# Bispectral index is a topographically dependent variable in patients receiving propofol anaesthesia

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**Background.** As very strong agreement has been reported between bispectral index (BIS) values measured from the occipital and frontal skull areas, we compared BIS values measured from central and parietal areas with those from frontal area to investigate whether BIS is really a topographically dependent or topographically independent variable.

**Methods.** Twenty patients, ASA I–II, non-obese, aged 18–62 yr and with no neurological disorders were enrolled. Based on the 10–20 international landmarks, five silver dome electrodes were positioned: F7, C3, P7, Cz (common reference) and Fp1 (ground). Using frontal (F7–Cz), central (C3–Cz) and parietal (P7–Cz) electrode montages, the corresponding BIS values were simultaneously recorded with an Aspect A-1000 monitor (software v3.12). The BIS values were recorded at the propofol concentration allowing laryngeal mask insertion, which was maintained during the 10 min data collection period in absence of additional external stimuli. Data were analysed using the Kruskall–Wallis, Wilcoxon paired sign with Bonferroni correction, Bland–Altman and linear correlation tests.

**Results.** At the predicted effect target propofol concentration 4–8 $\mu g\ ml^{-1}$, the 10 min mean BIS (median [min–max]) were 32 [20–44], 46 [28–68] and 58 [41–72] for the frontal, central and parietal leads, respectively. Differences between these BIS recordings were statistically significant ($P<0.0001$, Kruskall–Wallis; $P<0.005$, Wilcoxon paired sign test).

**Conclusions.** The present results provide evidence that BIS index is a topographically dependent variable in patients receiving propofol anaesthesia.

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Measurement of the bispectral index (BIS) is now popular for non-invasive assessment of memory loss, loss of consciousness and eventually depth of anaesthesia.[1] The BIS is derived from measurements of bipolar surface EEG collected in predetermined locations on the forehead. In a recent study, it was shown that the BIS values obtained from occipital *vs* frontal electrode placements were in strong agreement,[2] suggesting that BIS values could be considered as topographically independent. This recent observation and its logical interpretation is nevertheless contrasting to previous data provided with other signal treatment methods in anaesthetized patients, which have shown topographical EEG variations.[3 4]

The ability to perform BIS monitoring at locations other than the frontal portion of the skull is of clear practical interest given that some clinical situations make frontal access practically difficult. The hypothesis of the present study was to test, for the BIS algorithm, if EEG recordings derived from central and parietal regions provide values that are different from those obtained from the standard frontal region.

## Materials and methods

After approval of the study design by the local Ethics Committee, written informed consent was obtained from 20 non-obese (BMI<27), ASA I and II, adults who were undergoing orthopaedic surgery in supine position. Any neurological disorders and use of psychoactive medication was excluded.

To minimize the artifacts, two conditions were imposed: a standardized patient drug regimen of propofol was used and

no external stimuli on or around the patient were allowed during the data sampling period. Patients did not take any medication before the surgery. Each patient was monitored using ECG, non-invasive arterial pressure cuff and an ear/finger pulse oximetry device. An infusion line containing Ringer Lactate solution was connected to an i.v. cannula inserted in a large forearm vein. A face mask delivering 45% oxygen was applied and anaesthesia was induced by bolus sufentanil 0.2 μg $kg^{-1}$ i.v. and propofol administered according to a target-controlled infusion mode. Propofol was administered using a Pilot Anesthesia™ syringe (Becton Dickinson Inc., Franklin Lakes, NJ, USA) operated via a remote control system that was developed in the Department of Computer Science of the University Medical School[5] according to Gepts pharmacokinetic set.[6] The effect target concentration for propofol was initially set at 3 μg $ml^{-1}$.

After confirmation of the patient's loss of consciousness, the lungs were ventilated with oxygen enriched air ($F_{I_{O_2}}$ of 0.45). After the initial target concentration of propofol was reached and maintained for 3 min, laryngeal mask insertion was attempted. If the insertion of laryngeal mask was successful without patient movement, a pressure-controlled ventilation mode was initiated (semiclosed circuit, 40–45% oxygen in air) using a KION™ (Siemens Elema™, Solna, Sweden) anaesthesia machine. If the insertion was unsuccessful, the propofol target concentration was increased by 1–2 μg $ml^{-1}$ and maintained thereafter for 5 min before another attempt to insert the laryngeal mask until successful insertion was obtained. The propofol target concentration was maintained unchanged for the next 10 min. Once the pressure-controlled ventilation mode was set, end-tidal $CO_2$ pressure was maintained between 4.3 and 4.7 kPa (Multigas™ analyzer, Siemens Elema™, Solna, Sweden). During the 10 min period of data collection, no external stimuli were permitted on or around the patient.

Silver cup electrodes were attached to the frontal (F7), central (C3) and parietal (P7) regions of the left hemisphere and vertex (Cz) according to the international 10–20 reference system (Fig. 1). The ground was secured to Fp1 using Ten 20™ (DO Weaver™ Aurora, CO, USA) adhesive paste. Electrode impedance was maintained below 5000 Ω. EEG data were collected using the Aspect Medical System™ A 1000 monitor™ (software version 3.12 Aspect Medical System, Natick, MA, USA). The low- and high-frequency filters were set at 0.5 and 30 Hz, respectively. Data were sampled every 30 s. BIS was calculated using the Aspect Medical System™ monitor in 5 s epochs without smoothing. After laryngeal mask insertion, the BIS was simultaneously recorded every 30 s from F7–Cz (frontal), C3–Cz (central) and P7–Cz (parietal) pairs for 10 min (20 measurements).

For each patient, the 20 measurements obtained during the 10 min study period for each electrode pair were averaged. Data were analysed using Statistical Package for the Social Sciences (SPSS) software for Windows (Release 11.5) using the non-parametric Kruskall–Wallis test for comparing across electrode locations. For comparisons between C3-F7 and P7-F7 respective mean BIS values, Bland–Altman analysis, paired Wilcoxon sign test with Bonferroni correction and linear regression including correlation coefficient calculations were performed. An α-value of 0.05 was admitted for the limit of statistical significance.

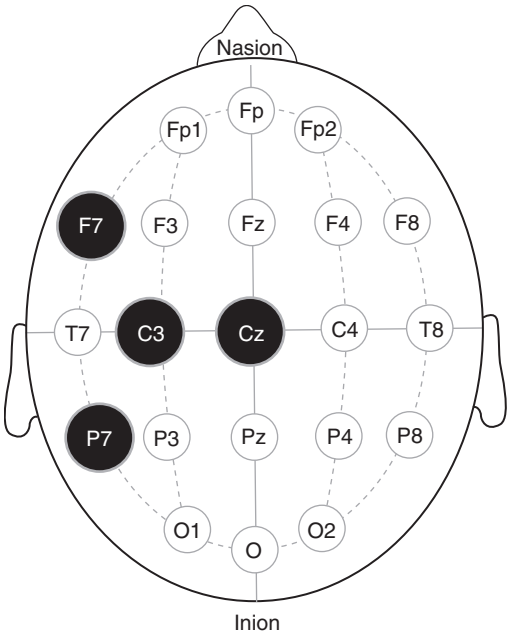


**Fig 1** Electrode positions referenced to the international 10–20 system. Black circles indicate the reference electrode montages used in this study.

## Results

Patients' age ranged between 18 and 56 yr, height between 166 and 187 cm, and weight between 65 and 87 kg (Table 1). The propofol target effect concentrations at successful insertion of laryngeal mask ranged between 4 and 8 μg $ml^{-1}$ ($n$=4 for 4, 5 and 7 μg $ml^{-1}$; $n$=3 for 8 μg $ml^{-1}$; $n$=5 for 6 μg $ml^{-1}$; Table 1). The mean BIS values obtained (median [min–max]) were 32 [20–44], 46 [28–68] and 58 [41–72] for the frontal, central and parietal leads, respectively. Figure 2 illustrates, for each patient, the arithmetic mean BIS determined from the 20 automatically recorded measurements for each lead. The differences in mean BIS values between the three electrode locations were statistically different ($P$<0.0001, Kruskall–Wallis). Intrapatient F7-C3 and F7-P7 values were statistically different ($P$<0.005, Wilcoxon paired sign test). The correlation coefficients and the linear regressions characteristics observed between fronto-central and fronto-parietal mean BIS values are shown in Figure 3. The linear regressions characteristics (angular coefficient, ordinate to the origin, correlation coefficient) were different; the respective values of 1.00, 25.31 and 0.66 were obtained for the F7-P7 comparison; whereas 0.74, 20.97 and 0.37 were calculated for the F7-C3

comparison. The Bland–Altman analysis performed[7] for F7-C3 and F7-P7 comparisons (Fig. 4) can be summarized as follows: (i) each individual (C3-F7) and (P7-F7) BIS values differences calculated were always positive giving respective mean (C3-F7) and (P7-F7) difference of 12 and 25 units; (ii) all differences existing between the compared BIS values were located within the agreement limits (mean±2 SD) used with this test; and (iii) no trend between the normalized C3-F7 and P7-C3 BIS value differences and the calculated (C3+F7)/2 and (P7+C3)/2 BIS values were noted.

## Discussion

The present results indicate that statistically and clinically significant differences between the BIS values collected from F7-Cz, C3-Cz and P7-Cz leads can be observed in anaesthetized patients receiving relevant concentrations of propofol in the absence of external stimuli.

We used propofol as a hypnotic agent because a sustained correlation between propofol blood concentrations, BIS and sedation score has been shown.[8] The condition of anaesthesia produced in the present study allowed the frontal BIS values to be in the recommended anaesthesia-related range (BIS<65).[9]

In accordance with electrophysiological recommendations for EEG methodology and EEG spatial analysis,[10] all the negative (measurement) electrodes (F7, C3 and P7) were connected to a common reference point (Cz), allowing a direct and simple quantitative comparison of the BIS collected at the three skull locations. Of the two possible reference points used by Glass and colleagues,[8] we preferred Cz to Fpz for two reasons. (i) We sought to reduce the interference of electromyographic artifacts with BIS calculation.[11] (ii) Glass and colleagues[8] only considered BIS values collected via the Fp1-Cz and Fp2-Cz leads when establishing the value of the BIS algorithm for unconsciousness and no-awareness probability functions.

Processing of EEG signals collected from frontal electrodes using the BIS algorithm is now a well-accepted method for assessing patient loss of consciousness and controlling lack of awareness in several pharmacological situations, including propofol administration.[12] Medical teams involved in BIS monitoring assessment and development have always focused on BIS calculations describing frontal or fronto/temporal EEG activity, even when multiple channel recordings are performed. Glass and colleagues,[8] using a monitoring device identical to the one used in this study, collected comparable BIS values by recording EEG activity from different electrode pairings in 72 volunteers receiving sedative concentrations of isoflurane, propofol, midazolam or alfentanil. They described the electrode locations using either a 'classical' description (referenced to the international 10/20 standard), Fp1-Cz (reference electrode) and Fp2-Cz, or as the preauricular area-Fpz (reference electrode) and eye outer corner-Fpz. Despite using two different

**Table 1** Patient characteristics and propofol target concentrations. Values are given as mean (SD)

| Propofol effect-site concentration ($\mu g\ ml^{-1}$) | Male/ female | Age (yr) | Weight (kg) | Height (cm) |
|---|---|---|---|---|
| 4.0 ($n$=4) | 1/3 | 31.2 (5.7) | 80.2 (8.6) | 171.2 (2.9) |
| 5.0 ($n$=4) | 3/1 | 31.7 (10.3) | 74.7 (8.4) | 175.2 (6.8) |
| 6.0 ($n$=5) | 1/4 | 40.4 (14.2) | 58.2 (9.3) | 167.2 (2.6) |
| 7.0 ($n$=4) | 3/1 | 47.0 (11.0) | 82.0 (10.0) | 172.2 (13.6) |
| 8.0 ($n$=3) | 2/1 | 37.3 (10.0) | 79.6 (11.0) | 168.6 (4.0) |
| Total ($n$=20) | 10/10 | 37.7 (11.4) | 73.9 (12.7) | 170.8 (7.1) |

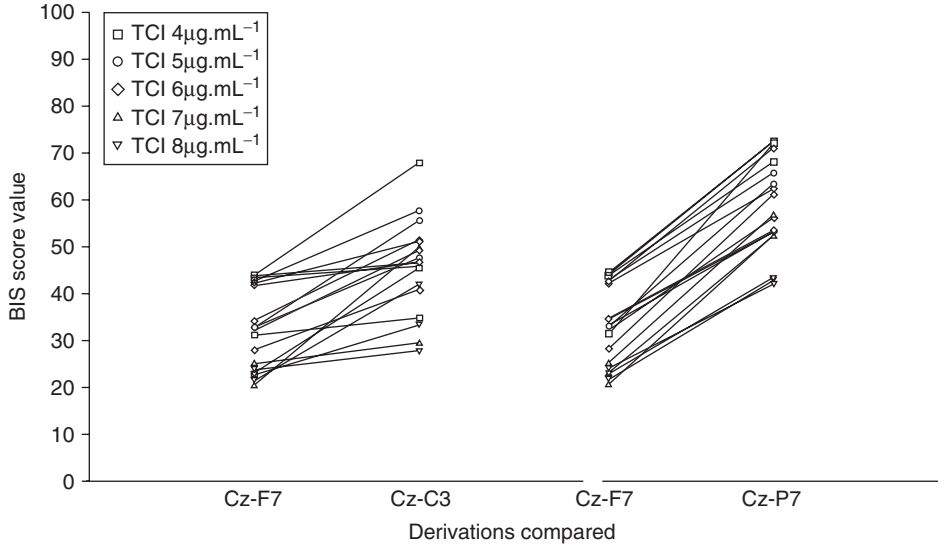


**Fig 2** Comparisons between the frontal (Cz-F7) *vs* central (Cz-C3) and frontal (Cz-F7) *vs* parietal (Cz-P7) individual mean BIS values. TCI, effect-site target using target-controlled infusion.

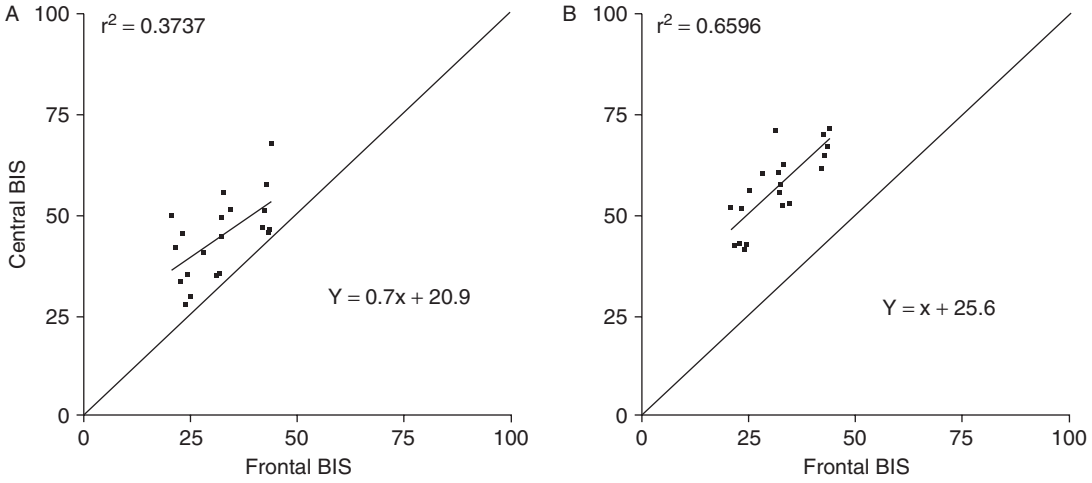


**Fig 3** Scatter plots of the linear regression calculated between (A) frontal *vs* central and (B) frontal *vs* parietal BIS values.

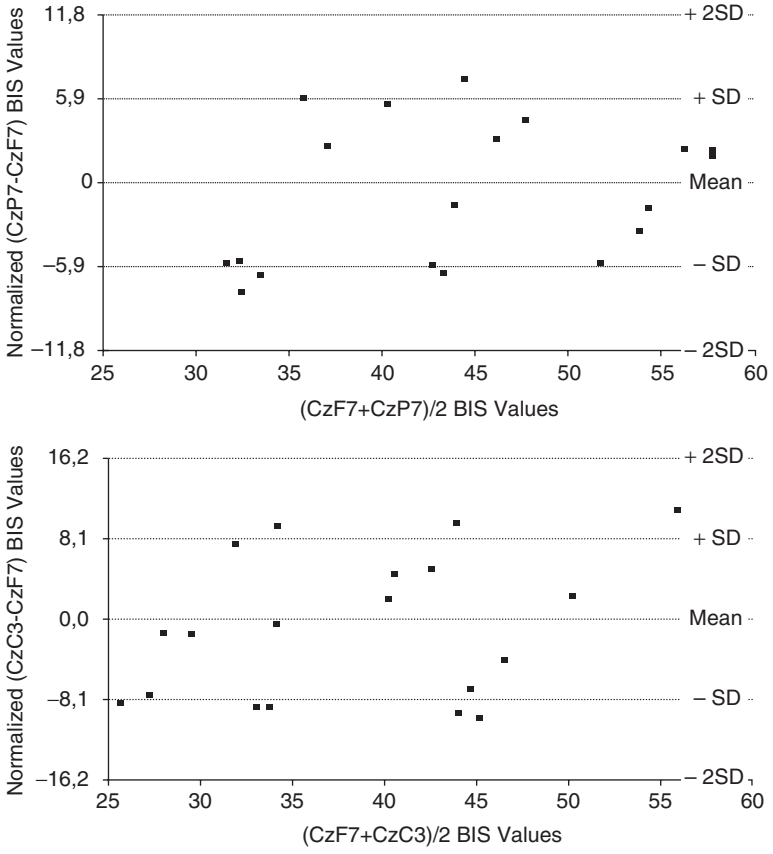


**Fig 4** Bland–Altman scatter plots for the F7-C3 and F7-P7 comparisons.

reference electrodes (Cz and Fpz) these authors reported that similar results were obtained in their study conditions. Unfortunately, the authors showed neither scatter plots, nor regression analysis, nor Bland–Altman analysis for comparing the magnitude of agreement between the BIS values derived from four different electrode pairings, including two different reference electrodes. However, as Glass and colleagues[8] did not investigate the possibility of a difference between BIS values derived from electrodes placed in other locations such as the central or parietal regions and, as more recently, Shiraishi and colleagues[2] provided evidence for very good agreement ($r^2$>0.95) between BIS values measured from frontal and occipital EEGs, all these elements further reinforce the prevailing

idea that the BIS could represent a topographically independent variable.

On the other hand, the present results confirm previous data reported by Hall and Lockwood,[13] obtained from Fp1-Fz/Fp2-Fz and Fp1-C3/Fp2-C4 electrode montages before and during surgery in 15 anaesthetized patients receiving different anaesthesia regimens. These authors found that, under these heterogeneous conditions, BIS values derived from each montage differed unpredictably. They found that BIS values derived from the central locations were approximately 13 units more elevated than those derived from the frontal locations. They, however, inferred that these differences were the result of the differing anaesthesia regimens, or, as was reported previously by Kochs and colleagues,[4] a result of topographical differences in the influence of surgery on EEG signals.

Even in normal awake[14] or anaesthetized[3 4 15–18] patients, EEG activity is not strictly homogeneous across the scalp. Thus, the lack of EEG homogeneity in some clinical situations, including the artifact-free conditions of the present study, is not particularly surprising. The ability of the BIS algorithm, such as other EEG-signal treatments, to identify these local variations is of interest for potential clinical applications. At the same time, our results provide evidence that BIS values derived from various electrode montages are not similar—the differences between respective means were, respectively, more than 12 and 24 units, when F7-C3 and F7-P7 derived BIS values were compared. Moreover, both correlation coefficients, Bland–Altman analysis and linear regressions describing F7-C3 and F7-P7 relationships indicate that a strong agreement between the central and parietal BIS values and those derived from frontally placed electrodes is not guaranteed. In particular, the F7-C3 comparison is characterized by both low correlation coefficient value and linear regression not parallel to the identity line.

In conclusion, the present data confirm that the BIS is not necessarily a topographically independent variable, even in unstimulated patients receiving propofol in relevant anaesthetic concentrations. BIS values derived from frontally placed electrodes do not necessarily strongly correlate with BIS values derived from central or parietal scalp regions. It appears that the general belief that the BIS classically collected between fronto-frontal or fronto-temporal electrodes is a unique value representing the best global measurement of whole-EEG activity is not entirely valid. Interpretation of BIS values derived from electrodes that are not frontally placed is a confounding factor that could potentially pose safety problems.

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