Archives Italiennes de Biologie, 147: 51-57, 2009.

Bispectral Index correlates with regional cerebral blood flow during sleep in distinct cortical and subcortical structures in humans

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ABSTRACT

The relationship between the Bispectral Index (BIS), an EEG-based monitor of anesthesia, and brain activity is still unclear. This study aimed at investigating the relationship between changes in BIS values during natural sleep and regional cerebral blood flow (rCBF) variations, as measured by Positron Emission Tomography (PET). Data were obtained from six young, healthy, right-handed, male volunteers (20-30 years old) using the $H_2{}^{15}O$ infusion method. PET scans were performed both during waking and various stages of sleep. BIS values were monitored continuously and recorded during each PET scan. Positive correlations were detected between BIS and rCBF values in dorsolateral prefontal, parietal, anterior and posterior cingulate, precuneal, mesiofrontal, mesiotemporal and insular cortices. These areas belong to a frontoparietal network known to be related to awareness of self, conscious sensory perception, attention and memory. BIS values also positively correlated with activity in brainstem and thalami, both structures known to be involved in arousal and wakefulness. These results show that BIS changes associated with physiological sleep depth co-vary with the activity of specific cortical and subcortical areas. The latter are known to modulate arousal, which in turn allows sustained thalamo-cortical enhancement of activity in a specific frontoparietal network known to be related to the content of consciousness. Thus, although mainly derived from frontal EEG, BIS could represent a wider index of cerebral activity.

Key words

Bispectral Index (BIS) • Positron Emission Tomography (PET) • Regional cerebral blood flow (rCBF) • Sleep

Introduction

The Bispectral Index (BIS, Aspect Medical Systems, Newton, USA) (Johansen and Sebel, 2000) was developed to follow changes in brain activity induced by anesthetic agents, in order to monitor the depth of the hypnotic component of anesthesia. The BIS is a combination of time domain, frequency domain and high order spectral parameters extracted from electroencephalogram (EEG) signals (Rampil, 1998). This mixture of parameters was empirically derived from a large volume of clinical data that correlates to the behavioral assessment of sedation and hypnosis (Rampil, 1998). Because sleep and anesthesia have similar behavioral characteristics (Tung and Mendelson, 2004), albeit physiologically

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different, BIS has also been proposed to monitor sleep depth (Sleigh et al., 1999; Nicholson et al., 2001; Nieuwenhuijs et al., 2002; Tung et al., 2002; Benini et al., 2005; Nieuwenhuijs, 2006). Similarly to anesthesia, BIS values decrease with increasing sleep depth during slow wave sleep (Sleigh et al., 1999; Nieuwenhuijs et al., 2002). In order to gain a better understanding of the relationship between BIS and brain activity, we studied changes in regional cerebral blood flow (rCBF), as measured by Positron Emission Tomography (PET), during physiological sleep monitored with BIS and classical polysomnography.

Methods

Data were obtained from previous sleep studies on consolidation of memory (Peigneux et al., 2003; Peigneux et al., 2004) conducted in our center using the $H_2{}^{15}O$ infusion method (Maquet, 2000). All subjects were young, healthy, right-handed, male volunteers (n = 6; age range 20-30 years) who gave their written informed consent to participate in studies approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. Experiments were conducted in accordance with the Declaration of Helsinki. All subjects had regular sleep-wake habits for at least 3 months prior to the experiment. None had any medical, surgical or psychiatric history, nor was taking any medication. Each subject spent three consecutive nights in the PET scanner at usual sleep time. Polysomnography monitoring during the first two nights allowed to check for any sleep abnormality and accustomed participants to the experimental setting. Participants were selected for the third night if they could maintain 20 min of continuous stage 2, stages 3-4 of non-REM sleep and REM sleep during both habituation nights. During the third night, PET scans were performed both during various stages of sleep when polysomnography showed steady characteristic sleep patterns for at least 4 minutes and during waking (W) at rest with eyes closed in complete darkness. Time of the PET scan did not depend of BIS values. At least two waking, two stage 2, two stages 3-4 and three REM sleep scans were obtained in all subjects. In the present manuscript, we used 71 PET scans (17 during W, 14 during stage 2 sleep, 19 during slow wave sleep and 21 during REM sleep) obtained in 6 subjects. Sleep stages are present along the whole night but their intensity varies during the night. Stages 3-4 are more present at the beginning of the night while REM sleep occurs towards the end of the night. Therefore the order of the scan was not counterbalanced during subjects and we acquired first the stages 3-4 scans and then the REM sleep scans.

Polysomnography was recorded using a Synamp (Neuroscan, NeuroSoft Inc.K, Sterling, Virginia) system at 500 Hz or 1000 Hz, with a band width of 0.15-100 Hz EEG on (at least) C3-A2 and C4-A1. In all cases, vertical and horizontal electrooculograms, chin electromyographic derivation and chest electrocardiogram were recorded on bipolar montages. Sleep scoring followed standard international criteria (Rechtschaffen and Kales, 1968).

BIS electrodes (BIS Standard Sensor, Aspect Medical Systems, Newton, USA) were placed on the temple and on the centre of the forehead after a skin preparation with isopropyl alcohol, as recommended by the manufacturer. Leads were connected to the portable EEG monitor Aspect A-2000 (BIS XP, Aspect Medical Systems, Newton, USA). EEG was sampled at 256 Hz, and filtered using the classical high-frequency (70 Hz) and low-frequency (0.3 Hz) filters implemented into the A-2000 monitor. BIS values were monitored continuously. BIS value for each PET scan was the mean of BIS values recorded during the whole duration of the 90-seconds scan. BIS values were stable over that period and were corrected for the fact that they are derived from at least 15 seconds of preceding data. Differences between BIS values at wake and distinct sleep stages were statistically assessed with a permutation test and Bonferroni correction for multiple comparison ($p < 0.05$). A permutation test has a better accuracy than a t-test while only few data sample are available. Furthermore, a permutation test does not request the data to be normally distributed.

PET data were acquired on a Siemens CTI 951 R 16/31 scanner in 3D mode. A detailed description can be found elsewhere (Maquet, 2000; Peigneux et al., 2003; Peigneux et al., 2004). The subject's head was stabilized using a thermoplastic facemask (Truscan imaging, MA, USA) and a venous catheter was inserted in a left antebrachial vein. A transmission scan was acquired to perform measured attenuation correction. Regional CBF was estimated

Table I. - Mean, standard deviation and range of Bispectral Index (BIS) values during each physiological sleep stage observed in our volunteers. All sleep stage can be distinguished from each other (corrected $p < 0.05$) but stage 2 to REM sleep.

	Number of scans	BIS values	Range
Wake	17	94 ± 4	88-98
Stage 2	14	67 ± 12	61-87
Slow wave sleep	19	40 ± 6	26-49
REM	21	82 ± 10	64-97

during 90-seconds emission scans using automated, non-arousing, slow intravenous water ($H_2{}^{15}O$) infusion (6 mCi/222 MBq in 5 cc saline). The injection was done before starting the scan. $H_2{}^{15}O$ is distributed quickly in the body, in proportion to local blood flow and has an half-life of 123s. CBF measurements can thus be made on a timescale ranging from 40 s to 2 min after injection.

Data were reconstructed using a Hanning filter (cutoff frequency: 0.5 cycle/pixel) and corrected for attenuation and background activity.

PET data were analyzed using statistical parametric mapping (SPM5; Welcome Department of Cognitive Neurology, Institute of Neurology, London, UK). All PET scans were realigned and normalized to the standard stereotactic Montréal Neurological Institute space (Friston et al., 1995). Gaussian filtering was applied in the spatial domain using a smoothing kernel of 16 mm full width at half maximum. The correlation between BIS and rCBF values was estimated according to the general linear model at each voxel with BIS values as predictor of interest and subject as confounding factor, generating statistical parametric maps. The results were corrected for multiple comparisons and thresholded at a false discovery rate p-value < 0.05 (Genovese et al., 2002).

Results

Variations in BIS values consistently followed the different sleep stages (waking, stage 2 sleep, slow wave sleep and REM sleep). BIS decreased with increasing depth of sleep (from stage 2 to stage 4 of slow wave sleep), and increased during REM sleep. All sleep stages can be significantly distinguished from each other (Table I).

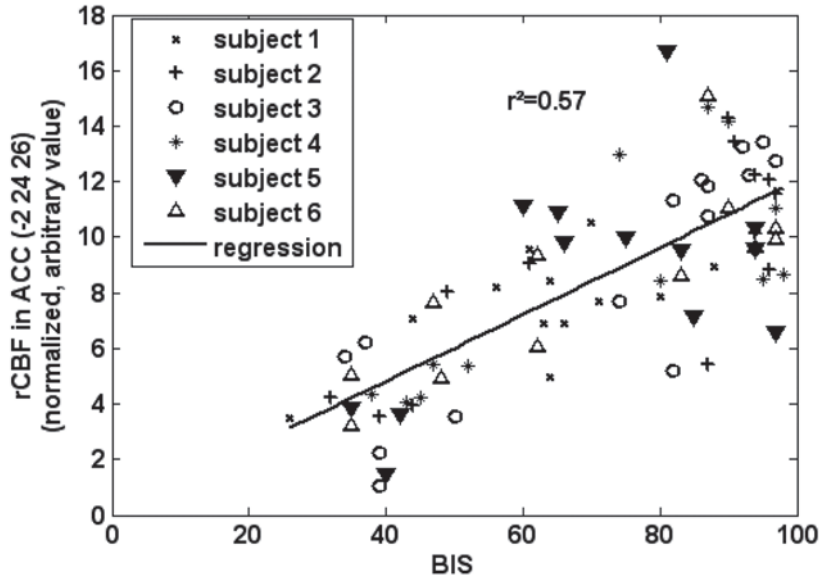

Fig. 1. - Scatter plot of regional cerebral blood flow (rCBF) in the anterior cingulate cortex (ACC) against Bispectral Index (BIS) values monitored during the different stages of natural sleep. The regression line between rCBF and BIS is also plotted with r^2 value.

Positive correlations were detected between rCBF and BIS values (Fig. 1) (Table II) in dorsolateral prefrontal (DLPFC), parietal (PC), anterior and posterior cingulate (ACC and PCC), precuneal (Pcu), mesiofrontal (MFC), mesiotemporal (MT) and insulae (Ins) cortices, as well as in both thalami (T) and in brainstem (BS) (Fig. 2).

Discussion

The main interest of BIS for the anesthesiologists is to monitor the loss of consciousness induced by pharmacological agents. Consciousness is often referred to only one of the two main components of consciousness: the level of consciousness (i.e., arousal), and not to the other: the content of

Table II. - Stereotaxic coordinates of peak voxels in areas that showed a positive correlation between Bispectral Index (BIS) values and regional cerebral blood flow during natural sleep.

Identified region*	x	y	z	Z value	FDR-corrected P†
DLPFC	-30	40	36	3.97	< 0.001
Parietal cortices	66	-44	40	4.89	< 0.001
ACC	-2	24	26	7.60	< 0.001
PCC	-6	-32	42	5.50	< 0.001
Precuneal cortex	-2	-50	36	3.54	0.008
MFC	2	56	6	5.35	< 0.001
MT	-28	28	-30	5.70	< 0.001
Insulae	-56	16	-4	7.04	< 0.001
Thalami	26	8	-4	6.88	< 0.001
Brainstem	-6	-24	-28	3.12	0.001

* Dorsolateral prefrontal (DLPFC), anterior and posterior cingulate (ACC and PCC), mesiofrontal (MFC), mesiotemporal (MT) cortices.
† FDR = False discovery rate.

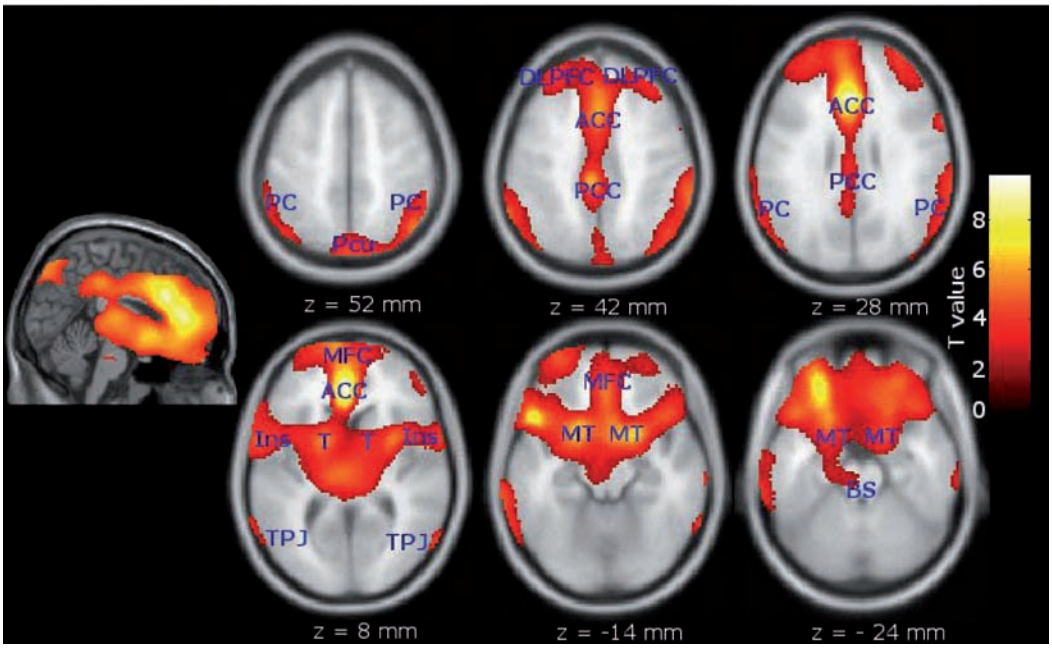

Fig. 2. - Brain areas showing positive correlation between Bispectral Index (BIS) and regional cerebral blood flow (rCBF) during natural sleep (transversal slices): dorsolateral prefrontal cortices (DLPFC), parietal cortices (PC), anterior and posterior cingulate cortices (ACC and PCC), the precuneal cortex (Pcu), the mesofrontal cortices (MFC), the thalami (T), the mesiotemporal cortices (MT), the insulae (Ins) and the brainstem (BS). A sagittal slice is also added to better evidence the medial cortical areas, as well as the thalamic and brainstem involvement.

consciousness (i.e., awareness). During anesthesia, arousal is pharmacologically decreased and hence are awareness and BIS values. Here we show that during physiological sleep BIS values changed with sleep stages but the range of BIS values overlapped between REM and sleep stage 2. BIS values decreased in non-REM sleep with depth of sleep and increased in REM sleep. These results are in accordance with previous studies on BIS and sleep which show that if BIS values can be significantly differentiate between sleep stages but the overlap among BIS values preclude the use of BIS as a sleep monitor (Nieuwenhuijs et al., 2002; Nieuwenhuijs, 2006). Despite the fact that BIS calculation is derived from frontal EEG activity only, in our six subjects, BIS correlated positively with activity in the brainstem and the thalami, both structures involved in arousal and wakefulness. To the best of our knowledge, former studies with EEG-based monitors of anesthesia – either BIS or spectral entropy (Viertio-Oja et al., 2004) – and anesthesic agents, did not report such a correlation (Kaisti et al., 2002; Maksimow et al., 2005). This can be due to the wider range of values reached by BIS during physiological sleep. While we have a continuum of BIS values from 100 to 30, anesthesic studies present a gap between the awake state and the first anesthesiological stage. BIS drops directly from 100 to near 40 and entropy falls from around 70 to near 40 (based on data from Kaisti et al., 2002 and Maksimow et al., 2005 respectively).

In turn, brainstem and thalami activity allowed sustained thalamo-cortical activity in proportion with BIS in a series of brain areas forming a frontoparietal network known to be related to awareness (Laureys, 2005) and to be the most active in resting non-stimulated conditions (Gusnard and Raichle, 2001). These areas are involved in attention (Fernandez-Duque and Posner, 2001), memory (Collette and Van der Linden, 2002) and conscious sensory perception (Boly et al., 2007). Decreased activity in this frontoparietal network has been acknowledged in previous studies in the vegetative state (Laureys, 2005) (i.e., absence of awareness with preserved wakefulness) and in states of decreased arousal such as general anesthesia (Alkire and Miller, 2005) and sleep monitored with polysomnography (Maquet et al., 1997). The network activity decreases while physiological sleep becomes deeper and return to near waking value in REM sleep (Maquet et al., 1997). A similar decrease in the activity of a frontoparietal network has been observed during anesthesia monitored with spectral entropy (Maksimow et al., 2005) but not in a former study on BIS and anesthesic agents (Kaisti et al., 2002), which found significant correlations in parts of the network only. This may also be due to differences in the range of explored BIS values, as explained above.

During stage 2 and REM sleep, the frontoparietal activity may form a breeding ground for the development of cognitive representation, which is distinctive of the content of consciousness. In that case, it can be seen as a network whose activity sustains an altered state of consciousness during sleep, which is dreaming (Hobson, 2005). These stages were included in our analysis, but are not encountered during anesthesia. This may be another explanation for the differences observed between sleep and anesthesia regarding brain areas whose activity co-vary with BIS.

The parameters involved in BIS calculation cover a wide range of measures that reflect global brain activity. The main parameters entering the BIS algorithm are β activity, burst suppression ratio (BSR), quasi-isoelectric activity (QUAZI) and synchronized fast slow activity (SFS) (Rampil, 1998). SFS calculation is based on the bispectral analysis of the EEG, which quantifies phase relationships between sinusoidal components of the EEG. The predominance of each sub-parameter in BIS calculation as a function of BIS value is the following: β activity for BIS between 100 and 80, SFS for BIS between 80 and 50, that is in the range of BIS values observed here, QUAZI for BIS between 50 and 30, and BSR for BIS between 30 and 0. Looking at the individual relationships between each BIS component and rCBF could allow going further into the understanding of the relationship between BIS and regional brain activity.

Limitations of the present study include the limited number of subject and the sampling of sleep stages. Due to the limited number of subject, this analysis relies on a fixed-effect model. In consequence, the results pertain only to the sampled population. The results should be extended to the general population with caution. Sleep stages 3-4 were mostly acquired at the beginning of the night while REM sleep stages were mostly sampled at the end of the night. If this does not change the results of the correlation

between BIS values and rCBF, it could influence the mean BIS values of the different sleep stages as they could change during the night (Nieuwenhuijs, 2006).

We conclude that, although mainly derived from frontal EEG, BIS could be more than a simple measure of frontal activity. In our study, BIS correlated with physiological sleep depth and co-varied with the activity in specific networks involved in the content of consciousness and with the activity in deep brain structures involved in arousal.

Acknowledgements

The author would like to thank the anonymous reviewers for their comments on a previous version of the paper. This work was supported by the Fonds National de la Recherche Scientifique de Belgique (FNRS), the Fondation Médicale Reine Elisabethe, the Mind Science Foundation (Texas, USA), the Action de Recherches Concertées de la Communauté française de Belgique (ARC), the European Funds Discos and Mindbridge. M.B, Q.N., C.P., P.M. and S.L. are respectively Research Fellow, Postdoctoral Researcher, Research Associate, Research Director and Senior Research Associate (FNRS).

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