Directional Information Flows between Brain Hemispheres during Presleep Wake and Early Sleep Stages

Mario Bertini[1], Michele Ferrara[1,2], Luigi De Gennaro[1], Giuseppe Curcio[1,3], Fabio Moroni[1], Fabrizio Vecchio[4,5], Marco De Gasperis[5], Paolo Maria Rossini[3,4,6] and Claudio Babiloni[4,5,6]

[1]Dipartimento di Psicologia, Università degli Studi di Roma "La Sapienza," Roma, Italy, [2]Dipartimento di Medicina Interna e Sanità Pubblica, Università di L'Aquila, L'Aquila, Italy, [3]Clinica Neurologica, Università di Roma "Campus Bio-medico," Roma, Italy, [4]AFaR, Dip. Neuroscienze, Ospedale San Giovanni Calibita Fatebenefratelli, Roma, Italy, [5]Dipartimento di Fisiologia Umana e Farmacologia, Università di Roma "La Sapienza," Roma, Italy and [6]IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

Neuroscientists' efforts to better understand the underlying processes of human consciousness are growing in a variety of multidisciplinary approaches. Relevant within these are the studies aimed at exploring the physiological substratum of the propagation and reduction of cerebral—namely, corticocortical—communication flows. However, the preferential direction of the information flow between brain hemispheres is as yet largely unknown. It is the aim of the present research to study the communication flows between brain hemispheres, their directionality, and their regional variations across wake–sleep states. A second aim is to investigate the possibility of an association between different brain rhythms and different preferred directions of the information flow. Scalp electroencephalograms (EEGs) were recorded in 10 normal volunteers from wakefulness to early sleep stages (viz., resting wakefulness, sleep stages 2 and 4, and rapid eye movement [REM] of the first sleep cycle). EEG rhythms of interest were delta (1–4 Hz), theta (5–7 Hz), alpha (8–11 Hz), sigma (12–15 Hz), and beta (16–30 Hz). The direction of the interhemispheric information flow was evaluated by computing directed transformation function from these EEG rhythms. Interhemispheric directional flows varied as a function of the state of consciousness (wake and early sleep stages) and in relation to different cerebral areas. Across wake to sleep states, we found that delta and beta rhythms convey interhemispheric signals with opposite directions: preferred right to left hemisphere direction for delta and left to right for beta rhythms. A log correlation confirmed that the trend of low to high EEG frequencies—traditionally associated with an increasing state of vigilance—was significantly related to the direction of the communication flow from the left to right hemisphere. This evidence might open the way for a variety of research lines on different psychophysiological and pathological conditions.

Keywords: cerebral hemispheres, corpus callosum, quantitative electroencephalography (qEEG), wake–sleep transition

Introduction

In a growing effort to explore the complex problem of human consciousness, studies of intra- and interhemispheric connectivity in the brain have been central to a variety of approaches. Recently, it has been proposed that consciousness depends critically not so much on firing rates, synchronization at specific frequency bands, or sensory input per se, but rather on the brain's ability to integrate information (Tononi 2005). Of interest, in this respect, are studies on interhemispheric and interareal broadband coherence in electroencephalogram (EEG) during sleep (Nielsen et al. 1990; Guevara et al. 1995; Achermann and Borbely 1998), and, in particular, the studies on

the propagation and reduction of information flows between cortical areas and between brain hemispheres (Berlucchi 1965; Bertini et al. 2004; Massimini et al. 2004, 2005). In a pioneering study, spontaneous neural activity was recorded in animals across wake–sleep stages by macroelectrodes placed in the splenium (posterior aspect) and genu (anterior aspect) of the corpus callosum (Berlucchi 1965). This activity declined after sleep onset, and a further drop was observed after the beginning of rapid eye movement (REM) sleep. These results suggested a functional modulation of transcallosal, bidirectional impulse transmission between the cerebral hemispheres across wake–sleep stages.

Callosal activity along the wake–sleep cycle has not been directly recorded in humans, due to intrinsic methodological limitations of intracerebral EEG techniques. A suitable approach was recently employed using paired-pulse transcranial magnetic stimulation of the 2 primary motor cortices (Bertini et al. 2004). This approach revealed a reduction of transcallosal inhibition between the 2 primary motor areas across sleep stages, which culminated in the last REM sleep of the night. In particular, the decrease in transcallosal inhibition was stronger from right to left hemisphere than from left to right hemisphere. It was concluded that the callosal function between the 2 primary motor cortices declines across the wake–sleep stages with interhemispheric preferred directionality. Recently, Massimini et al. (2004) investigated the neural synchronization mechanisms by which the callosal function and its directionality might be modulated during the wake–sleep stages. By analyzing the EEG rhythms representing the sequence of depolarization and hyperpolarization of the cortical neurons generating the scalp potentials, they showed that slow sleep EEG oscillations are traveling waves that scan the human cerebral cortex with a cycle of up to once per second. Each slow EEG oscillation has an intra- and interhemispheric direction of propagation varying from one cycle to the next. It has also been shown that slow EEG oscillations originate more frequently at anterior cortical regions and propagate in an anteroposterior and laterolateral direction, as an effect of corticocortical connections (Steriade at al. 1993). Propagation can be disrupted by disconnecting intracortical pathways through surgical and pharmacological manipulations (Amzica and Steriade 1995). The small delay differences observed for the interhemispheric propagation of the slow EEG oscillations are due to the high density of homotopic transcallosal fibers (Jacobson and Trojanowsky 1975). More recently, EEG potentials have been directly evoked by transcranial magnetic stimulation of the premotor cortex during wakefulness and early sleep stages (stages 3/4, early in

the night) (Massimini et al. 2005). Before sleep, activation of the premotor cortex largely propagated intra- and interhemispherically. During early nonrapid eye movement (NREM) sleep stages, cortical activation induced by transcranial magnetic stimulation rapidly extinguished and showed a limited intra- and interhemispheric propagation.

All these studies provide information on the propagation and decline of information flows within and between hemispheres; particularly, the work by Massimini et al. (2005) supports the idea that the decline of effective connectivity may be an important contributing factor in the fading of human consciousness. To date, however, there is little knowledge on the dynamics of information exchanges between hemispheres. Therefore, to bridge this gap, it seems relevant, as a first step, to study the directionality of the information flows between hemispheres. Consequently, the main aim of the present research was to investigate the directionality of the interhemispheric flows of information and their changes as a function of the cortical areas and of the physiological state (i.e., presleep wake vs. sleep stages of the first sleep cycle). A further and more ambitious goal was to evaluate whether there is any preferential direction of the interhemispheric information flows related to or depending upon the different EEG frequency bands.

The direction of the interhemispheric information flows was evaluated by computing the directed transformation function (DTF) of EEG rhythms (Kaminski and Blinowska 1991; Kaminski et al. 1997; Korzeniewska et al. 1997; Mima et al. 2000; Babiloni C, Babiloni F, et al. 2004; Babiloni, Vecchio, et al. 2004). In recent years, the DTF method has shown that the presleep period is characterized by a parietooccipital to frontal direction of the cortical information flow, whereas the opposite holds true at sleep onset (De Gennaro et al. 2004). After selective slow-wave sleep deprivation, the frontal to parietooccipital direction shows up in the presleep period, possibly due to sleep pressure (De Gennaro et al. 2005).

Materials and Methods

Subjects
Ten male volunteers (mean age = 23.3 years; standard error = 0.58; range = 20-26 years) were selected from a university student population to participate in the present study. All subjects were right-handed, as assessed by a lateral preference questionnaire (Salmaso and Longoni 1985) (scores >0.70) and, based on a clinical interview, did not suffer from epilepsy or any other neurological, psychiatric, or serious medical condition. Further requirements for inclusion were normal sleep duration and schedule, no daytime nap habits, no excessive daytime sleepiness, and no other sleep disorder, as assessed by a 1-week sleep log. The protocol of the study was approved by the local Institutional Ethical Committee and the subjects gave their written informed consent, according to the Declaration of Helsinki.

Participants were required to avoid napping throughout the experiment. An actigraph (AMI Mini motion logger) measured wrist activity every 30 s from the nondominant hand and distinguished sleep from wakefulness with a high degree of accuracy (e.g., Cole et al. 1992). Compliance was controlled by checking the wrist activity data monitored by the actigraph.

EEG Recordings
A VEGA 24 polygraph (Esaote Biomedica, Firenze, Italy) was used for polygraphic recordings. EEG recordings started at about 11:30 PM and ended after 7.5 h of accumulated sleep.

EEG signals were high pass filtered with a time constant of 0.3 s and low pass filtered at 30 Hz (sampling rate of 128 Hz). EEG electrodes were placed at 19 sites of the international 10-20 system and were referenced to linked earlobes (electrode impedance lower than 5 kΩ). Standard electromyographic and electrooculographic derivations were used to visually score sleep stages in 20-s epochs, according to standard criteria (Rechtschaffen and Kales 1968).

Preliminary EEG Data Analysis
The EEG epochs with ocular, muscular, and other types of artifact were preliminarily identified by 2 independent experimenters. Artifact-free EEG data were staged and selected for further analysis. In particular, a wakefulness EEG interval lasting 2 min (closed eye condition) served as a presleep period. Sleep EEG intervals of interest for the present study were 2-min EEG segments relative to the beginning of each sleep stage (first stage 2, first stage 4, and first REM stage).

EEG Power Density Spectrum
For each stage of interest (wake, stage 2, stage 4, and REM), artifact-free EEG epochs were re-referenced to a common average and were analyzed by a standard Fast Fourier Transform algorithm (Matlab 6.0; Mathworks Inc., Natrick, MA) at F3, F4, C3, C4, P3, and P4 electrode sites. Frequency resolution was of 1 Hz (no phase shift). EEG bands of interest were delta (1-4), theta (5-7 Hz), alpha (8-11 Hz), sigma (12-15 Hz), and beta (16-28 Hz). The analysis of the EEG power density spectra across the presleep and early sleep stages allowed the evaluation of the quality of the EEG data as an input for the DTF analysis.

"Direction" of the Functional Connectivity Estimated by the Mvar Model
Before computing the DTF, the EEG data (linked earlobes reference) were preliminarily normalized by subtracting the mean value and dividing by the variance, according to standardized rules by Kaminski and Blinowska (1991). An important step of the DTF method was the computation of the so-called Multivariate autoregressive (Mvar) model (Kaminski and Blinowska 1991; Kaminski et al. 1997; Korzeniewska et al. 1997; Blinowska et al. 2004; Kus et al. 2004). EEG data at 9 electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4) were simultaneously given as an input to the Mvar model toward the computation of the directional information flux among all the pair combinations of these electrodes. This model was used to estimate the "direction" of the information flow between the left and right hemispheres (F3-F4, C3-C4, and P3-P4). In nonmathematical terms, coefficients of the Mvar model fitted to the data can be interpreted as causal influence of signal recorded over electrode A on signal recorded on electrode B or information flow between electrodes A and B. A direction of information flow from A to B is stated when that case is statistically more probable than a directionality from B to A. This Mvar model has already been used successfully to estimate the direction of the corticocortical and corticomuscular information flow (Mima et al. 2001; Babiloni C, Babiloni F, et al. 2004; Babiloni, Vecchio, et al. 2004).

The mathematical core of the Mvar algorithm used in this work is based on the ARfit programs running on the platform Matlab 6.0. The model order was 7, as estimated by the Akaike criterion suggested in previous DTF studies (Kaminski and Blinowska 1991; Kaminski et al. 1997; Korzeniewska et al. 1997). The goodness of fit was evaluated by visual inspection of the values of noise matrix V of the Mvar model.

The Mvar model is defined as,

$$\sum_{j=0}^{p} A_j X_{t-j} = E_t,$$

where X_t is the L-dimensional vector representing the L-channel signal at time t; E_t is white noise; A_j is the $L \times L$ matrix of the model coefficients; and p is the number of time points considered in the model. From the identified coefficients of the model A_j, spectral properties of the signals can be obtained by the following z-transformation of the above equation:

$$X(z) = H(z)E(z),$$

where $H(z)$ is a transfer function of the system

$$H(z) = \left(\sum_{j=0}^{p} A_j z^{-j} \right)^{-1},$$

and

$$z^{(-j)} = \exp(-2\pi ijf\,dt),$$

where f is frequency and dt is the time step.

Since the transfer function $H(f)$ is not a symmetric matrix, the information transmission from the jth to the ith channel is different from that from the ith to the jth channel. The DTF from the jth channel to the ith channel is defined as the square of the element of $H(f)$ divided by the squared sum of all the elements of the relevant row:

$$DTF_{ij}(f) = \frac{|H_{ij}|^2}{\sum_{m=1}^{L}|H_{im}(f)|^2}.$$

A substantial difference between $DTF(f)_{ij}$ and $DTF(f)_{ji}$ may suggest an asymmetric information flow from electrode i to electrode j. When $DTF(f)_{ij}$ is greater in magnitude than $DTF(f)_{ji}$, the direction of the information flow is from electrode j to electrode i. On the other hand, the direction of the information flow is from electrode i to electrode j when $DTF(f)_{ji}$ is greater in magnitude than $DTF(f)_{ij}$. Of note, the normalization of the DTF depends on the denominator of the previous formula.

To simplify the visualization and statistical analysis of the DTF results, the directional flow of information was given as "left to right" minus "right to left" direction of the DTF. Positive values of this subtraction (DTFdiff values higher than zero) showed the predominance of the left to right direction over the right to left direction of the DTF. On the other hand, negative values of this subtraction (DTFdiff values lower than zero) showed the predominance of the right to left direction over the left to right direction of the DTF.

Of note, DTFdiff values could be both positive (prevailing left to right direction of the DTF) and negative (prevailing right to left direction of the DTF) at different frequency bins of a given band. To disentangle the positive (maximum) and negative (minimum) values of the DTFdiff for each frequency band, the following procedure was followed. For each frequency band, the most positive (or less negative) DTFdiff value was called the "max DTFdiff" and the most negative (or less positive) DTFdiff value was called the "min DTFdiff." The max DTFdiff reflected the strongest trend toward left to right direction of the DTF, whereas the min DTFdiff reflected the strongest trend toward right to left direction of the DTF. They were considered separately in the final statistical analysis.

The fact that the DTF analysis was done on the difference between the 2 reciprocal DTF directions should require a careful interpretation of the results. A zero value of such a difference meant equivalence of the 2 opposite DTF directions within the 2 min, namely, that the DTF directions were equally strong or equally weak or both equal to zero in the 2 min taken into account. It should be emphasized that this equivalence is true for the whole period of 2 min but not necessarily for subperiods within the 2 min. At this preliminary stage of the study, we preferred evaluating the DTF values for the entire 2-min period because the DTF values for shorter periods are supposedly less reliable from the statistical point of view (Babiloni C, Babiloni F, et al. 2004; Babiloni, Vecchio, et al. 2004).

Statistical Analysis

Statistical comparisons were performed by repeated-measure analyses of variance (ANOVAs). The Mauchley test evaluated the sphericity assumption, and correction of the degrees of freedom was carried out using the Greenhouse-Geisser procedure. Subjects' age and lateralization of the EEG power density at the frontal, central, and parietal electrodes were used as covariates in the statistical design. The Duncan test was used for post hoc comparisons ($P < 0.05$).

Statistical analysis of the DTFdiff values (direction of the information flow) was performed using a 2-way ANOVA including the factors stage (wakefulness, sleep stage 2, sleep stage 4, and REM sleep) and band (delta, theta, alpha/sigma, and beta). This ANOVA was performed twice. In the first analysis, the focus was on the maximum values of the DTFdiff, concentrating our attention on the left to right direction of the DTF. In the second analysis, the focus was on the minimum values of the DTFdiff, concentrating on the right to left direction of the DTF.

Results

Power Density Spectra of EEG across Wake–Sleep Stages

Figure 1 plots the grand average ($N = 10$) of the EEG power density spectra for the electrodes of interest (F3, F4, C3, C4, P3, and P4) across the wake-to-sleep transition. These spectra depicted the typical increase of delta, theta, and sigma power during NREM sleep stages as compared with wakefulness and REM sleep stages (e.g., Finelli et al. 2001). Furthermore, there was a clear decrease of alpha and beta power in the NREM stages with respect to the wakefulness stage.

Interhemispheric DTF of EEG Waves across Wake–Sleep Stages

Figure 2 shows the grand average ($N = 10$) of the interhemispheric DTF values for the frontal (F3-F4), central (C3-C4), and parietal (P3-P4) electrode pairs. These values particularly referred to the DTF difference between left to right and right to left directions (i.e., DTFdiff) across the subjects. The values are low in magnitude (around 0.1) as expected by the fact that they represent the difference between the absolute DTF values of the opposite DTF directions. To corroborate the statistical meaning of this DTF result, the same preponderant DTF directions were observed in the large majority of the individual subjects.

The first important item of information provided by Figure 2 is the evident increasing trend of left to right preferred direction in relation to the increasing frequency of the EEG waves in the parietal area. EEG frequencies showed preponderant right to left DTF directional flows at low delta rhythms. The right to left DTF flow decreased as EEG frequencies increased and showed a brisk inversion toward left to right DTF direction at theta rhythms. The left to right direction of DTFdiff values markedly increased up to alpha rhythms and then remained in the left to right direction along the entire beta band.

To better clarify the relationships between DTF direction and EEG frequencies, a nonparametric correlation (Spearman test, $P < 0.05$) and nonlinear correlations (evaluating the coefficient of determination for exponential and logarithmic trends) were computed. Table 1 reports the results of these correlation analyses for the parietal electrode pairs. In general, r^2 values for logarithmic analysis showed the maximum values for wake, stage 2, and REM stage.

In the frontal and central areas, the 2 DTF directions were quite balanced for all frequencies (i.e., DTFdiff close to zero). As an exception, sleep stage 2 showed a dominant right to left DTF direction on frontal electrode pairs (i.e., negative DTFdiff). In contrast, left to right DTF direction generally prevailed in the parietal areas (i.e., positive DTFdiff, see Fig. 2).

To better disentangle the left to right and right to left DTF directions within each band, the maximum and minimum values of the DTFdiff were used as data for separate ANOVAs. For each frequency band, the ANOVA design included the factors stage (wakefulness, sleep: stage 2, stage 4, and REM) and scalp site (frontal, F3-F4; central, C3-C4; and parietal, P3-P4). The analysis of the max DTFdiff values (emphasizing the left to right DTF direction) showed main effects of the factor stage for the sigma ($F_{3,27} = 3.82$; $P = 0.02$) and beta ($F_{3,27} = 3.45$; $P = 0.03$) bands. Left to right DTF direction was more predominant during wakefulness than stage 2 sleep for the sigma band ($P < 0.004$) and during wakefulness versus sleep stages 2 and 4 for the beta
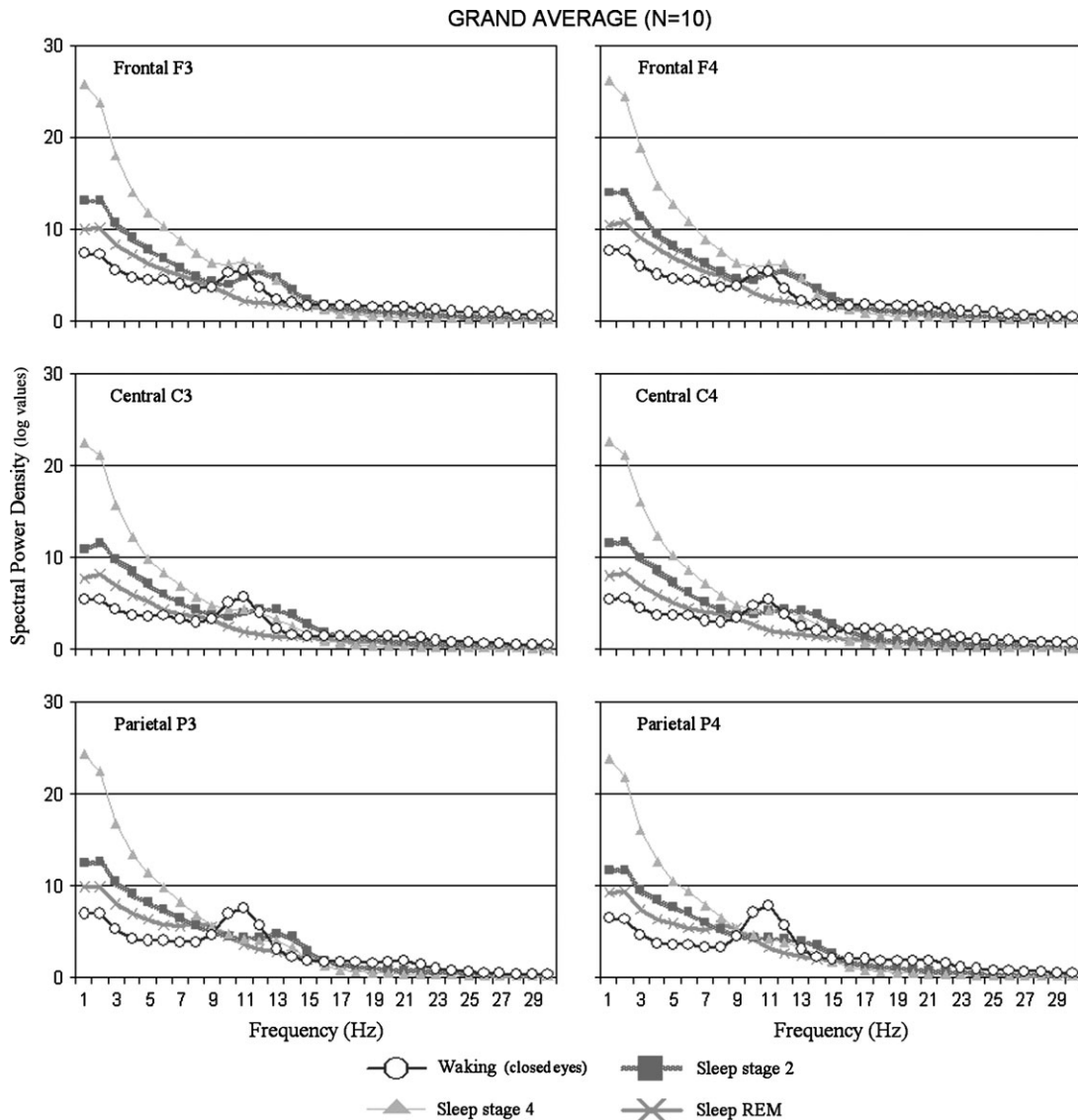
GRAND AVERAGE (N=10)

Figure 1. Grand average ($N = 10$) of the EEG power density spectra for the electrodes of interest (F3, F4, C3, C4, P3, and P4) across the wake–early sleep stages. These spectra depicted the typical increase of delta, theta, and sigma power during NREM sleep stages as compared with wakefulness and REM sleep stages.

band ($P < 0.01$ to $P < 0.02$). Furthermore, a close-to-significance interaction was observed between the factors scalp site and stage for the beta band ($F_{6,54} = 2.35$; $P = 0.06$). Post hoc tests showed that left to right DTF direction for the beta band in parietal areas was stronger in wakefulness than in any early sleep stages ($P < 0.004$ to $P < 0.0002$). Moreover, max DTFdiff values pointed to main effects of the scalp site factor for the theta ($F_{2,18} = 12.61$; $P = 0.0006$), alpha ($F_{2,18} = 14.56$; $P = 0.0001$), sigma ($F_{2,18} = 26.65$; $P = 0.000005$), and beta ($F_{2,18} = 30.22$; $P = 0.000001$) bands. For all bands, left to right DTF direction was higher in parietal than central and frontal areas ($P < 0.04$ to $P < 0.007$).

The above results were substantially confirmed by the ANOVA on the min DTFdiff values (main effects of the scalp site factor for the theta, alpha, sigma, and beta bands; $P < 0.003$ to $P < 0.0000006$). As a peculiar contribution of the ANOVA of the min DTFdiff values (i.e., negative DTFdiff values), a significant interaction was shown between the factors scalp site and

stage for the delta band ($F_{6,54} = 3.16$; $P = 0.01$). Post hoc tests showed that in parietal areas, the right to left DTF direction was predominant during wakefulness than any early sleep stages ($P < 0.03$ to $P < 0.01$). In frontal areas, the right to left DTF direction was instead lower during wakefulness than sleep stage 4 ($P < 0.04$). The mentioned statistical effects of the ANOVAs are illustrated in the right and left sides of Figure 3. The figure depicts maximum and minimum mean DTFdiff values, separately.

Measurements of DTFdiff in the delta and beta bands for individual subjects are reported in Table 2. Most subjects showed DTFdiff values in agreement with the group data. In 7 out of 10 subjects, right to left DTF direction of the parietal delta band was higher in magnitude during wakefulness than early sleep stages. In 6 out of 10 subjects, left to right DTF direction of the parietal beta band was higher in magnitude during wakefulness than early sleep stages. In 8 out of 10 subjects, right to left DTF direction of the frontal delta band was lower in magnitude during wakefulness than early sleep stages.
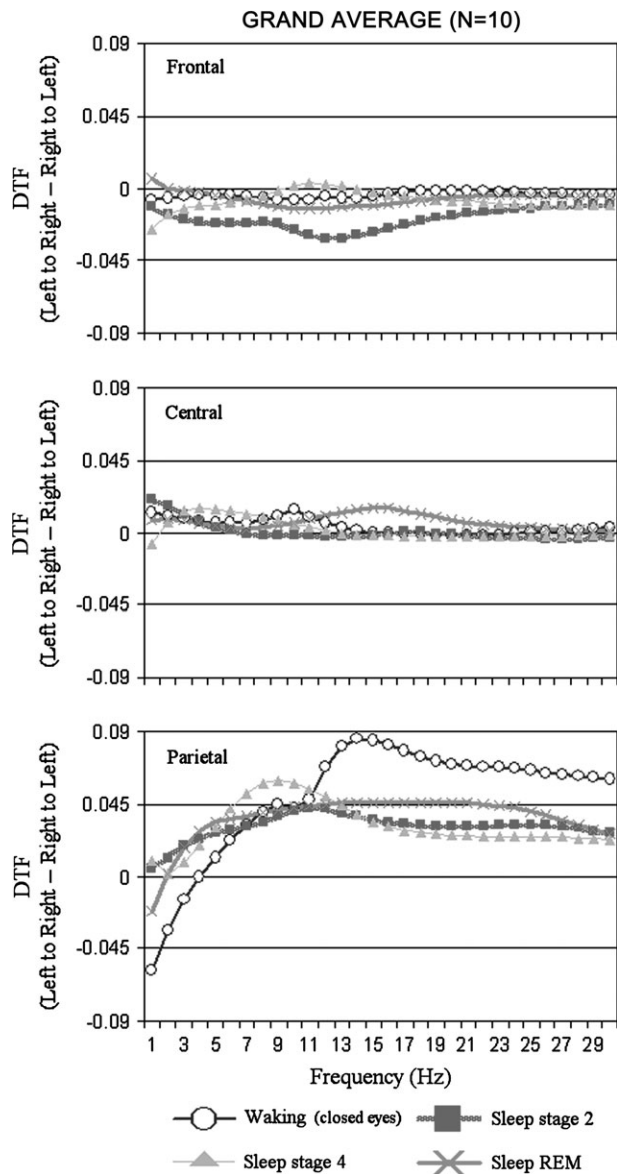
Figure 2. Grand average ($N = 10$) of the interhemispheric DTF values for the frontal (F3–F4), central (C3–C4), and parietal (P3–P4) electrode pairs. These values refer to the DTF difference between left to right and right to left directions (i.e., DTFdiff). The DTFdiff values were illustrated for all EEG frequencies of interest.

Figure 3. Grand average ($N = 10$) of the maximum and minimum means ($\pm$standard errors) of the DTFdiff values for the delta and beta bands (see Methods for further details). Max DTFdiff values indexed left to right direction of the DTF (most positive DTF values). Min DTFdiff values indexed right to left direction of the DTF (most negative DTF values). The means illustrate the results of 2 statistically significant ($P < 0.05$) 2-way ANOVA interactions. The ANOVA included the factors scalp site and stage for each band.

Table 1

Results of the correlation analysis of DTFdiff values across all frequency bins for parietal electrode pairs during wake, stage 2, stage 4, and REM stage

		Wake	Stage 2	Stage 4	REM
Spearman	p	0.000939	0.392086	0.098683	0.113111
	r^2	0.318678	0.025368	0.091214	0.084287
Log	r^2	0.8572	0.5194	0.0005	0.6064
Exp	r^2	0.5348	0.1769	0.0431	0.244

A nonparametric correlation was computed with the r^2 values of the Spearman test ($P < 0.05$). Furthermore, nonlinear correlations were computed evaluating the coefficient of determination r^2 for exponential and logarithmic trends.

Control Analyses

Two control analyses were done. The first included all recorded (i.e., 19) channels as an input to the Mvar model because interhemispheric f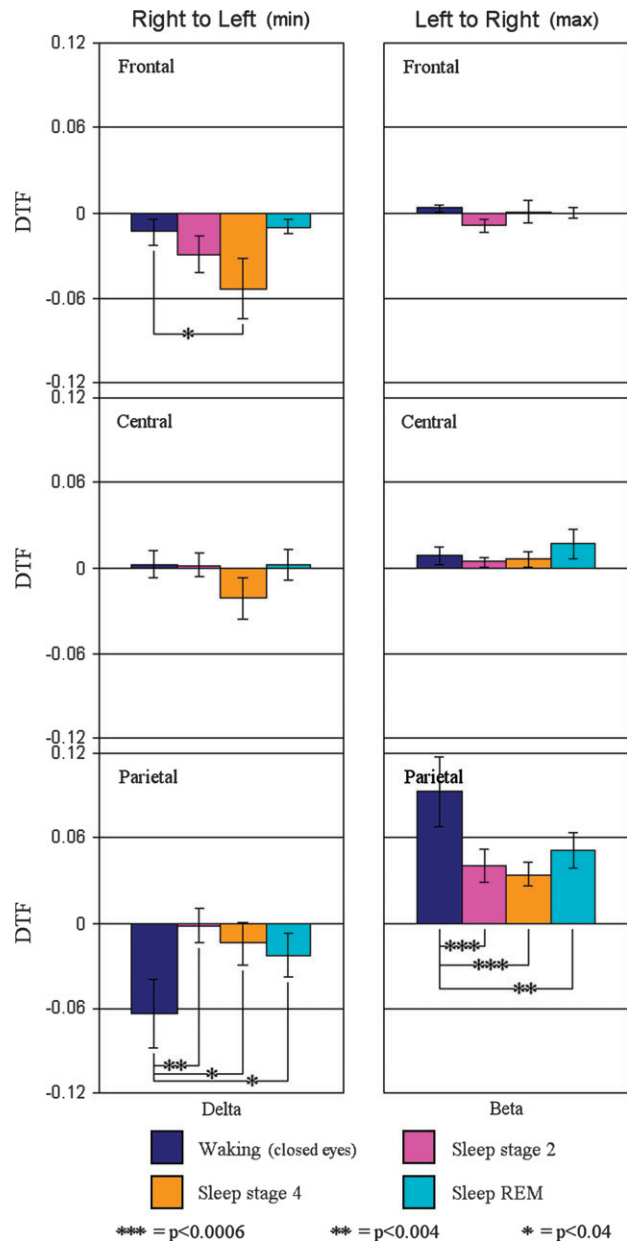low may come from the different phase delays of EEG potentials propagating by channels not taken into account in the Mvar model (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4). As in the main analysis, the maximum and minimum values of the DTFdiff were used as inputs for separate ANOVA designs. The analysis of the max DTFdiff values (left to right DTF direction) showed main effects of the factor stage for the sigma ($F_{3,27} = 3.86$; $P = 0.025$) and beta ($F_{3,27} = 3.91$; $P = 0.039$) bands. Post hoc tests showed that left to right DTF direction for the beta band was predominant in parietal areas during wakefulness compared with all early sleep stages ($P < 0.005$ to $P < 0.0001$). Besides, the min DTFdiff values (i.e., negative DTFdiff values)

Table 2
Individual values of delta and beta band directionality

	Waking		Stage 2		Stage 4		REM	
	Delta	Beta	Delta	Beta	Delta	Beta	Delta	Beta
Frontal								
Subject 1	−0.0069	0.0046	−0.0921	−0.0503	−0.0040	0.0138	−0.0049	0.0262
Subject 2	−0.0710	−0.0057	−0.0064	−0.0042	−0.0943	0.0054	−0.0137	−0.0003
Subject 3	0.0143	−0.0058	−0.0105	−0.0060	−0.1848	−0.0479	−0.0027	−0.0038
Subject 4	0.0019	0.0005	0.0008	−0.0080	−0.0221	0.0102	−0.0115	0.0039
Subject 5	−0.0069	−0.0006	−0.0714	−0.0121	−0.0202	−0.0076	−0.0562	−0.0187
Subject 6	−0.0609	0.0026	−0.0080	0.0001	−0.0531	−0.0026	−0.0041	0.0008
Subject 7	0.0028	0.0017	−0.0040	0.0029	−0.0353	0.0047	0.0012	0.0006
Subject 8	0.0032	0.0076	−0.0115	−0.0058	−0.1464	−0.0068	0.0020	−0.0070
Subject 9	−0.0095	0.0106	−0.0946	−0.0186	0.00041	0.0570	−0.0054	−0.0005
Subject 10	−0.0012	0.0142	0.0076	0.0107	0.0230	−0.0166	−0.0046	−0.0035
Mean	−0.0134	0.0030	−0.0290	−0.0091	−0.0533	0.0010	−0.0100	−0.0002
SE	0.0090	0.0021	0.0127	0.0052	0.0215	0.0083	0.0054	0.0035
Central								
Subject 1	0.0073	0.0148	−0.0258	−0.0035	−0.0420	0.0436	0.0078	0.0053
Subject 2	0.0119	0.0007	0.0048	0.0038	0.0260	0.0176	−0.0066	0.0000
Subject 3	0.0644	0.0040	0.0513	0.0104	−0.0414	−0.0087	0.0517	0.0083
Subject 4	0.0044	0.0051	0.0233	0.0019	−0.0014	0.0155	−0.0032	0.0043
Subject 5	−0.0148	0.0014	0.0263	0.0292	−0.0195	−0.0017	0.0198	0.0217
Subject 6	−0.0002	−0.0216	−0.0124	−0.0028	−0.1324	0.0107	−0.0529	0.0043
Subject 7	0.0102	0.0149	0.0098	0.0001	0.0157	−0.0036	−0.0100	0.0007
Subject 8	0.0031	0.0064	−0.0273	−0.0020	0.0005	−0.0083	−0.0428	0.0074
Subject 9	−0.0028	0.0591	0.0006	0.0002	0.0147	−0.0070	0.0530	0.1140
Subject 10	−0.0589	0.0040	−0.0316	0.0020	−0.0344	0.0021	0.0042	0.0020
Mean	0.0025	0.0089	0.0019	0.0039	−0.0214	0.0060	0.0021	0.0168
SE	0.0095	0.0064	0.0085	0.0031	0.0146	0.0052	0.0109	0.0110
Parietal								
Subject 1	−0.1574	0.1188	−0.0783	−0.0253	−0.0043	0.0029	0.0442	0.0118
Subject 2	−0.2176	0.2035	0.0273	0.0676	−0.0135	0.0398	−0.0613	0.0934
Subject 3	−0.0036	0.1326	0.0429	0.0945	0.0080	0.0295	−0.0177	0.0142
Subject 4	−0.0574	0.0659	0.0343	0.0499	−0.0812	0.0377	−0.0802	0.0663
Subject 5	−0.0061	0.0426	0.0140	0.0427	0.0320	0.0562	0.0073	0.0837
Subject 6	−0.1032	−0.0110	−0.0475	0.0027	−0.0128	0.0162	−0.0673	0.0010
Subject 7	−0.0018	0.0434	0.0105	0.0884	0.0262	0.0195	0.0048	0.0843
Subject 8	−0.0031	0.0088	−0.0055	0.0368	−0.1133	0.0204	−0.0030	0.0724
Subject 9	−0.0862	0.2207	−0.0108	0.0129	0.0285	0.0296	−0.0820	0.0002
Subject 10	−0.0085	0.1025	−0.0087	0.0367	−0.0120	0.0948	0.0358	0.0858
Mean	−0.0645	0.0928	−0.0022	0.0407	−0.0142	0.0346	−0.0229	0.0513
SE	0.0240	0.0246	0.0118	0.0118	0.0151	0.0081	0.0155	0.0124

pointed to a significant scalp site × stage interaction for the delta band ($F_{6,54} = 3.09$; $P = 0.019$). Post hoc tests indicated that the right to left DTF direction was predominant during wakefulness compared with all early sleep stages at the parietal sites ($P < 0.04$ to $P < 0.02$). These results were fully in agreement with those of the main analysis, based on a 9-channel Mvar model.

The second control analysis modeled the relationships between anterior and posterior midline cortical areas, to validate on a new data set the results of a previous EEG-DTF study of our group (De Gennaro et al. 2004). In the present analysis, we evaluated this flow direction by adding left and right hemispheres (F3–P3 and F4–P4) to the midline derivations (Fz–Pz). For each band of interest, we performed the analysis of the maximum DTF values (DTF direction). The ANOVA design included the factors stage (wakefulness, stage 2 sleep, stage 4 sleep, and REM sleep), scalp site (left, F3–P3; midline, Fz–Pz; and right, F4–P4), and direction (anterior-to-posterior and posterior-to-anterior). The delta band showed a significant stage × direction interaction ($F_{3,24} = 3.32$; $P < 0.04$), pointing to a reduction of posteroanterior DTF direction and to an increase of DTF anteroposterior direction ($P < 0.04$) from wake to stage 2. The theta band showed a significant stage × scalp site × direction interaction ($F_{6,48} = 4.17$; $P < 0.009$), pointing to an increase of DTF anteroposterior direction and to a decrease of DTF posteroanterior direction in the right hemisphere from

wakefulness to the sleep stages. The alpha band showed a close-to-significance stage × direction interaction ($F_{3,24} = 2.52$; $P < 0.089$), pointing to a reduction of DTF posteroanterior direction from wake to stage 2. The sigma band also showed a significant stage × direction interaction ($F_{3,24} = 3.54$; $P < 0.03$), indicating a reduction of DTF posteroanterior direction ($P < 0.04$) from wake to stage 2. The beta band showed a close-to-significance stage × direction interaction ($F_{3,24} = 2.77$; $P < 0.068$), pointing to a reduction of DTF posteroanterior direction from wake to stage 2. On the whole, there was a predominant posterior-to-anterior DTF direction during the presleep period and a predominant anterior-to-posterior DTF direction during the early sleep periods. These results confirmed on a new data set those reported in the mentioned EEG-DTF study (De Gennaro et al. 2004).

Discussion

The results clearly show the presence of interhemispheric directional flows that vary both across wake and early sleep states and in relation to different cerebral areas. More importantly, in our opinion, they also show preferred and selective directionality for different EEG frequency bands.

In particular, these data provide 3 intriguing findings.

1. While high-frequency bands both in wake and sleep convey more left to right information flows, low-frequency bands

both in wake and sleep convey more right to left information flows. To our knowledge, this finding represents the first evidence that slow and fast rhythms reflect a continuum of opposite preferred directions of information flows between brain hemispheres both in wake and sleep states. Some hints of interpretational and heuristic relevance may be put forward. Psychophysiological literature traditionally associates increasing frequencies of EEG rhythms with an increasing state of vigilance. Thus, the finding that the trend of increasing frequencies of EEG rhythms appears significantly related to a trend of increasingly left to right direction of the communication flows is by no means irrelevant. Neuropsychological literature has provided a large amount of knowledge on cognitive and emotional specialization of brain hemispheres (e.g., Demaree et al. 2005; Halpern et al. 2005). However, the principles underlying human interhemispheric communication are poorly understood. According to Stephan (2003) "This is highly regrettable because (i) it is one of the most fundamental principles how human brains seem to be organized and (ii) changes in hemispheric specialization (and particularly interhemispheric integration) are believed to be connected to a variety of psychiatric disorders." The opportunity to use the frequency bands as a physiological indicator of directionality may open the door to a variety of important investigations in these areas.

2. Further reflections are suggested by the data showing variations of directionality at different regional sites.

   As we can see in Figure 3, significant regional differences of the flow directionality across stages appear at the delta and beta bands. The delta band conveys a prevalence of information flow from right to left hemisphere both in different regional areas and across wake to sleep states. However, within this general frame, whereas in the parietal areas the prevalence of the right to left direction is significantly higher during wake than during all sleep stages, including stage 4, the opposite trend is found in the frontal areas, where the tendency toward a right to left direction is higher during sleep stage 4 than in wake. No differences for directionality were found in the central areas. On the other hand, the beta band shows a general orientation toward the left to right direction at the parietal sites; no directionality difference was found at the frontal and central areas. Furthermore, a significant prevalence of the left to right direction is present in wake as compared with all the other sleep stages. What is the meaning of these differential patterns of information flows? In general, these data emphasize the functional diversity of brain areas in relation to the different states. In particular, in the transition from wake to sleep, they highlight the special role of frontal areas. In fact, the main interhemispheric information flow is conveyed by delta rhythms between frontal areas. This nicely fits with the role of frontal area in early sleep processes (De Gennaro et al. 2001, 2005), as well as with the frontal predominance of the delta EEG power during human NREM sleep (Werth et al. 1996) and during animal sleep (Vyazovskiy et al. 2002). Furthermore, they extend to the domain of interhemispheric information flow previous evidence showing that sleep onset is characterized by an increment of the functional coupling from frontal to parietooccipital areas (De Gennaro et al. 2004) and that such a directional process is already present in the presleep period when sleep

pressure is enhanced by sleep deprivation (De Gennaro et al. 2005). Observations on delta waves have been receiving increasing attention in the sleep literature. The low-frequency rhythms defining slow-wave sleep have long been regarded as epiphenomena, with negligible or no functional significance, because this physiological state was previously regarded as associated with global inhibition of the cerebral cortex and subcortical structures, which underlies the annihilation of consciousness. However, studies using intracellular recordings of electrophysiologically characterized cortical cell types in naturally awake and sleeping animals have shown unexpectedly high levels of spontaneous neuronal activity during slow-wave sleep (Steriade et al. 2001). And, although the thalamic gates are closed for signals from the outside world during slow-wave sleep, due to the obliteration of synaptic transmission in thalamocortical neurons, the intracortical dialog and the responsiveness of cortical neurons are maintained and even increased during this quiescent state. These data suggest that slow-wave sleep may serve important cerebral functions, among which was the consolidation of memory traces acquired during wakefulness (e.g., Huber et al. 2004; Peigneux et al. 2004). Our observations may have heuristic value in designing specific research projects geared toward clarifying the sources and dynamics of the "intracortical dialog" during this quiescent state.

   Altogether, our findings lend further support for the notion of use-dependent local sleep (e.g., Finelli et al. 2001; Ferrara et al. 2002; Vyazovskiy et al. 2002) in the specific domain of state-related interhemispheric variations.

3. Finally, the present results extend, in terms of "directionality," several previous lines of evidence: 1) the reduction of spontaneous neural activity in the splenium of the corpus callosum across sleep stages in animals (Berlucchi 1965); 2) the reduction in transcallosal inhibition especially from right to left motor areas across sleep stages in humans (Bertini et al. 2004); 3) evidence of slow sleep EEG oscillations as traveling waves having intra- and interhemispheric directions of propagation (Massimini et al. 2004); 4) the drop in functional interhemispheric connectivity during early sleep stages (Massimini et al. 2005); 5) the modulation of interhemispheric EEG coherence across wake–sleep stages in normal subjects (Nielsen et al. 1990; Guevara et al. 1995; Achermann and Borbely 1998) and in patients with partial resection or agenesis of the corpus callosum (Montplaisir 1990; Nielsen et al. 1993); and 6) the decrement of regional cerebral blood flow in the left parietal area during slow-wave sleep (Kajimura et al. 1999).

Conclusions

The above considerations are fundamentally limited to description and further clarification of the empirical findings on the interhemispheric relationships during wake and early sleep stages. These relations are part of a complex matrix of cortical and subcortical connections underlying the cognitive processes during wake–sleep states (Kaminski et al. 1997; Balkin et al. 2002; Massimini et al. 2005). Nevertheless, the current approach may suggest new research strategies to increase knowledge on the interhemispheric functional coupling in different psychophysiological and pathological conditions.

At the psychophysiological level, one prospect is to investigate the relationship between physiological indicators of directionality and thinking processes in relative independence of the traditional categorizations of wake and sleep states. States of consciousness are traditionally viewed through the eyes of the nosologist, who distinguishes and separates waking from sleep stages with their stereotyped correlation with thinking processes. What is often lacking is the effort to look through the states, by searching for unifying principles and organizational coherence (Bertini 1986). As far as our findings do associate different directions of information flow between hemispheres to different EEG rhythms and indicate specific variation of dominance between these rhythms in the transition from wake to sleep states, they invite us to break the imagined walls of the states of consciousness. For example, following the traditional attitude of associating the beta rhythm with wakefulness, we may fail to acknowledge the presence and to understand the functional meaning of this rhythm in the sleep state; in the same vein, we may pay little attention to the delta waves so often appearing during the wake and REM state. The prospect is to understand the functional continuity of the same physiological rhythms which might change in their hierarchical integration along the 24-h cycle in strict dependence on the physiological and mental requirements of the internal and external environments.

Specific suggestions may also come from investigations in the pathological domain. For example, the hypothesis that the presence of slow waves routinely observed in the EEG records of epileptic patients is associated with the right to left predominance of directional flow is clearly testable. Within these perspectives, we are currently carrying on a large validation study involving multilevel approaches concerning both normal and pathological conditions.

Notes

Address correspondence to Dr Mario Bertini, MD, PhD, Dipartimento di Psicologia, Università degli Studi di Roma "La Sapienza," Via dei Marsi, 78, 00185 Rome, Italy. Email: mario.bertini@uniroma1.it.

References

Achermann P, Borbely AA. 1998. Temporal evolution of coherence and power in the human sleep electroencephalogram. J Sleep Res. 7:36–41.

Amzica F, Steriade M. 1995. Disconnection of intracortical synaptic linkages disrupts synchronization of a slow oscillation. J Neurosci. 15:4658–4677.

Babiloni C, Babiloni F, Carducci F, Cincotti F, Vecchio F, Cola B, Rossi S, Miniussi C, Rossini PM. 2004. Functional frontoparietal connectivity during short-term memory as revealed by high-resolution EEG coherence analysis. Behav Neurosci. 118:687–697.

Babiloni C, Vecchio F, Babiloni F, Brunelli GA, Carducci F, Cincotti F, Pizzella V, Romani GL, Tecchio FT, Rossini PM. 2004. Coupling between "hand" primary sensorimotor cortex and lower limb muscles after ulnar nerve surgical transfer in paraplegia. Behav Neurosci. 118:214–222.

Balkin TJ, Braun AR, Wesensten NJ, Jeffries K, Varga M, Baldwin P, Belenky G, Herscovitch P. 2002. The process of awakening: a PET study of regional brain activity patterns mediating the re-establishment of alertness and consciousness. Brain. 125(Pt 10):2308–2319.

Berlucchi G. 1965. Callosal activity in unrestrained, unanesthetized cats. Arch Ital Biol. 103:623–634.

Bertini M. 1986. Some implication of Witkin's teaching for sleep and dreaming psychophysiology. In: Bertini M, Pizzamiglio L, Wapner S, editors. Field dependence in psychological theory, research and application. London: LEA. p 15–26.

Bertini M, De Gennaro L, Ferrara M, Curcio G, Romei V, Fratello F, Cristiani R, Pauri F, Rossini PM. 2004. Reduction of transcallosal inhibition upon awakening from REM sleep in humans as assessed by transcranial magnetic stimulation. Sleep. 27:875–882.

Blinowska KJ, Kus R, Kaminski M. 2004. Granger causality and information flow in multivariate processes. Phys Rev E Stat Nonlin Soft Matter Phys. 70(5 Pt 1):050902.

Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. 1992. Automatic sleep/wake identification from wrist activity. Sleep. 15:461–469.

De Gennaro L, Ferrara M, Curcio G, Cristiani R. 2001. Antero-posterior EEG changes during the wakefulness-sleep transition. Clin Neurophysiol. 112:1901–1911.

De Gennaro L, Vecchio F, Ferrara M, Curcio G, Rossini PM, Babiloni C. 2004. Changes in fronto-posterior functional coupling during sleep onset in humans. J Sleep Res. 13:209–217.

De Gennaro L, Vecchio F, Ferrara M, Curcio G, Rossini PM, Babiloni C. 2005. Antero-posterior functional coupling at sleep onset: changes as a function of increased sleep pressure. Brain Res Bull. 65:133–140.

Demaree HA, Everhart DE, Youngstrom EA, Harrison DW. 2005. Brain lateralization of emotional processing: historical roots and a future incorporating "dominance". Behav Cogn Neurosci Rev. 4:3–20.

Ferrara M, De Gennaro L, Curcio G, Cristiani R, Corvasce C, Bertini M. 2002. Regional differences of the human sleep electroencephalogram in response to selective slow-wave sleep deprivation. Cereb Cortex. 12:737–748.

Finelli L, Borbely AA, Achermann P. 2001. Functional topography of the human non-REM sleep electroencephalogram. Eur J Neurosci. 13:2282–2290.

Guevara MA, Lorenzo I, Arce C, Ramos J, Corsi-Cabrera M. 1995. Inter- and intrahemispherical EEG correlation during sleep and wakefulness. Sleep. 18:257–265.

Halpern ME, Gunturkun O, Hopkins WD, Rogers LJ. 2005. Lateralization of the vertebrate brain: taking the side of model systems. J Neurosci. 25:10351–10357.

Huber R, Ghilardi MF, Massimini M, Tononi G. 2004. Local sleep and learning. Nature. 430:78–81.

Jacobson S, Trojanowski JQ. 1975. The appearance of dendrites of callosal and corticothalamic neurons in somatosensory cortex of immature rats demonstrated by horseradish peroxidase. Adv Neurol. 12:319–333.

Kajimura N, Uchiyama M, Takayama Y, Uchida S, Uema T, Kato M, Sekimoto M, Watanabe T, Nakajima T, Horikoshi S, et al. 1999. Activity of midbrain reticular formation and neocortex during the progression of human non-rapid eye movement sleep. J Neurosci. 19:10065–10073.

Kaminski MJ, Blinowska KJ. 1991. A new method of the description of the information flow in the structures. Biol Cybern. 65:203–210.

Kaminski MJ, Blinowska KJ, Szclenberger W. 1997. Topographic analysis of coherence and propagation of EEG activity during sleep and wakefulness. Electroencephalogr Clin Neurophysiol. 102:216–227.

Korzeniewska A, Kasicki S, Kaminski M, Blinowska KJ. 1997. Information flow between hippocampus and related structures during various types of rat's behavior. J Neurosci Methods. 73:49–60.

Kus R, Kaminski M, Blinowska KJ. 2004. Determination of EEG activity propagation: pair-wise versus multichannel estimate. IEEE Trans Biomed Eng. 51(9):1501–1510.

Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. 2005. Breakdown of cortical effective connectivity during sleep. Science. 309:2228–2232.

Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G. 2004. The sleep slow oscillation as a traveling wave. J Neurosci. 24:6862–6870.

Mima T, Matsuoka T, Hallett M. 2000. Functional coupling of human right and left cortical motor areas demonstrated with partial coherence analysis. Neurosci Lett. 287:93-96.

Mima T, Matsuoka T, Hallett M. 2001. Information flow from the sensorimotor cortex to muscle in humans. Clin Neurophysiol. 112:122-126.

Montplaisir J, Nielsen T, Cote J, Boivin D, Rouleau I, Lapierre G. 1990. Interhemispherical EEG coherence before and after partial callosotomy. Clin Electroencephalogr. 21:42-47.

Nielsen T, Abel A, Lorrain D, Montplaisir J. 1990. Interhemispherical EEG coherence during sleep and wakefulness in left- and right-handed subjects. Brain Cogn. 14:113-125.

Nielsen T, Montplaisir J, Lassonde M. 1993. Decreased interhemispherical EEG coherence during sleep in agenesis of the corpus callosum. Eur Neurol. 33:173-176.

Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, Phillips C, Degueldre C, Del Fiore G, Aerts J, et al. 2004. Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron. 44:535-545.

Rechtschaffen A, Kales A. 1968. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles (CA): Brain Information Service/Brain Research Institute, University of California. p. 1-58.

Salmaso D, Longoni AM. 1985. Problems in the assessment of hand preference. Cortex. 21:533-549.

Stephan KE, Marshall JC, Friston KJ, Rowe JB, Ritzl A, Zilles K, Fink GR. 2003. Lateralized cognitive processes and lateralized task control in the human brain. Science. 301:384-386.

Steriade M, Contreras D, Curro Dossi R, Nunez A. 1993. The slow (<1 Hz) oscillation in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation in interacting thalamic and neocortical networks. J Neurosci. 13:3284-3299.

Steriade M, Timofeev I, Grenier F. 2001. Natural waking and sleep states: a view from inside neocortical neurons. J Neurophysiol. 85:1969-1985.

Tononi G. 2005. Consciousness, information integration, and the brain. Prog Brain Res. 150:109-126.

Vyazovskiy VV, Borbely AA, Tobler I. 2002. Interhemispheric sleep EEG asymmetry in the rat is enhanced by sleep deprivation. J Neurophysiol. 88:2280-2286.

Werth E, Achermann P, Borbely AA. 1996. Brain topography of the human sleep EEG: antero-posterior shifts of spectral power. Neuroreport. 8:123-127.