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Measuring depth of anaesthesia using changes in directional connectivity: a comparison with auditory middle latency response and estimated bispectral index during propofol anaesthesia *

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Summary

General anaesthesia is associated with changes in connectivity between different regions of the brain, the assessment of which has the potential to provide a novel marker of anaesthetic effect. We propose an index that quantifies the strength and direction of information flow in electroencephalographic signals collected across the scalp, assess its performance in discriminating 'wakefulness' from 'anaesthesia', and compare it with estimated bispectral index and the auditory middle latency response.

We used a step-wise slow induction of anaesthesia in 10 patients to assess graded changes in electroencephalographic directional connectivity at propofol effect-site concentrations of 2, 3, and 4 $mcg.ml^{-1}$. For each stable effect-site concentration, connectivity was estimated from multichannel electroencephalograms using Directed Coherence, together with middle latency response and estimated bispectral index. We used a linear support vector machine classifier to compare the performance of the different electroencephalographic features in discriminating wakefulness from anaesthesia.

We found a significant reduction in the strength of long-range connectivity (inter-electrode distance > 10 cm) ($p < 0.008$), and a reversal of information flow from markedly postero-frontal to fronto-posterior ($p<0.006$) between wakefulness and a propofol effect-site concentration of 2 $mcg.ml^{-1}$, which then remain relatively constant as effect-site concentration increases, consistent with a step change in Directed Coherence with anaesthesia. This contrasts with the gradual change with increasing anaesthetic dose observed for estimated bispectral index and middle latency response. Directed Coherence performed best in discriminating wakefulness from anaesthesia with an accuracy of 95%, indicating the potential of this new method (on its own or combined with others) for monitoring adequacy of anaesthesia.

The neurobiology mechanisms by which anaesthetics induce loss of consciousness remain unclear [1] so our ability to assess the level of consciousness during anaesthesia is limited. However, the sensitivity of EEG temporal and spectral features to anaesthetic-induced changes has prompted the commercial development of a series of EEG-derived 'depth of anaesthesia' monitors, for example aePEX, BIS, M-Entropy and Narcotrend. Although the indexes generated by these devices correlate well with the delivered anaesthetic concentration, they provide only limited insight into the cerebral mechanisms underlying anaesthetic action [2].

The potential of brain connectivity to quantify the global organized behaviour of neural circuits and provide insight into the neural mechanisms underlying loss of consciousness [3] has prompted a series of investigations of anaesthetic modulation of brain connectivity. Disruption of long-range connectivity [4,5] and changes in fronto-parietal coupling [6] have been reported as crucial mechanisms. A small number of recent studies have investigated EEG connectivity during anaesthesia, with promising results. These studies are characterized by a variety of experimental protocols and connectivity estimators, either linear Granger Causality estimators [6,7,8] or non-linear approaches based on information theory or phase dynamics [9,10]. However, it is not clear how directional connectivity measures correlate with established depth of anaesthesia indexes because, to our knowledge, a comparison of connectivity changes during anaesthesia with other indexes has not been performed.

In this exploratory work we assessed EEG directional connectivity using Directed Coherence, a well-established multivariate method [11] that provides information about the strength, direction and spectral content of linear dependencies between EEG time series. The objectives of this work are to:

1) understand how Directed Coherence, BIS and middle latency response features are affected by propofol anaesthesia
2) assess the performances of Directed Coherence features in comparison with BIS and middle latency response in discriminating wakefulness from anaesthesia at different propofol effect-site concentration

3) propose an index of anaesthetic effect that could be incorporated into future anaesthetic monitors.

Methods

The study was approved by the Southampton and Southwest Hampshire Research Ethics Committee (ref 002/98) and all patients provided written informed consent. Ten cardiac surgical patients (three females) aged between 44 and 79 years (BMI 23-28 $kg.m^{-2}$) participated in the study. None were diabetic or had abnormal renal function. Cardiac surgical patients were chosen because there is a predictable duration to the first procedure on these surgical lists, allowing time for the study to take place in the anaesthetic room with the second case of the day. Patients were selected from the operating schedule the day before their planned operation, based on their ability to tolerate an additional 90 min of anaesthesia before surgery, and did not receive premedication.

Routine monitoring with 12-lead ECG and pulse oximetry was started on arrival in the anaesthetic room. Under local anaesthesia, a 14G cannula was inserted into a forearm vein, and a 20G cannula into a radial artery for blood pressure measurement. The EEG was collected continuously throughout the study using a 32-channel system with active electrodes (Biosemi BV, Amsterdam) built into a head cap according to the International 10-20 system. Once the EEG monitoring set-up was completed, the patients were asked to lie quietly with their eyes closed for 10 min (awake state). A target-controlled infusion of propofol 1% (B Braun, Melsungen, Germany) was then started by syringe driver (Alaris PK, Carefusion, Sheffield, UK) to achieve an effect-site concentration of 2 $mcg.ml^{-1}$ using the Marsh pharmacokinetic model, which allows comparison with other work in this field [12,13]. All patients breathed spontaneously via a Hudson mask, supplemented with oxygen at 4-6 $l.min^{-1}$ to maintain SpO_2 >90%. We allowed an equilibration period of 5-10 min to reach a stable effect-site concentration that was then maintained for 10 min; this equilibration procedure was repeated as the propofol effect-site concentration was increased to 3 $mcg.ml^{-1}$ and subsequently 4 $mcg.ml^{-1}$. In the absence of surgical stimulation, all patients required intermittent bolus doses of

phenylephrine 100 mcg to maintain mean arterial pressure within 10% of awake baseline at effect-site concentration 3 and 4 mcg.ml^{-1}. During the first 5 min of each stable effect-site concentration period, auditory evoked responses were measured. Auditory stimuli were delivered binaurally using a computer-controlled CEDmicro1401 interface (Cambridge Electronic Design, Cambridge, UK), a headphone amplifier (Creek Audio Ltd, Hemel Hempstead, UK) and ER-2 insert headphones (Etymotic Research Inc, Elk Grove Village, IL). Chirps sweeping from 0.1 to 10 kHz over 10.4 ms were delivered at 60 dB above the normal hearing threshold at a stimulation rate of 143 Hz using maximum length sequences [14] (see Supplementary Material for more detail on the experimental protocol). After 10 min of recording at a propofol effect-site concentration of 4 mcg.ml^{-1}, fentanyl 1 mcg.kg^{-1} and pancuronium 0.2 mg.kg^{-1} were given, the patient's trachea was intubated and mechanical ventilation commenced. Five minutes later, the target effect-site concentration was reduced to 2 mcg.ml^{-1} and EEG recording was continued until this was achieved. The patients were then prepared for surgery.

EEG data were subsequently processed off-line, and underwent different pre-processing steps depending on the index computed.

For middle latency response estimation, EEG data from channels Fz and Cz were used, referenced to the occipital electrode Oz [15]. Data were zero-phase notch (50Hz) and band pass (15-250 Hz) filtered, then down-sampled from 4 kHz to 1 kHz before extracting the middle latency response as previously reported [14,15]. Previous work reports a significant reduction of middle latency response amplitude and/or an increase of the negative peak Nb latency during anaesthesia as compared to wakefulness [14,16]. We therefore assessed changes in middle latency response power (related to the average amplitude – see supplementary information) and Nb latency. In order to allow comparison with other EEG indexes, middle latency response was estimated from 600 epochs (time resolution of 60 s as for BIS and Directed Coherence).

BIS is a combination of EEG parameters obtained in the time domain (burst suppression ratio) and frequency domain (beta ratio and Synch-Fast-Slow). Our methodologies for BIS estimation were designed to reproduce as far as possible the proprietary algorithm for the computation of BIS and the published computation of BIS sub-parameters [17]. All the sub-parameters were computed for the 2 s epochs and then smoothed by averaging in 60 s segments. The BIS proprietary algorithm combines the sub-parameters with weights extracted from a multivariate model based on a database of EEG recordings matched to corresponding hypnotic drug concentrations. We therefore focused our analysis on the trends and variability of the different raw BIS sub-parameters. An estimated BIS index was also defined by algebraically summing the sub-parameters [18] (see Supplementary Material).

To determine connectivity measures, the EEG time series were band pass filtered (1-45 Hz) and zero-phase notch filtered (50 Hz), then down-sampled to 250 Hz and digitally referenced with respect to the average of the T7 and T8 channels (linked mastoid electrodes) [19]. Only continuous and artefact-free epochs were included in the analysis.

Directional connectivity was estimated from the multivariate model of multi-channel EEG time-series using Directed Coherence as previously described [20,21]. Due to its straightforward interpretation in terms of amount of spectral power transferred from one source channel to another [22], we used the squared modulus of Directed Coherence to estimate functional connectivity. A subset of 12 electrodes evenly distributed across the scalp was selected and connectivity was estimated for epochs of 60 s, in order to ensure an appropriate number of EEG samples for multivariate model estimation. The statistical significance of each Directed Coherence link was tested with surrogate analysis and all subsequent analysis was only performed on the significant long-range connections (> 10 cm inter-electrode distance). We also corrected for multiple comparisons using a false discovery rate approach. In addition to the statistical threshold, we applied thresholds to retain only the 10%, 30%, and 50% of strongest connections.

In order to quantify the dominant direction of information flow on the fronto-posterior axis we defined an index ($Dir_{P\rightarrow A}$) as the normalized differences of the number of long-range links in the α frequency band in both forward and rearward directions [21]. To summarize the individual Directed Coherence features in a unique parameter for each subject and 60 s epoch, we summed the normalized strength of long-range links and the $Dir_{P\rightarrow A}$ to obtain what we have called the DCindex. The rationale behind the proposed index is to be found in its physiological foundation, as we expect that a measure of brain connectivity may more efficiently capture changes in the level of consciousness of the subject than measures based on the local neuronal activity, such as BIS or middle latency response. See Supplementary Material for more details of Directed Coherence estimation and validation, and the computation of $Dir_{P\rightarrow A}$ and DCindex.

As well as a cohort analysis, we investigated the variability of EEG features across individuals and epochs of the same propofol effect-site concentration to assess the potential to apply this index for monitoring individual patients.

To test the performances of different EEG indexes in discriminating wakefulness from the different anaesthetic levels we used a binary classification procedure based on a linear support vector machine approach [23]. A linear support vector machine classifier estimates the optimal linear combination of features (in this case middle latency response, estimated BIS, and DCindex sub-parameters) that separates the samples in distinct classes. The optimal weights were found by training the support vector machine model using a leave-one-out approach (more details are given in the Supplementary Material). We used a support vector machine binary classifier to distinguish wakefulness from anaesthesia at each of the different propofol effect-site concentrations and more generally awake vs anaesthesia, providing four separate binary classifications. Another aim of the analysis was to test whether a combination of the various EEG features (middle latency response, estimated BIS and Directed Coherence) would improve the classification performances, or if the performances of the different measures combined were comparable with those of one 'optimal'

index. We therefore also applied the paradigm to all the features combined. In order to reliably characterize the performances of the different indexes, we described them in terms of sensitivity, specificity and global accuracy, defined as the number of correctly classified epochs over total number of observations.

Analysis was carried out in Matlab® (MathWorks Inc, Natick, MA). Differences in the EEG indexes as a function of the experimental stages were assessed using the Friedman test, followed by a Tukey's honestly significant difference test. Statistical significance was accepted with $p < 0.05$.

Results

EEG signals at different propofol effect-site concentration presented the characteristic changes associated with increasing anaesthetic effect [12]. In all the frequency bands (except δ) there was a decrease in long-range connectivity and a reversal of the dominant direction of links during anaesthesia as compared with wakefulness (Supplementary Material, Figure S3). In agreement with previous work [8,24] we observed that Directed Coherence features in the α band were more sensitive to the level of anaesthesia, so focused on this range of frequencies (Figure 1). The strength of long-range links decreased at effect-site concentration 2 $mcg.ml^{-1}$ compared to wakefulness and then remained relatively constant with increasing propofol effect-site concentration, significantly distinguishing the awake state from deep anaesthesia at group level (p values less than 0.008 in all four pairwise comparisons). The strength of postero-anterior links decreased during anaesthesia compared to wakefulness, while the contribution of fronto-posterior connections became dominant. Consequently, $Dir_{P\rightarrow A}$ reversed with the onset of anaesthesia. A step effect, rather than a gradual change with increasing effect-site concentration, was also observable for $Dir_{P\rightarrow A}$ that distinguished the awake state from the different propofol effect-site concentrations ($p<0.006$). The connectivity networks estimated using the 10%, 30% or 50% of strongest connections exhibited very similar trends, indicating that the choice of threshold does not critically affect the results. In the following

we therefore only show results for the Directed Coherence networks obtained retaining the 30% strongest links.

With the exception of one patient who had normal hearing, the majority of patients presented with mild hearing loss at low frequencies and seven patients had moderate to severe hearing loss at high frequencies. However, a clear auditory middle latency response was evoked during wakefulness in all the subjects (with the exception of subject 5 where technical issues compromised middle latency response recordings during wakefulness).

Individual results are reported in Supplementary Material, while cohort averages of middle latency response power and latency, connectivity features, and BIS sub-parameters are shown in figures 2-4.

The amplitude of the evoked response was significantly reduced, and the latency of Nb wave progressively increased, with increasing propofol effect-site concentration (Figure 2). Middle latency response power and Nb latency significantly distinguished wakefulness from effect-site concentrations 3 and 4 mcg.ml^{-1} but not from effect-site concentration 2 mcg.ml^{-1} (p=0.23). However, it was not always possible to reliably identify the Nb peak, as the middle latency response evoked during anaesthesia was increasingly within the 95% critical values for the null distribution estimated from a bootstrap procedure as effect-site concentration increased (see Supplementary Material). The BIS sub-parameters behaved as previously reported [18] and both estimated BIS and DCindex distinguished wakefulness from the different anaesthetic effect-site concentrations (Figures 3 and 4, respectively).

In order to investigate whether the changes observed for the different EEG features were both consistent across subjects and across epochs of the same propofol effect-site concentration, Figure 5 shows changes across subjects for the middle latency response, estimated BIS and DCindex for the duration of the study. The middle latency response amplitude varied considerably across subjects and, as a result, values in the awake and effect-site concentration 2 mcg.ml^{-1} ranges broadly overlapped. Both estimated BIS and the DCindex showed a clear boundary between wakefulness and anaesthesia, although the estimated BIS exhibited a more gradual trend with increasing propofol

effect-site concentration. On the other hand, a step change at effect-site concentration 2 mcg.ml^{-1} and a near plateau for increasing propofol effect-site concentration characterized the DCindex. Table 1 shows how a linear support vector machine classifier is able to distinguish different stages in the experiment with different features as inputs. In the analysis of middle latency response performance only the amplitude was considered, as we could not reliably assess Nb latency in all the subjects. The linear support vector machine classifier trained on middle latency response power showed the poorest performance, with the percentage of correctly classified epochs lower than 80% for all the binary classifications. In particular, it often misclassified wakefulness as anaesthesia (Figure S7). Among the different EEG features, the DCindex showed the best classification performances with more than 90% correctly classified observations and very low misclassification rate. When the BIS and Directed Coherence parameters were combined, the performance improved above 93% for all the binary classifications, with an accuracy higher than 96% for the wakefulness vs anaesthesia classification (Table 1 column 5). Including the middle latency response variance did not further improve performance (Table 1 column 6). Table 2 shows how a linear support vector machine classifier is able to classify single subjects as either awake or anaesthetised based on different input parameters and gives an indication of the potential of the DCindex as a clinical monitor of anaesthesia. Directed Coherence performance at individual level was quite robust across subjects, with very high specificity and sensitivity in most cases. In order to test if a more complex classifier would improve performances, we also compared linear support vector machine classification with a non-linear classifier based on a multilayer neural network [25]. The linear support vector machine and neural network classifiers show remarkably similar performances (Table S2), indicating that the BIS and Directed Coherence features are linearly separable and the use of a more complex classifier does not improve the discrimination performances. A detailed description of how neural network classification was implemented and results are provided in Supplementary Material.

Discussion

Irrespective of its physiological interpretation, the DCindex step change identifies a clear boundary between wakefulness and anaesthesia, leading to very high classification performance, better than estimated BIS and middle latency response. This exploratory work shows the potential of the proposed method and goes beyond previous work on EEG connectivity measures for the assessment of adequacy of anaesthesia in two important points. First, we investigated changes in Directed Coherence during a slow induction of propofol anaesthesia in both cohort and individual subjects and epochs. The majority of previous studies have focused on average results across the cohort, ignoring the individual data, and have investigated other connectivity estimators than Directed Coherence. Directed Coherence has the advantage of giving a straightforward interpretation of connectivity in the frequency domain in terms of the normalized amount of EEG power transferred from one channel to another. Secondly, we compared Directed Coherence connectivity features with more established anaesthesia indexes in their ability to discriminate wakefulness from anaesthesia.

In order not to interfere with the natural fading of consciousness during the slow anaesthetic induction, we did not assess the responsiveness of patients, which might itself rouse the patients and disrupt the measurements. Rather, effect-site concentration was used to define the stages of anaesthesia, despite the potential limitations of pharmacokinetic models in predicting true effect-site concentration [26], so that a limitation of our study is that we do not have a 'gold standard' measure of consciousness. However, the accuracy of verbal assessment may be reduced when the study protocol involves auditory stimulation, because irrespective of the loudness of the stimuli, the insert headphones interfere with normal hearing. Other studies using a similar effect-site concentration regimen have identified an effect-site concentration around 2 mcg.ml^{-1} as the threshold for loss of behavioural responsiveness [12,13,24,26], though there may be some hysteresis in the pharmacodynamic response [26]. Further work is needed to establish the relationship between the

connectivity measures and clinical assessments of changes in consciousness below a propofol effect-site concentration of 2 mcg.ml^{-1}.

Directed Coherence has been applied in the study of different behavioural tasks [26], showing remarkable agreement with anatomical and neuroimaging evidence [19]. The decrease in strength of long-range Directed Coherence connectivity is consistent with reports of a disruption of large-scale information flow and a general impairment of brain network integration (with fronto-parietal connectivity particularly affected) in functional magnetic resonance imaging and transcranial magnetic stimulation studies of propofol anaesthesia [4,28,29]. Activity in the fronto-parietal associative network is also altered in other states of diminished consciousness such as vegetative states, coma or NREM sleep [30,31]. Our results support the important role of the fronto-parietal association cortices in the maintenance of consciousness and also support the hypothesis that the breakdown of information flow may affect the signalling between the sensory posterior areas and the associative frontal cortices that is essential for a conscious experience [29].

The observed switch in the direction of connectivity from wakefulness to anaesthesia is consistent with other studies investigating EEG directional connectivity during anaesthesia [6,7,8]. In contrast with our results, some studies have reported an impairment of fronto-posterior connectivity with loss of consciousness [9,10]. These conflicting findings are likely to result from the use of different estimators of connectivity that may quantify diverse effects. Partial Directed Coherence has also been investigated during propofol anaesthesia [7], with similar results to ours, although in our previous study on sleep we found that Partial Directed Coherence was less sensitive to changes in the level of consciousness than Directed Coherence [20].

The commercially available depth of anaesthesia indexes (BIS, M-Entropy, AEPindex, Narcotrend) exhibit graded changes with increasing anaesthetic dose, presented as a scalar index usually ranging

from 0 to 100 (the estimated BIS and middle latency response ranges in this work are different as we did not apply the proprietary weights to the different sub-parameters). Depth of anaesthesia indexes correlate strongly with the anaesthetic drug concentration in the body but may not reflect the level of consciousness of the patient that results from the complex balance of hypnosis, analgesia, and external stimulation [2,26,32]. On the other hand, the step transition of the DCindex that occurs at anaesthetic onset may more closely reflect the physiological mechanisms of anaesthetic-induced loss of consciousness [6]. In the clinical setting, such an 'on-off' response may be useful during anaesthetic onset, but potentially less useful during offset unless the DCindex switch becomes 'on' before the patient becomes responsive. Further studies are required to determine when the switchover occurs in relation to conscious responsiveness, especially on regaining consciousness. Further investigations could also determine if an abrupt transition in connectivity still occurs for effect-site concentration < 2 mcg.ml^{-1}. EEG-derived depth of anaesthesia monitors are now recommended in some areas of clinical practice with the specific purpose of reducing the risk of intraoperative awareness [33], yet the performances of these devices is limited [34,35]. Our findings suggest that Directed Coherence features may complement other depth of anaesthesia indexes, or multimodal cardo-respiratory variables [36], to improve consistency and performance.

Due to the design of the experimental protocol, the number of epochs available in wakefulness and anaesthesia was highly unbalanced (27 and 99 respectively). This may bias classifier performance towards a higher sensitivity to the detriment of specificity. In our study the sensitivity obtained with the DCindex is ideal (100%) in 9 out of 10 subjects, while in one subject the specificity is zero, because the number of observations in wakefulness is very low compared with anaesthesia (e.g. Table 2: in subject 3 with a DCindex specificity of zero, the observations in wakefulness are only two). Nonetheless, the average values of specificity are high (around 80% on average and 100% in 6 out of 10 subjects), indicating that despite the relatively low number of observations in wakefulness,

Directed Coherence shows promising performance that may improve if more wakefulness epochs are included.

Using the commercially available BIS monitor requires the application of a large strip of electrodes on the forehead of the patient. In this exploratory study, we decided not to compromise the integrity of the electrode cap and therefore to estimate the BIS parameters *a posteriori* from our frontal EEG recordings. However, the reproduction of BIS values is challenging as the algorithm is proprietary and the monitors apply a sophisticated artifact rejection procedure that maximizes BIS performance in the noisy environment of the surgical theatre [17]. For this study, we applied standard pre-processing steps, but the presence of residual artifacts may be a reason why, in the analysis of individual trends, the step change in Directed Coherence features was clearly observed in only 8 out of 10 subjects (Figure S4). However, our results clearly show the potential of DCindex to at least supplement BIS in assessing loss of consciousness. Future work should include an anaesthetic study where Directed Coherence estimation and BIS monitoring are performed simultaneously in order to more reliably compare their performances.

In this study Directed Coherence was estimated from successive EEG epochs of 60 s. Whether this is an optimal time resolution for a monitor of depth of anaesthesia is unknown, but in commercially available monitors the index values are typically updated every 30-60 s. The delay could be decreased in future applications by reducing the number of electrodes considered and therefore the time required for the calculation of the DCindex, which has the potential (on its own or combined with other indexes) for monitoring adequacy of anaesthesia.

In conclusion, the proposed new index of connectivity, that takes both the strength and direction of connectivity into account, gave promising results for the development of improved measures of depth of anaesthesia.

Declaration of interests

DCS has received equipment loans and / or honoraria from GE Healthcare, Aspect Medical, and Medical Device Management. He was specialist committee member for NICE DG6, and national moderator for the NAP5 project.

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Authors' contributions

GL: performed the EEG data collection and analysis, wrote the first draft of the manuscript.

SLB: obtained partial funding, supervised data analysis/research, revised the manuscript.

DCS: obtained ethical approval and partial funding, designed the anaesthetic protocol, revised the manuscript.

DMS: supervised data analysis/research, revised the manuscript.

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Table 1. Classification accuracy results. The percentage of correctly classified observations and corresponding number of observations tested (in brackets; number of 60 s epochs assessed across all 10 subjects) for each of the four binary classifications (rows) and for different combinations of EEG-derived parameters (columns). MLR = middle latency response amplitude, eBIS = estimated BIS, DCi = DCindex

	MLR	**eBIS**	**DCi**	**eBIS+DCi**	**eBIS+DCi+MLR**
Awake vs 2 mcg.ml^{-1}	61.8 (61)	89.2 (65)	90.2 (61)	96.7 (61)	91.8 (61)
Awake vs 3 mcg.ml^{-1}	73.3 (60)	85.7 (63)	95.0 (60)	96.7 (60)	93.3 (60)
Awake vs 4 mcg.ml^{-1}	73.3 (59)	87.3 (63)	94.9 (59)	93.2 (59)	87.9 (58)
Awake vs all anaesthesia	77.9 (154)	90.0 (131)	94.9 (126)	96.8 (126)	94.3 (124)

Table 2. Global ‘wakefulness' vs `anaesthesia' classification performances, based on a leave-one-out procedure, for all the subjects (SUB) using the support vector machine classifier trained on estimated BIS (eBIS), DCindex (DCi), and a combination of both (eBIS+DCi).

SUB	**Accuracy (%)**			**Specificity**			**Sensitivity**		
	eBIS	DCi	eBIS+DCi	eBIS	DCi	eBIS+DCi	eBIS	DCi	eBIS+DCi
1	78	93	93	0	0.67	0.67	1	1	1
2	92	100	100	0.50	1	1	1	1	1
3	90	80	80	1	0	0	0.87	1	1
4	92	92	100	1	0.67	1	0.89	1	1
5	100	83	092	1	0.67	1	1	0.89	0.89
6	100	100	100	1	1	1	1	1	1
7	81	100	100	1	1	1	0.75	1	1
8	82	100	100	0	1	1	1	1	1
9	92	100	100	0.67	1	1	1	1	1
10	93	100	100	1	1	1	0.90	1	1
mean	**90**	**95**	**95**	**0.72**	**0.80**	**0.87**	**0.94**	**0.99**	**0.99**

Legends for figures

Figure 1. Scalp topography of connectivity networks, averaged across all 10 subjects, plotted for the 10%, 30%, and 50% thresholds of strongest statistically significant directed coherence links. The first column (white dashed box) refers to wakefulness, while plots in the other columns (grey dashed box) indicate, from left to right, propofol effect-site concentrations of 2, 3 and 4 mcg.ml^{-1}. The upper row at each threshold represents the Grand Average across subjects of long-range connections, with the colour and thickness of arrows coding for the average strength of each link. The lower row indicates the average strength of postero-anterior (black) and antero-posterior (red) connections in the α band coded by the length and thickness of the arrows. Corresponding statistics are shown in Supplementary Material, Figure S4.

Figure 2. Change in auditory middle latency response features for increasing propofol effect-site concentrations: awake (white), 2 mcg.ml^{-1} (light grey), 3 mcg.ml^{-1} (dark grey), 4 mcg.ml^{-1} (black). Each bar represents the mean and standard error: n=10 at all points for power; for Nb latency, n=9 awake, 8 at 2 mcg.ml^{-1}, 7 at 3 mcg.ml^{-1}, and 6 at 4 mcg.ml^{-1}. * $p < 0.05$; ** $p < 0.01$.

Figure 3. Changes in BIS sub-parameters and estimated BIS for increasing propofol effect-site concentrations: awake (white), 2 mcg.ml^{-1} (light grey), 3 mcg.ml^{-1} (dark grey), 4 mcg.ml^{-1} (black). Each bar represents the mean and standard error (n=10) of the specific feature. * $p < 0.05$; ** $p < 0.01$.

Figure 4. Changes in directed coherence features for increasing propofol effect-site concentrations: awake (white), 2 mcg.ml^{-1} (light grey), 3 mcg.ml^{-1} (dark grey), 4 mcg.ml^{-1} (black). Each bar represents the mean and standard error (n=10) of the specific feature. $Dir_{P \to A}$ = relative direction of postero-anterior links. * $p < 0.05$; ** $p < 0.01$.

Figure 5. Middle latency response power (green), estimated BIS (blue) and DCindex (red) trends in wakefulness and at stable propofol effect-site concentrations. The plots represent average values (n=10) and 99% confidence intervals. Each time point represents a 60 s epoch.