5, end of induction before intubation was assigned a 0, early surgical plane was assigned a 0, spontaneous somatic events during maintenance were assigned a 3, approximately 10 min before return of consciousness (eye opening) during emergence was assigned a 2.5 and return of consciousness (eye opening) was assigned a 4. It is noted that no significant site by state interactions were found (repeated measure ANOVA (P=0.15)), which served as assurance that the states were similar across the international sites.

Statistical analyses

The hypothesis that the PSI index would be significantly related to arousal state, that is the level of hypnosis, was tested using ANOVA for the significance of the difference between PSI values at baseline as compared with each of the other states, for all anaesthetics and for each class of anaesthetics separately. Additionally, the significance of the relationship between PSI and level of hypnosis was evaluated using regression analysis, with PSI as the

independent variable and arousal score as the dependent variables.

Results

Sixty-eight males and 108 females (mean age 41.1 yr (17–72 yr); 62% ASA I, 35% ASA II, and 3% ASA III) were enrolled in the study from two sites, Brigham and Women's Hospital, Boston, Massachussetts and University Hospital Charité, Humboldt University of Berlin. The mean weight and height was 78.7 kg (56.7–120.2 kg) and 179.4 cm (162.6–196.0 cm) for the males, and 65.8 kg (49.9–97.5 kg) and 164.2 (152.4–177.8 cm) for the females. Surgical procedures included gynaecological (45%), urological (31%), and general/other surgical (24%) procedures

Induction of anaesthesia was achieved by injection of a bolus of etomidate (in 36% of the cases), thiopental (in 27% of the cases), propofol (26% of the cases), inhalation via a facemask (4% of the cases), or injection of other agents (7% of the cases). For maintenance of anaesthesia, there were 49 TIVA cases, 68 GAS cases, and 59 N/N cases.

Nitrous oxide was used in 71% of the GAS cases. For patients whose anaesthetic was maintained with TIVA, propofol was administered at an infusion rate ranging from 100 to 200 $\mu g\ kg^{-1}\ min^{-1}$. Eighty-four per cent (84%) of the TIVA cases received nitrous oxide, with an end-tidal concentration of 50–60%. In the nitrous oxide narcotic technique, the end-tidal concentration of nitrous oxide was 60–70%. The distribution, duration of analgesic/anaesthetic agents and length of surgery are shown in Table 1. Table 2 gives the average concentration of administered anaesthetic agents during the maintenance stage.

Table 2 Average concentration of administered anaesthetic agents during maintenance, given as average infusion rate; **+ nitrous oxide used at approximately the same rate as indicated for nitrous in the table

Anaesthesia	Mean (SD)
Nitrous oxide (%)	67.55 (6.84)
Isoflurane	1.60 (0.56)
Isoflurane + nitrous oxide**	0.90 (0.37)
Desflurane (%)	6.22 (3.2)
Desflurane (%) + nitrous oxide**	4.39 (0.96)
Sevoflurane (%)	2.76 (0.94)
Sevoflurane (%) + nitrous oxide**	1.27 (0.68)
Propofol ($\mu g\ kg^{-1}\ min^{-1}$)	148.62 (61.74)

PSI vs *stage of procedure*

The PSI changed in a systematic manner from induction, throughout loss of consciousness, intubation, and the various surgical procedures, and during emergence until return of consciousness. This performance was consistent, independent of the agents used for sedation, induction or maintenance of anaesthesia, as we have demonstrated elsewhere.[4 20] Figure 1 shows the mean (±95% confidence level) performance of the population across selected stages, separated for class of anaesthetic. It can be seen that, overall, change in state was accompanied by clear changes in the PSI value, for all anaesthetic types.

Table 3 shows the mean PSI values across all anaesthetics, and separately by anaesthetic, for selected stages or events. Table 4 presents data as in Table 3, but across all cases in which inhalation anaesthetics were used for: (i) all volatile anaesthetics combined (n=63), (ii) desflurane (n=21), (iii) isoflurane (n=30), and (iv) sevoflurane (n=2). (It is noted that nitrous oxide was sometimes used during delivery of volatile anaesthetics.)

Highly significant differences were seen between mean PSI values obtained during different stages. The mean PSI value for spontaneous arousal events was quite high, approximately at the same PSI level as seen at return of consciousness. Note that the PSI during surgery is higher for the N/N anaesthesia than for the other anaesthetics, reflecting the 'lighter' state of sedation/hypnosis achieved by this anaesthetic. Highly significant differences (P<0.0001) were seen for all states, except for somatic events and return of consciousness, as expected. In addition, highly significant differences were found (P<0.0001) between PSIs for uneventful periods during surgery and PSIs *approximately 1 min before spontaneous somatic events*.

PSI vs *OAA/S*

The regression curves for the relationship between PSI value and OAA/S score are presented in Figure 2, for: (i) all cases combined, independent of anaesthetic (n=176, Fig. 2A); (ii) only volatile anaesthetics, GAS (n=63, Fig. 2C); (iii) only TIVA (n=46, Fig. 2B); and (iv) only N/N (n=57, Fig. 2D).

Regression analyses for prediction of arousal level using PSI were found to be highly significant (R^2=0.63, $P\leqslant$0.0001) for all anaesthetics combined, and for GAS (R^2=0.71, $P\leqslant$0.0001), TIVA (R^2=0.65, $P\leqslant$0.0001), and N/N (R^2=0.56, $P\leqslant$0.0001) anaesthetics alone. The error of prediction is shown by the dotted lines around each curve.

Discussion

The PSI is an index of level of hypnosis/awareness derived from systematic study of the complex of changes in brain state, which were observed to reversibly accompany loss and return of consciousness, independent of anaesthetic class.[4 21 22] The variables selected for incorporation in the PSI displayed very significant heterogeneity of variance at different levels of sedation/hypnosis (sensitivity) but non-significant differences across anaesthetic agents at any specified level (specificity). These include measures of power, power gradients, and covariances among regions. Using this strategy, it was believed that the PSI would demonstrate high sensitivity to changes in state and changes

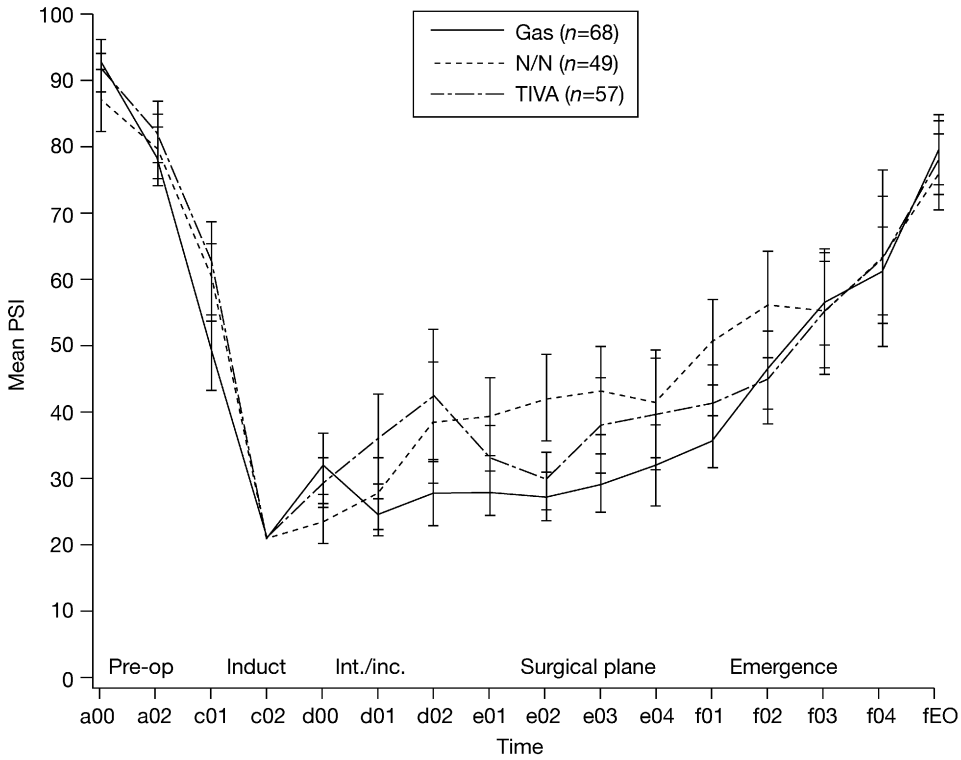

Fig 1 Group average curves of PSI values (means and ±95% confidence) as a function of state throughout the surgical procedure. Shown separately for TIVA, GAS, and N/N. The states graphed include: a00=day before surgery, with no medication; a02=day of surgery, with pre-operative sedation given (note: taken as baseline in this study since a00 was only obtained in a subset of patients); c01=beginning of induction, patient starts counting; c02=at point where patient stops counting, loss of consciousness; d00=just before intubation; d01=just after intubation; d02=incision; e01–e04=anaesthetic maintenance at surgical plane; f01—f04=emergence, decreasing anaesthetic; fEO=eyes open, return of consciousness.

Table 3 Mean PSI values at selected stages throughout anaesthetic delivery. The first row shows the mean values for all anaesthetics combined, rows 2–4 show the mean PSI values separately by type of anaesthesia. In each cell of the table, the first row is the mean PSI, the middle row is ±95% confidence interval and the last row is the number of subjects in the mean. ***P<0.0001; **P<0.001; *P<0.01=significance level for comparisons with baseline, awake/sedated (first column). For all anaesthetics, TIVA and N/N, there were significant differences (P<0.0001) between PSI approximately 1 min before spontaneous somatic events and uneventful surgical plane. There was not sufficient n to test this for GAS (3269-6TJ) and n too small to calculate confidence interval. EO, eyes open

Mean PSI values	Baseline awake/sedated	Early surgical plane	Uneventful surgical plane	Approximately 1 min before somatic events	Emergence –2 approximately 10 min before EO	Emergence –1 approximately 5 min before EO	EO ROC
All study anaesthetics	80.0 (77.3–82.6) (n=166)	32.2*** (29.1–35.3) (n=155)	33.6*** (32.2–35.1) (n=672)	72.1 (63.2–81.1) (n=21)	56.4*** (52.0–60.9) (n=125)	62.7*** (58.7–66.7) (n=148)	75.6 (72.0–79.1) (n=150)
Inhalation anaesthetic (GAS)	78.5 (74.1–82.8) (n=63)	26.9*** (23.2–30.5) (n=58)	28.6*** (26.9–30.2) (n=266)	54.7 (&) (n=2)	54.5*** (47.6–61.5) (n=48)	62.4*** (55.0–69.9) (n=53)	77.1 (71.2–83.1) (n=53)
TIVA	82.1 (77.5–86.6) (n=46)	28.3*** (24.1–32.6) (n=44)	32.2*** (27.5–38.2) (n=190)	74.1 (48.5–99.8) (n=7)	60.6*** (52.4–68.9) (n=42)	70.2* (63.0–77.5) (n=44)	79.0 (72.7–85.4) (n=44)
Nitrous/narcotic anaesthesia (N/N)	79.9 (75.1–84.8) (n=57)	41.2*** (34.3–48.2) (n=53)	41.1*** (38.0–44.2) (n=216)	73.9 (65.2–82.6) (n=12)	53.9*** (45.3–62.5) (n=35)	56.5** (50.4–62.6) (n=51)	71.1 (64.6–77.6) (n=53)

between successive stages of awareness, independent of any particular anaesthetic agents. In this study, the overall performance of the PSI was found to be significantly related to the state of the patient, for inhalation, TIVA or N/N anaesthesia. Despite the inherent variability of anaesthetic administration under standard clinical practice, similar differences between stages of awareness were demonstrated across anaesthetics.

Table 4 Mean PSI values at selected stages throughout anaesthetic delivery using inhalation anaesthesia. The first row shows the mean values for all anaesthetics combined, rows 2–4 show the mean PSI values separately by type of anaesthetic. In each cell of the table, the first row is the mean PSI, the middle row is ±95% confidence interval and the last row is the number of subjects in the mean. EO, eyes open

Mean PSI	Baseline awake/sedated	Early surgical plane	Uneventful surgical plane	Approximately 1 min before spontaneous somatic events	Emergence –2 approximately 10 min before EO	Emergence –1 approximately 5 min before EO	EO ROC
All GAS	78.5	26.9	28.6	54.7	54.5	62.4	77.1
	(74.1–82.8)	(23.2–30.5)	(26.9–30.2)	(&)	(47.6–61.5)	(55.0–69.9)	(71.2–83.1)
	(*n*=63)	(*n*=58)	(*n*=266)	(*n*=2)	(*n*=48)	(*n*=53)	(*n*=53)
Desflurane/+ MIX	75.2	22.4	25.6	69.1	51.0	61.3	81.6
	(66.7–83.7)	(18.3–26.6)	(23.7–27.5)	(NA)	(32.2–69.8)	(41.8–80.7)	(72.1–91.1)
	(*n*=21)	(*n*=18)	(*n*100)	(*n*=1)	(*n*=11)	(*n*=13)	(*n*=13)
Isoflurane/+ MIX	80.5	32.8	32.4	40.3	64.1	68.6	80.9
	(75.0–85.9)	(26.5–39.0)	(29.6–35.2)	(NA)	(57.2–70.9)	(59.8–77.4)	(72.9–89.0)
	(*n*=30)	(*n*=28)	(*n*=123)	(*n*=1)	(*n*=26)	(*n*=28)	(*n*=28)
Sevoflurane/+ MIX	79.3	19.7	24.5	NA	35.5	49.2	63.4
	(65.7–92.9)	(13.6–25.9)	(20.3–28.6)		(19.7–51.3)	(31.7–66.7)	(47.8–78.9)
	(*n*=12)	(*n*=12)	(*n*=43)		(*n*=11)	(*n*=12)	(*n*=12)

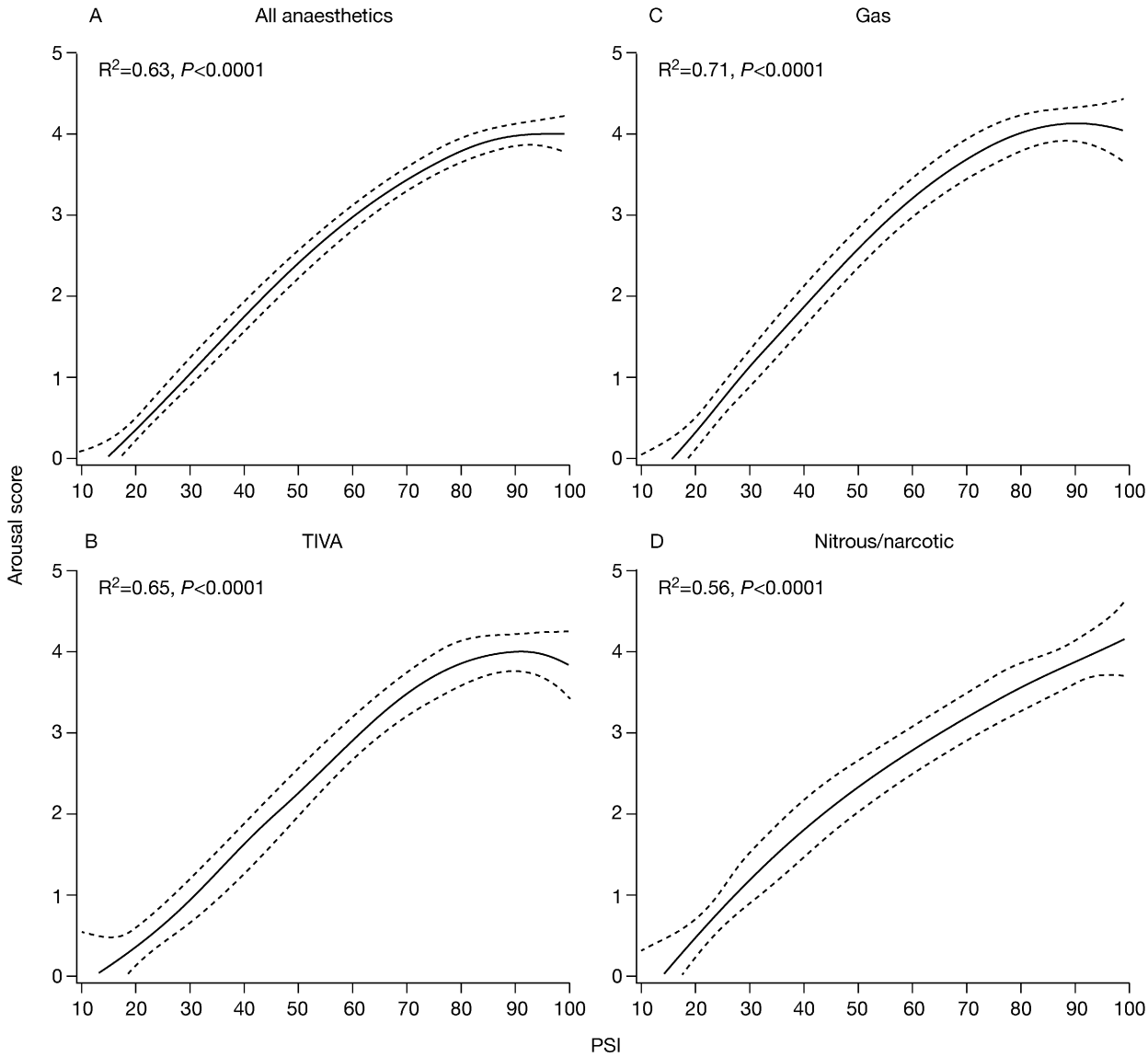

Fig 2 Regression curves for the prediction of arousal level from the PSI for all anaesthetics (A), TIVA (B), GAS (C) and N/N (D). For each curve the R^2 values are given, all are significant at greater than $P<0.0001$. Note that confidence intervals shown on the regression plots are the error of predictions.

The stable relationships, which have been retrospectively ascertained between clinical state and the value of the PSI in these numerous individual clinical cases, support the proposal that real-time computation of the PSI might serve as a reliable clinical monitor to assess the level of consciousness (sedation/hypnosis) throughout surgical procedures and with a wide variety of anaesthetic regimens. Further, while only a small number of spontaneous somatic events occurred in this population, the highly significant increase in PSI observed just before the event, suggests the clinical value of the index for predicting changes in state.

A further demonstration of the predictable relationship between anaesthetic state and PSI value was obtained in a normal volunteer study, in which more precise relationships between anaesthesia delivery and level of hypnosis could be evaluated. These results, presented elsewhere[21] support the sensitivity of the index. Taken as a whole, such data suggest the clinical utility of monitoring QEEG, using PSI, throughout anaesthesia delivery, as an adjunct to standard clinical monitors. A prospective multi-site validation of the PSI is underway and results are presented elsewhere.[20]

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References

1 Rampil IJ, Matteo RS. Changes in EEG spectral edge frequency correlate with the hemodynamic response to laryngoscopy and intubation. *Anesthesiology* 1987; **67**: 139–42

2 Schultz B, Schultz A, Grouven U, Zander I, Pichlmayr I. Changes with age in EEG during anesthesia. *Anaesthesist* 1995; **44**: 467–72

3 Werry C, Neulinger A, Eckert O, Lehmkuhl P, Pichlmayr I. Age-related correlation between EEG parameters and depth of anesthesia under propofol. Effect of fentanyl. *Anaesthesist* 1996; **45**: 722–30

4 John ER, Prichep LS, Kox W, *et al.* Invariant reversible QEEG effects of anesthetics. *Conscious Cognit* 2001; **10**: 165–83

5 Kearse LA, Rosow C, Zaslavsky A, Connors P, Dershwitz M, Denman W. Bispectral analysis of the electroencephalogram predicts conscious processing of information during propofol sedation and hypnosis. *Anesthesiology* 1998; **88**: 25–34

6 Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology* 1998; **89**: 980–1002

7 Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; **86**: 836–47

8 Sebel PS, Lang E, Rampil IJ, *et al.* A multicenter study of bispectral electroencephalogram analysis monitoring anesthetic effect. *Anesth Analg* 1997; **84**: 891–9

9 Payne FB, Sebel PS, Glass PS. Bispectral Index (BIS) monitoring allows faster emergence from propofol, alfentanil/N_2O anesthesia. *Anesthesiology* 1996; **85**: A1056

10 Song D, Joshi G, White PF. Titration of volatile anesthetics using bispectral index facilitated recovery after ambulatory anesthesia. *Anesthesiology* 1997; **87**: 842–8

11 Viertio-Oja H, Sarkela M, Talja P, Tolvanen-Laakso H, Yli-Hankala A. Entropy of the EEG signal is a robust index for depth of hypnosis. In: *2000 ASA Meeting Abstracts*. San Francisco, CA: Lippincott Williams & Wilkins, 2000

12 Roy RJ, Zhang XS. Clinical evaluation of EEG complexity measure for depth of anesthesia estimation. In: *2000 ASA Meeting Abstracts*. San Francisco, CA: Lippincott Williams & Wilkins, 2000

13 Mantzaridis H, Kenny GN. Auditory evoked potential index: a quantitative measure of changes in auditory evoked potentials during general anaesthesia. *Anaesthesia* 1997; **52**: 1030–6

14 Prichep LS, Gugino LD, John ER, Chabot RJ, Rausch L, Kox W. In: *Annual Meeting of Society for Technology in Anesthesia*. San Diego, CA: Lippincott, Williams & Wilkins, 1999

15 Jasper HH. The 10/20 electrode system of the International Federation. *EEG Clin Neurophysiol* 1958; **10**: 371–5

16 Wolberg G. *IEEE Computer Society Press.* Los Alamitos, CA: Digital Image Warping, 1990

17 John ER, Prichep LS, Friedman J, Easton P. Neurometrics: computer assisted differential diagnosis of brain dysfunctions. *Science* 1988; **239**: 162–9

18 John ER, Prichep LS. In: Niedermeyer E, Lopes Da Silva F, eds. *EEG: Basic Principles, Clinical Applications and Related Fields*. Amsterdam: Williams and Wilkins, 1993; 989–1003

19 Gugino LD, Chabot RJ, Aglio LS, Maddi R, Gosnell J, Aranki S. QEEG and neuropsychological profiles of patients prior undergoing cardiopulmonary bypass surgical procedures. *Clin EEG* 1997; **28**: 87–97

20 Drover D, Lemmens H, Loyd G, *et al.* Patient state index (PSI): Sensitivity to changes in anesthetic state and optimization of delivery and recovery from anesthesia. *Anesthesiology* 2002; **97**: 82–89

21 Gugino LD, Chabot RJ, Prichep LS, John ER, Formanek V, Aglio LS. Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anesthetized with propofol or sevoflurane. *Br J Anaesth* 2001; **87**: 421–8

22 John ER. A field theory of consciousness. *Conscious Cognit* 2001; **10**: 184–213