Functional frontoparietal connectivity during encoding and retrieval processes follows HERA model
A high-resolution study

Claudio Babiloni [a,b,c,*], Fabrizio Vecchio [a,c], Stefano Cappa [d], Patrizio Pasqualetti [b,c],
Simone Rossi [e], Carlo Miniussi [b], Paolo Maria Rossini [b,c,f]

[a] *Dipartimento di Fisiologia Umana e Farmacologia, Sezione di EEG ad Alta Risoluzione,*
Università degli Studi di Roma "La Sapienza", P.le Aldo Moro 5, 00185 Rome, Italy
[b] *IRCCS S Giovanni di Dio, Fatebenefratelli, Brescia, Italy*
[c] *AFaR, S. Giovanni Calibita, Fatebenefratelli Isola Tiberina, Roma, Italy*
[d] *Centro di Neuroscienze Cognitive, Università Salute-Vita S. Raffaele, Milano, Italy*
[e] *Dipartimento di Neuroscienze, Sezione Neurologia, Università di Siena, Italy*
[f] *Neurologia, Università Campus Biomedico, Roma, Italy*

Abstract

Recent neuroimaging studies of long-term episodic memory have suggested that left prefrontal cortex predominates in encoding condition, whereas right prefrontal cortex predominates in retrieval condition (hemispheric encoding and retrieval asymmetry, HERA model). The present electroencephalographic (EEG) study investigated the functional coupling of fronto-parietal regions during long-term memorization of visuo-spatial contents (i.e. landscapes, interiors of apartments), to test the predictions of the HERA model. Global fronto-parietal coupling was estimated by spectral coherence, whereas the "direction" of the fronto-parietal information flow was estimated by directed transfer function (DTF). The EEG rhythms of interest were theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz), and gamma (30–45 Hz). Statistically significant coherence in line with the HERA model was obtained at the gamma band. Namely, the fronto-parietal gamma coherence prevailed in the left hemisphere during the encoding condition and in the right hemisphere during the retrieval condition. The DTF estimates of the gamma band showed a dominant parietal-to-frontal directional flow in the right hemisphere during the encoding condition and in the left hemisphere during the retrieval condition (i.e. hemisphere-condition combination not involved by the HERA model). In contrast, a balanced bidirectional flow of the fronto-parietal coupling was observed in the left hemisphere during the encoding condition and in the right hemisphere during the retrieval condition (i.e. hemisphere-condition combination involved by the HERA model). In conclusion, the present encoding-retrieval conditions induced maximal fronto-parietal gamma coupling with bidirectional information flow in the hemisphere-condition combination predicted by the HERA model.
© 2005 Elsevier Inc. All rights reserved.

Keywords: Encoding and retrieval; Cerebral cortex; Electroencephalography (EEG); Coherence; Directed transfer function (DTF)

1. Introduction

Previous functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have shown that bilateral prefrontal areas are engaged alongside the medial temporal lobes for the encoding and subsequent retrieval of episodes in long-term memory [10,12,17]. Unexpectedly, several of these studies have pointed to a hemispheric asymmetry. There was a prevalence of activity in the left prefrontal cortex during the encoding of verbal and spatial materials [32,39,54], while an enhanced activity was present in the right prefrontal cortex during the retrieval of that information content. These findings have led Tulving et al. [54] to propose a general model of brain function subserving episodic memory. According to the hemispheric encoding-retrieval asymmetry (HERA) model, the left hemisphere plays a crucial role in encoding, while the right hemisphere is dominant for retrieval [54].

---

* Corresponding author. Tel.: +39 06 49910989; fax: +39 06 49910917.
E-mail address: claudio.babiloni@uniroma1.it (C. Babiloni).

In line with the HERA model, repetitive transcranial magnetic stimulation (rTMS) of the prefrontal cortex has been able to temporarily interfere with the encoding and consecutive retrieval of both visuospatial [48] and verbal [49] episodes. It should be remarked that the HERA pattern is not an absolute feature of cortical activity during long-term memorization. Rather, the level or existence of the HERA pattern is affected and in some cases abolished by the nature of the material to be memorized, such as verbal content, difficulty, familiarity, level of detail, etc. [10,12,23,44,57].

Beyond the issue of its generalization, the HERA model has been able to explain the experimental data produced by a design in which young adults were asked to remember a set of pictures representing interiors of apartments ("interiors") and landscapes ("landscapes"; [48]). That design has been also utilized by a recent electroencephalographic (EEG) study aimed at evaluating the role of brain rhythms in the processes of encoding and retrieval, in the light of the predictions of the HERA model [2]. In that study, the HERA model was only fitted by EEG gamma responses (about 40 Hz) observed in an unexpected posterior location. The encoding phase was associated with a magnitude increment of the gamma EEG oscillations over the left parietal cortex. Instead, the retrieval phase was associated with the magnitude increment of the gamma EEG oscillations predominantly over the right parietal cortex. Summarizing, the amplitude of the parietal but not frontal gamma rhythms fitted the hemisphere-condition combination of the HERA model. Why did not frontal cortex entrain into the modulation of the gamma response in line with HERA model? The issue was crucial since HERA model was constructed on the basis of prefrontal activity during encoding-retrieval processes, as revealed by the mentioned neuroimaging and TMS studies [32,39,48,49,54]. This discrepancy was explained as due to the differential sensitivity of neuroimaging methods to different components of long-term episodic memory. In particular, the strict relation between the EEG gamma responses and perception suggested that the retrieval processes of long-term memory may be deeply impinged upon the sensory representations of the stored material in the parietal lobe.

In explaining the results of the mentioned EEG study [2], we could not exclude a remote functional control of the prefrontal over parietal areas in the modulation of the gamma rhythms during the encoding and retrieval processes. Indeed, that EEG study [2] has just disclosed the topographical distribution of brain reactivity during the task, without testing whether the frontal and parietal areas were working in parallel or in series with a precise hierarchy (i.e. one is being functionally more relevant than the other within the whole network). A reasonable reconciliatory hypothesis was that the parietal gamma rhythms (following HERA model) would be functionally interrelated to the frontal gamma rhythms. We could not address that hypothesis at the time of the previous study [2]. Indeed, our implementation of the required methodological approach had not been yet fully validated.

The present EEG study re-analyzed the EEG data recorded in the previous study [2], in order to test the working hypothesis that the parietal gamma rhythms (following HERA model) were functionally coordinated to the frontal gamma rhythms during the encoding and retrieval processes. Global fronto-parietal coupling was estimated by spectral coherence, whereas the "direction" of the fronto-parietal information flow was estimated by directed transfer function (DTF). It should be remarked that no coherence and DTF finding was published in the previous study [2], so that the present results are entirely original and unedited.

Concerning the present methodological approach, EEG spectral coherence between pairs of cortical regions have been interpreted as an evidence of functional coupling [18,53], mutual information exchange [45], functional co-ordination [19], and integrity of connection pathways [33]. In addition, DTF estimates have been proved to roughly model the "direction" of the information flow between pairs of cortical sites [1,3,10,26,29,34].

2. Materials and methods

Details on the participating subjects, experimental task, EEG recordings, and preliminary data analysis were provided in the mentioned study [2]. Briefly, EEG recordings were performed in 12 healthy, right-handed (Edinburgh Inventory) volunteers (22–41 years). The subjects kept their forearms resting on armchairs, with their right index finger resting between two buttons spaced 6 cm apart. The experimental paradigm included an "encoding" (ENC) and a "retrieval" (RET) phase in which 50 complex colored magazine pictures were shown after a red central target given as a visual warning stimulus (presentation time of 1 s). In the encoding phase, 25 figures representing interiors of apartments ("interiors") were randomly intermingled with 25 figures representing landscapes ("landscapes"). The figures were shown one-by-one (cue period, presentation time of 5 s). The subjects were instructed to press with right index finger one of the two close buttons (left = "interiors"; right = "landscapes") as quickly as possible after the appearance of a green central target at the center of the figure (go stimulus, presentation time of 1 s). Remarkably, no mention to a RET phase was made before the encoding phase, according a standard paradigm of "incidental memory".

About 1 h later, the RET phase started. In this phase, 25 figures representing previously presented "interiors" ("tests") were randomly intermingled with 25 figures representing novel "interiors" ("distractors"). The subjects were again asked to answer by pressing one of the two buttons (left = "tests"; right = "distractors") immediately after the go signal. The timing of warning and go signals, picture presentation, and intervals were as in the "encoding" phase. Of note, the correct choice in both "encoding" and "retrieval" phases was always on the left button. Furthermore, a 10 min training before the "encoding" phase was performed with a different set of figures, to familiarize subjects with the experimental apparatus.

EEG data were recorded (256 Hz sampling frequency, 0.1–60 Hz bandpass; linked ear reference) with a 46 tin electrode cap in which the electrodes were disposed according to an augmented 10–20 system. Electrooculogram monitored blinking or eye movements, whereas electromyogram monitored operant movement as well as mirror movements and involuntary slight muscle activations.

The collected EEG data were segmented in individual trials spanning from −2.5 to +7.5 s, the zerotime being the presentation onset of the figures. The EEG trials associated with wrong cognitive performances as well as those contaminated by mirror or involuntary finger movements (about 5%), inadvertent motor acts, slight muscle activations (about 5%) and instrumental artifacts were discarded. Of note, the EEG trials associated with wrong cognitive performances and artifact-free EEG trials were too few to address an analysis on them.

The spatial resolution of artifact-free EEG data was enhanced by surface Laplacian estimation [4,5] applied on careful single trial analysis Laplacian-transformed EEG data. The data of two subjects did not overcome this preliminary analysis and were not further considered. In the remaining 10 subjects, the mean of the artifact free single trials was of 29 (±3 standard error, S.E.) for the ENC condition and of 26 (±3S.E.) for the RET condition.

2.1. Estimation of the functional connectivity: between-electrode coherence analysis

EEG coherence is a normalized measure of the coupling between two EEG signals at any given frequency [31,45]. The coherence values were calculated for each frequency bin by the Eq. (1).

$$\text{Coh}_{xy}(\lambda) = \left| R_{xy}(\lambda) \right|^2 = \frac{\left| f_{xy}(\lambda) \right|^2}{f_{xx}(\lambda) f_{yy}(\lambda)}. \tag{1}$$

Eq. (1) is the extension of the Pearson's correlation coefficient to complex number pairs. In this equation, f denotes the spectral estimate of two EEG signals x and y for a given frequency bin (λ). The numerator contains the cross-spectrum for x and y (f_{xy}), while the denominator contains the respective autospectra for x (f_{xx}) and y (f_{yy}). For each frequency bin (λ), the coherence value (Coh_{xy}) is obtained by squaring the magnitude of the complex correlation coefficient R. This procedure returns a real number between 0 (no coherence) and 1 (max coherence).

According to the aims of the present study, the EEG coherence was computed from the electrodes overlaying bilateral dorsolateral prefrontal (F3, F4) and posterior parietal (P3, P4) cortical areas, namely the electrode pairs F3-P3 and F4-P4. At these internal electrodes, the surface Laplacian estimates from the spatial information content of 46 electrodes can be considered as highly reliable [5,36,42]. The EEG coherence was calculated at three consecutive periods lasting 1 s each, namely the "rest" (pre-stimulus) period, the first 1-s period of the figure (T1), and the second 1-s period of the figure (T2). This was true for both ENC and RET conditions.

The spectral coherence was computed at theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz), and gamma (30–45 Hz) bands, since previous studies have shown that functional connectivity as revealed by EEG coherence can be observed in a wide range of frequencies [50,55,56]. It should be stressed that the present EEG coherence values at baseline and event were somewhat low. This may be due to the large distance between the two temporal recording sites at which EEG data for the coherence analysis were recorded. Previous findings have shown that EEG coherence between electrodes is inversely proportional to the inter-electrode distance [53]. These low values were also due to the strong deflation of coherence induced by volume conductor effects thanks to surface Laplacian estimation [38]. Of note, the statistical analysis considered only EEG data from subjects showing coherence values above statistical threshold posed at $p < 0.05$, i.e. statistically significant coherence values. The calculation of the statistical threshold level for coherence was made according to Halliday and collaborators [24], taking into account the number of single valid EEG trials used as an input for the analysis of EEG coherence. This procedure was to compute the statistical thresholds for the present coherence data. These thresholds were 0.10 and 0.11 for ENC and RET condition, respectively. The final statistical analysis was then performed on the coherence data of all 10 subjects.

2.2. "Direction" of the functional connectivity estimated by Mvar model

Before computing the DTF, the EEG data were preliminarily normalized by subtracting the mean value and by dividing for the variance, according to mandatory suggestions by Kaminski and Blinowska [27]. Therefore, the DTF can be considered as a normalized value ranging from 0 to 1. An important step of the DTF method was the computation of the so-called Mvar model [26,27,29]. Laplacian transformed data at four electrodes (F3, P3, F4, P4) were given as an input to the Mvar model towards the computation of the directional information flux (DTF) among all these electrodes (F3-P3, F4-P4, F3-F4, P3-P4, F3-P4, etc.). Therefore, the procedure fully overcame the issues due to DTF computation from only two electrodes (binary model; [9,30]). In particular, our interest was focused on the estimation of the "direction" of the information flow between F3-P3 and F4-P4 for the frequency bands in which significant event-related coherence values were found for the ENC versus RET conditions. In non-mathematical terms, the Mvar model estimates information flow between the electrodes A and B by computing the extent to which the EEG data at the electrode A can be predicted based on the EEG data of the elec-

trode B and vice-versa. A direction of the information flow from A to B is stated when that case is statistically more probable than a directionality from B to A. In precedence, that Mvar model has been successfully used to estimate the "direction" of the cortico-cortical and cortico-muscular information flow [1,3,35].

The mathematical core of the Mvar algorithm is based on the ARfit programs running on the platform (Matlab 5.3, Mathworks Inc., Natrick, MA). The model order was 7, as estimated by Akaike criterion suggested in previous DTF studies [26,27,29]. 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 the time t, E_t is the white noise, and A_j is the $L \times L$ matrix of model coefficients, 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 and

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

$$z^{-i} = \exp(-i2\pi f dt)$$

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 elements of the relevant row.

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

A substantial difference between $\text{DTF}(f)_{ij}$ and $\text{DTF}(f)_{ji}$ may suggest an asymmetric information flow from the electrode i to electrode j. When $\text{DTF}(f)_{ij}$ is greater in magnitude than $\text{DTF}(f)_{ji}$, "direction" of the information flow would be from electrode j to electrode i. On the other hand, the "direction" of the information flow would be from electrode i to electrode j, when $\text{DTF}(f)_{ji}$ is greater in magnitude than $\text{DTF}(f)_{ij}$.

To control the DTF results obtained using Laplacian estimates from four electrodes (F3, P3, F4, P4), the analysis of the information flow was repeated on the recorded EEG potentials. In this control analysis, EEG data from 30 electrodes (Table 1) were given as an input to the MVAR model and the information flow between frontal and parietal regions were evaluated for the left (DTF mean of F3-P3 and F3-P5) and right (DTF mean of F4-P4 and F4-P6) hemispheres.

Table 1

List including 30 electrodes (augmented 10–20 System) used for the control Mvar model on the recorded EEG potentials

Electrodes
AFz
F5, F3, F1, Fz, F2, F4, F6
FC3, FCZ, FC4
C5, C3, Cl, Cz, C2, C4, C6
CP3, CPz, CP4
P5, P3, P1, Pz, P2, P4, P6
POz
Oz

2.3. Statistical analysis

Statistical comparisons for the ENC and RET conditions were performed by ANOVA analyses for repeated measures. Mauchley's test evaluated the sphericity assumption and correction of the degrees of freedom was made by Greenhouse-Geisser procedure. Duncan test was used for post-hoc comparisons ($p < 0.05$).

The statistical analysis of the event-related EEG coherence (Laplacian data) was performed using three-ways ANOVA for each frequency band of interest. The ANOVA design included the factors condition (ENC, RET), electrode pair (F4-P4, F3-P3), and time (*T*1, *T*2). The working hypothesis of functional fronto-parietal connectivity in line with the HERA model implied a statistical interaction including the factors condition and electrode pair ($p < 0.05$) as well as a post-hoc testing showing a significant increase ($p < 0.05$) of the coherence in the left hemisphere during the encoding (ENC) condition and in the right hemisphere during the retrieval (RET) condition.

The statistical analysis of the Laplacian DTF values ("direction" of the information flow) was performed using three-ways ANOVA for the bands and the periods showing statistically significant coherence values. The ANOVA design included the factors condition (ENC, RET), direction (frontal-to-parietal, F→P; parietal-to-frontal, P→F), and electrode pair (F3-P3, F4-P4). The working hypothesis of hierarchical fronto-parietal connectivity in line with the HERA model implied a statistical interaction including the factors condition, direction, and electrode pair ($p < 0.05$) as well as a post-hoc testing showing a significant change ($p < 0.05$) of directionality in hemisphere-condition combination predicted by the HERA model.

The statistical analysis of the DTF values from the recorded EEG data (no Laplacian estimation) was performed using three-ways ANOVA for the bands and the periods showing statistically significant coherence values. The ANOVA design included the factors condition (ENC, RET), direction (frontal-to-parietal, F→P; parietal-to-frontal, P→F), and electrode pair (DTF mean of F3-P3 and F3-P5; DTF mean of F4-P4 and F4-P6). The working hypothesis stated the confirmation of the results obtained using surface Laplacian data ($p < 0.05$).

3. Results

The behavioral results were described in detail in the previous study (Babiloni et al. [1]). In brief, the percentage of the correct responses was significantly greater ($p < 0.001$) during the ENC (91% ±3S.E.) than the RET condition (74% ±3S.E.). Furthermore, there was no statistical difference in the mean reaction time during the ENC (696 ms ±31S.E.) compared to the RET condition (734 ms ±34S.E.).

3.1. Functional fronto-parietal connectivity as revealed by the spectral coherence

Fig. 1 illustrates the grand average of the coherence spectra computed from the fronto-parietal electrode pairs of the left (F3-P3) and right (F4-P4) hemispheres for the ENC and RET conditions. The data refer to both periods of interest (*T*1 and *T*2). Table 2 reports absolute EEG coherence values and statistical thresholds ($p < 0.05$, computed according to Halliday [24]) in the experimental conditions (ENC and RET) for both periods of interest. On the whole, absolute coherence values were relatively low in magnitude but above the corresponding statistical thresholds ($p < 0.05$). This was true for almost all EEG frequency bands. To emphasize the task effects with respect to the pre-stimulus or baseline period, Fig. 2 plots the event-related coherence (ERCoh) computed in a representative subject (Sub-

Table 2

Statistical thresholds of coherence and mean coherence values at both periods of interest (*T*1 and *T*2)

	Coherence at *T*1		Threshold	Coherence at *T*2	
	F3-P3	F4-P4		F3-P3	F4-P4
Encoding					
Theta	0.13	0.12	0.10	0.17	0.14
Alpha	0.10	0.17	0.10	0.15	0.17
Beta	0.13	0.13	0.10	0.20	0.19
Gamrnal	0.24	0.21	0.10	0.26	0.20
Retrieval					
Theta	0.10	0.02	0.11	0.16	0.14
Alpha	0.18	0.15	0.11	0.27	0.24
Beta	0.29	0.21	0.11	0.25	0.24
Gamrnal	0.23	0.28	0.11	0.24	0.26

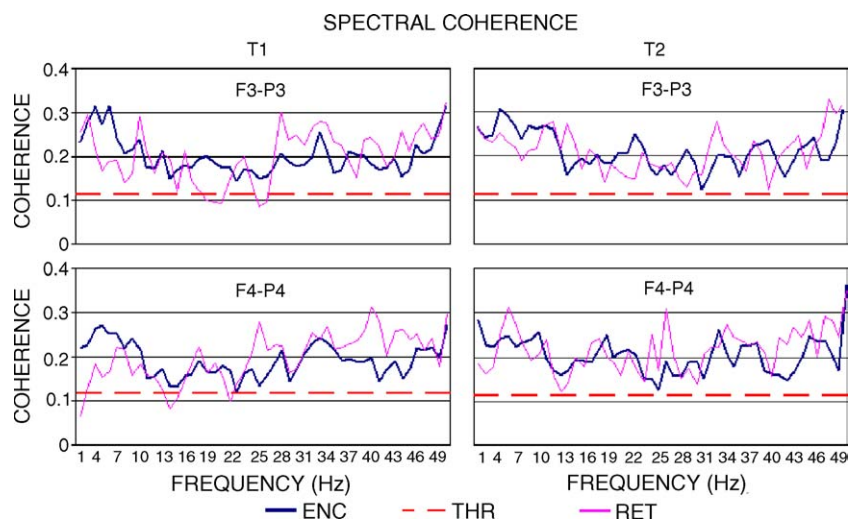Values refer to the experimental conditions (ENC, RET) and to four EEG bands.

Fig. 1. Grand average across subjects of the EEG coherence spectra computed from the fronto-parietal (F3-P3, F4-P4) electrode pairs during *T*1 and *T*2 periods (they lasted 1 s each after the onset of the figure presentation). These spectra refer to the encoding (ENC) and retrieval (RET) conditions of the present long-term memory task (visuo-spatial contents). Coherence threshold level is indicated by dashed line.
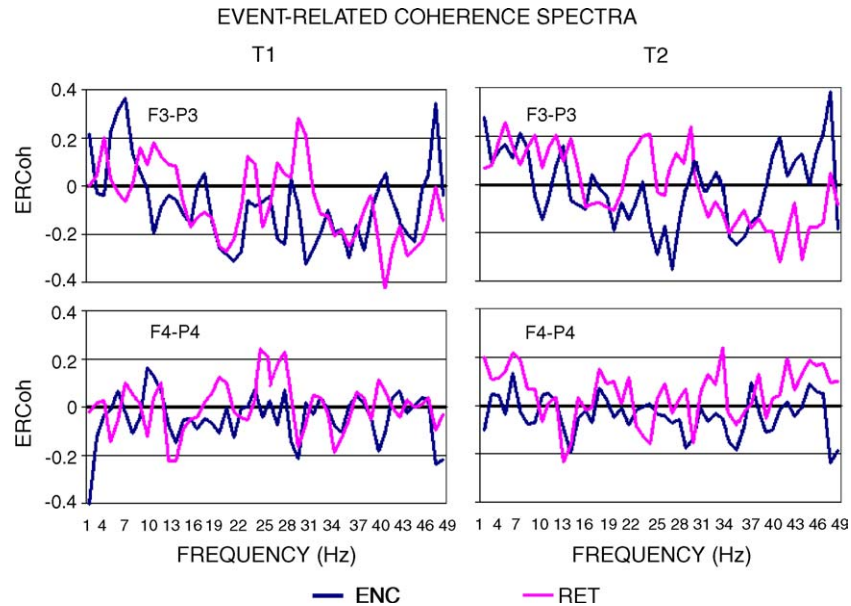
EVENT-RELATED COHERENCE SPECTRA

Fig. 2. Event-related coherence (ERCoh) computed in a representative subject (Subject 7) from the fronto-parietal (F3-P3, F4-P4) electrode pairs during *T*1 and *T*2 periods. These spectra refer to the encoding (ENC) and retrieval (RET) conditions. The ERCoh was defined as the difference between the coherence values at the periods of interest (*T*1, *T*2) with respect to the coherence at the pre-stimulus period.

ject 7) from the same electrode pairs and periods. The ERCoh was computed as the difference of the coherences at *T*1 or *T*2 and the coherence at the pre-stimulus period. In general, the ERCoh at all frequency bands was higher during the RET than the ENC condition. It should be stressed that the magnitude of ErCoh is usually smaller than the absolute coherence values. However, it has the advantage to take into account the inter-subject variability of baseline coherence. Of note, the ERCoh of the grand average data was not illustrated, since the frequency of the coherence peak within the gamma band differed subject-by-subject and induced some smoothness in the graphs. Frequencies of the coherence peak values for all bands and subjects and for the ENC and RET conditions were reported in Table 3.

A statistical interaction was observed among all the factors of the ANOVA design such as condition (ENC, RET), electrode pair (F3-P3, F4-P4), and time (*T*1, *T*2) ($F(1,9) = 8.94; p < 0.015$). The mean across subjects of the ERCoh for that interaction is illustrated in Fig. 3. Duncan post-hoc testing indicated that, at *T*2 period, the ERCoh between the left fronto-parietal electrodes (F3-P3) was stronger for the ENC than the RET condition ($p < 0.05$) in the gamma band. In contrast, the ERCoh between the right fronto-parietal electrodes (F4-P4) was stronger for the RET than the ENC condition ($p < 0.05$). These results fitted the HERA model. Of note, the ANOVA analysis for the other bands of interest revealed no statistically significant interaction including the factors condition and electrode pair.

3.2. "Direction" of the fronto-parietal connectivity as revealed by DTF

In line with the coherence results, only the EEG data relative to the gamma band at *T*2 were used as an input for the computation of the DTF. A significant interaction ($F(1,9) = 5.65; p < 0.041$) was observed among the factors of the ANOVA design such as condition (ENC, RET), direction (frontal-to-parietal, F→P; Parietal-to-frontal, P→F), and electrode pair (F3-P3, F4-P4). The mean across subjects of the DTF for that interaction is illustrated in Fig. 4. Duncan post-hoc testing indicated that the parietal-to-frontal "direction" was significantly predominant when compared to the frontal-to-parietal "direction" in the right hemisphere during the ENC condition and in the left hemisphere during the RET condition ($p < 0.05$). Namely, the hemisphere-condition combination not involved by the processes predicted by the HERA model. Instead, the parietal-to-frontal and frontal-to-parietal "directions" had similar strength (i.e. no prevailing directional flow) in the left hemisphere during the ENC condition and in the right hemisphere during the RET condition. Namely, the hemisphere-condition combination involved by the processes predicted by the HERA model. Similarly to the coherence results, characteristic features of the front-parietal coupling were observed in the hemisphere-condition combination of that model.

The control analysis of the DTF from the recorded EEG potentials showed a significant ANOVA interaction ($F(1,9) = 8,18; p < 0.019$) among the factors condition (ENC, RET), direction (frontal-to-parietal, F→P; parietal-to-frontal, P→F), and electrode pair (DTF mean of F3-P3 and F3-P5; DTF mean of F4-P4 and F4-P6). The mean across subjects of the DTF for that interaction is illustrated in Fig. 5. Duncan post-hoc testing indicated that the parietal-to-frontal "direction" was significantly predominant when compared to the frontal-to-parietal "direction" in the right hemisphere during the ENC condition and in the left hemisphere during the RET condition ($p < 0.02$). These results are very similar to those obtained computing the DTF from surface Laplacian estimates.

Table 3
The frequencies of the ERCoh peak values for all bands and subjects in the left and in the right hemisphere (F3-P3, F4-P4), both for the encoding (ENC) and retrieval (RET) conditions

Individual EEG Er-coherence frequencies								
Encoding (ENC)								
	F3-P3				F4-P4			
Subjects	Theta	Alpha	Beta	Gamma	Theta	Alpha	Beta	Gamma
Sub. 1	7	8	24	34	7	8	23	45
Sub. 2	5	10	19	37	4	11	19	33
Sub. 3	7	9	16	45	6	10	25	44
Sub. 4	4	11	26	36	6	11	17	32
Sub. 5	7	9	14	45	7	12	28	32
Sub. 6	7	12	22	42	7	8	19	33
Sub. 7	5	11	15	40	5	9	14	37
Sub. 8	4	10	28	45	4	9	16	37
Sub. 9	6	11	21	45	7	13	28	31
Sub. 10	5	8	29	39	6	13	17	44
Mean	5.7	9.9	21.4	40.8	5.9	10.4	20.6	36.8
S.D.	1.25	1.37032	5.378971	4.211096	1.197219	1.897367	5.059644	5.573748
S.E.	0.40	0.43	1.70	1.33	0.38	0.60	1.60	1.76
Retrieval (RET)								
Sub.1	5	9	23	34	5	9	24	32
Sub. 2	6	10	17	44	5	9	17	30
Sub. 3	7	13	23	31	7	11	26	44
Sub. 4	4	12	18	35	4	10	21	35
Sub. 5	7	10	22	38	6	10	27	43
Sub. 6	4	10	24	44	7	11	16	45
Sub. 7	7	10	29	43	4	10	17	33
Sub. 8	6	13	16	31	4	10	16	33
Sub. 9	7	12	21	42	7	9	25	31
Sub. 10	7	10	22	45	6	9	17	32
Mean	6	10.9	21.5	38.7	5.5	9.8	20.6	35.8
S.D.	1.247219	1.449138	3.807887	5.578729	1.269296	0.788811	4.501851	5.82714
S.E.	0.39	0.46	1.20	1.76	0.40	0.25	1.42	1.84

These frequencies were the same in the two periods of interest ($T1$, $T2$).

4. Discussion

4.1. Methodological remarks

In the present study, the working hypothesis focused on HERA model of encoding and retrieval processes and on the related fronto-parietal functional connectivity of brain rhythms as revealed by spectral coherence and DTF. These rhythms are considered as mainly non-phase locked, as opposed to phase-locked activity reflected by event-related potentials [43]. The discussion of possible functional "decoupling" of the brain activity phase locked to these processes is, hence, beyond the scope of this study but would merit to be addressed by future research [11].

The present experimental design allowed a selective analysis (even if partial) of the fronto-parietal coupling related to the encoding/retrieval processes and the preparation for the motor response occurring after the go signal. The period of the analysis was limited to the first 2 s after the onset of the figures with internals and landscapes. This avoided the possible contamination of motor preparation on the encoding and retrieval processes. Indeed, the periods of interest for the evaluation of the encoding and retrieval processes were taken more than 3 s before the onset of the go signal. In line with the methodological approach, we applied the DTF analysis only to the encoding-retrieval periods showing statistically significant coherence values at the fronto-parietal electrodes, namely the $T2$ period.

In the present study we combined two independent mathematical methods for the reconstruction of the fronto-parietal functional connectivity, namely the spectral coherence and DTF analyses. These techniques were applied on the same individual data sets, namely the spline surface Laplacian estimates. The basic idea was to follow the methodological streamline of a vast literature on EEG coherence and to exploit the unique opportunities of the DTF analysis for the reconstruction of the directional flow of the information between electrode pairs. In this regard, the preliminary spline surface Laplacian estimation removed the effects of the electrode reference from the recorded EEG data, an important step before the computation of the spectral coherence. Furthermore, the spline surface Laplacian estimation deflated the coherence values from the head volume conduction. Indeed, recent investigations on simulated and real EEG data have shown that artifactual effects on coherence [8,46] are negligible when the spline Laplacian functions are correctly implemented and
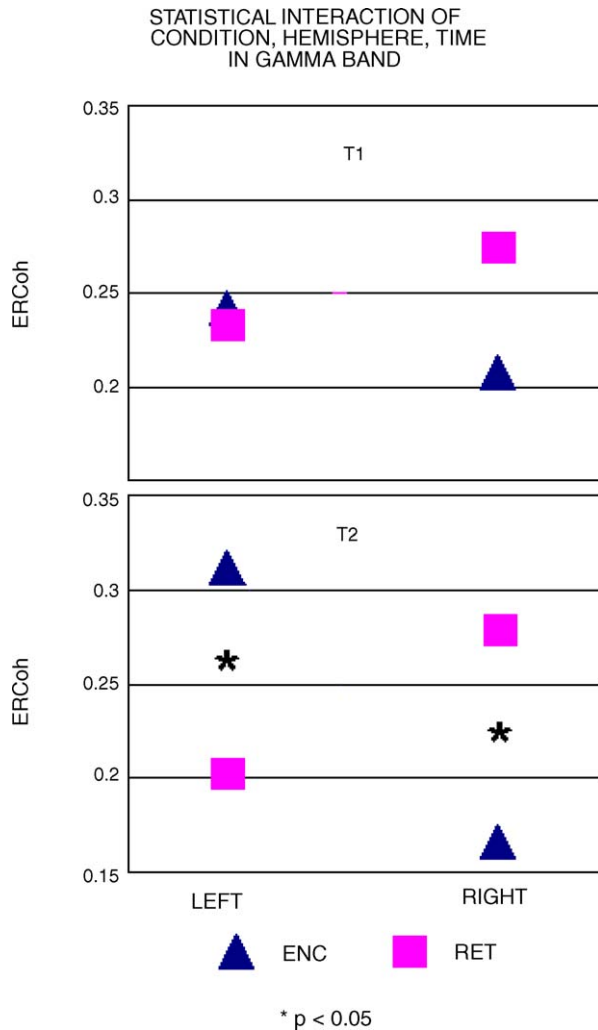
Fig. 3. Means across subjects of the event-related coherence (ERCoh) at the gamma frequencies (around 40 Hz) computed from the fronto-parietal (F3-P3, F4-P4) electrode pairs during $T1$ and $T2$ periods. These values were given as an input to an ANOVA design for repeated measures including the factors condition (ENC, RET), electrode pair (F3-P3, F4-P4), and time ($T1$, $T2$). There was a statistical interaction ($F(1,9) = 8.94$; $p < 0.015$) among these factors, Duncan post-hoc testing results are indicated by the asterisk ($p < 0.05$).

used [37,40,41]. Furthermore, we strictly followed the aforementioned guidelines for the use of surface Laplacian estimation for EEG coherence analysis. This was important not only for the precision of the coherence estimation but also for the DTF estimation, which is sensitive to artifactual correlations between electrodes. As a limitation of the present surface Laplacian estimation, the relevant coherence between ventral prefrontal and temporal (including hippocampus) cortical regions could not be reliably computed. Indeed, the spline surface Laplacian estimate at a given brain or scalp site needs substantial EEG data from surrounding electrodes to be reliable [36] and this was not the case of the present scalp montage with electrodes overlying frontal-ventral and temporal regions.

However, one might argue that the DTF computation from Laplacian estimates is affected by the correlations introduced by these estimates into the MVAR model. One might also argue that more than four electrodes (F3, P3, F4, P4) should be taken

into account for the study of the front-parietal network. In order to control the DTF results obtained using Laplacian estimates from four electrodes, we repeated the analysis of the information flow on the recorded EEG potentials (no preliminary surface Laplacian estimation as in [26,27,29]). In this control analysis, EEG data from thirty electrodes (border electrodes discarded) were given as an input to the MVAR model and the information flow between frontal and parietal regions were evaluated for the left (F3-P3, F3-P5) and right (F4-P4, F4-P6) hemispheres. The results from the recorded EEG data fully confirmed those obtained using preliminary surface Laplacian estimation.

4.2. Long-term episodic memory: fronto-parietal coupling in line with HERA model

In the present study, the encoding of visuospatial contents (i.e. "interiors" or "landscapes") induced a marked increase of EEG gamma coherence (about 40 Hz) between frontal and parietal electrodes, which was stronger in the left than right hemisphere. In the retrieval condition, the recognition of these contents with respect to "distractors" produced marked fronto-parietal gamma coherence, which was prominent to the right than left hemisphere. This pattern of fronto-parietal coupling fitted the HERA model. However, did it merely depend on visuo-spatial information processing rather than encoding-retrieval processes [13,14,20,28,47,51,52]? We do not think so, since the present visual stimuli were quite similar in the encoding and retrieval conditions (identical in the cases of target figures).

An alternative explanation is that the prominent left fronto-parietal gamma coherence of the encoding condition would reflect the functional "binding" among the visuospatial and "pragmatic" representations of the visual scene, the generic representations of "interiors" and "landscapes" in the semantic memory, and the subjects' intentions following the experimental demands [7,16,21,25]. In the retrieval condition, the right fronto-parietal gamma coherence would be related to the functional "binding" of the representations elicited by the visual scene with those of previous similar episodes, i.e. the so called "retrieval mode" [1,6,15,32,39,54,55]. The gamma frequency (about 40 Hz) would be the specific "binding" code of the coordinated fronto-parietal coupling, because of parallel amplitude and coherence of the alpha rhythms during encoding and retrieval processes did not follow the HERA model [2]. In this conceptual framework, the previous evidence of increased parietal gamma during the encoding and retrieval processes (Babiloni et al. [1]) should be re-considered in the light of the present finding of a coordinated coupling of the fronto-parietal gamma rhythms. In that sense, even the previous evidence become fully compatible with the predictions of the HERA model focused on the prefrontal cortex [32,39,48,49,54].

To evaluate the hierarchical role of the prefrontal and posterior parietal cortices in the above functional coupling, the analysis of the information flow between fronto-parietal electrodes was performed with the DTF method [26,27,29]. The DTF computation for the gamma rhythms showed a predominance of the parietal-to-frontal "direction" in the right hemisphere during the encoding condition and in the left hemisphere during
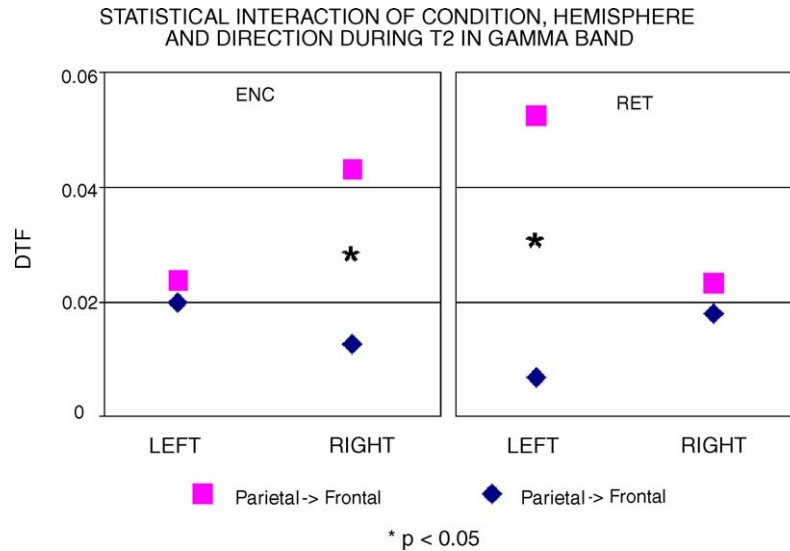
Fig. 4. Means across subjects of the directed transformation function (DTF) estimates at the gamma frequencies (around 40 Hz) computed from the fronto-parietal (F3-P3, F4-P4) electrode pairs at the $T2$ period. These values were given as an input to an ANOVA design for repeated measures including the factors condition (ENC, RET), electrode pair (F3-P3, F4-P4), and direction of the information flux (frontal-to-parietal, parietal-to-frontal). There was a statistical interaction ($F(1,9) = 5.65$; $p < 0.041$) among these factors, Duncan post-hoc testing results are indicated by the asterisk ($p < 0.05$).

the retrieval condition (i.e. hemisphere-condition combination not involved by the typical HERA effects). This is in line with the mainstream of the visual information into the cerebral cortex [58] and would indicate prevalent visual processes from visual (parietal) to executive (frontal) areas for visuo-motor transformations. The same mainstream of the visual information was observed in a previous DTF study showing preponderant parietal-to-frontal information flow during visuo-motor demands [1].

As an intriguing result, the DTF estimates showed a balanced bidirectional pattern of the fronto-parietal coupling in the hemispheres involved by the typical HERA effects, namely the left hemisphere during the encoding condition and the right hemisphere during the retrieval condition. According to the HERA model, in that hemisphere-condition combination, the parietal-

to-frontal direction accompanying the visual analysis of the episodes would parallel an opposite "top-down" flow of information from the frontal to the parietal areas. This speculation is in accordance with the typical predictions of the HERA model on the increasing role of the prefrontal cortex in the memory encoding and retrieval [32,39,48,49,54]. Furthermore, the same balance between the fronto-parietal information flows was seen in the previous DTF study during short-term memory demands [1]. Unlikely, low spatial resolution of the present EEG approach could not allow the functional dissociation of inferior (Brodmann area 46) and superior (Brodmann areas 9 and 8) parts of the lateral prefrontal cortex in the encoding-retrieval processes and in the maintenance of the representations in working memory. Analogously, it was not possible to disentangle the role of cingulated systems in the parallel "top down" attentional processes.
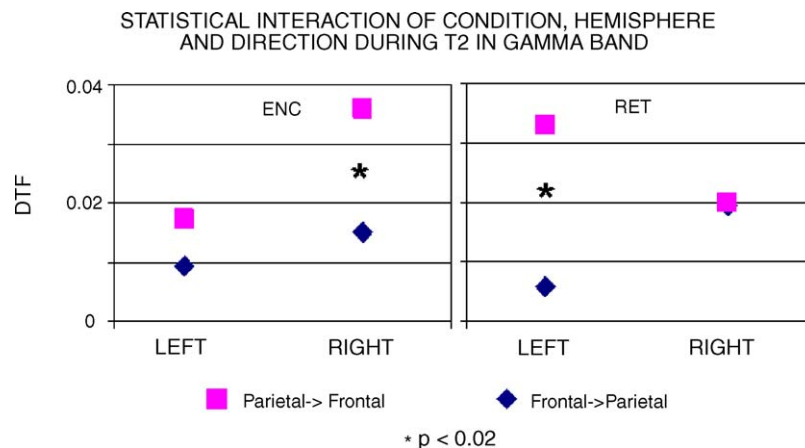

Fig. 5. Means across subjects of the DTF estimates at the gamma frequencies (around 40 Hz) computed from the fronto-parietal electrode pairs at the $T2$ period on the recorded potentials. These values were given as an input to an ANOVA design for repeated measures including the factors condition (ENC, RET), electrode pair (DTF mean of F3-P3 and F3-P5; DTF mean of F4-P4 and F4-P6), and direction of the information flux (frontal-to-parietal, parietal-to-frontal). There was a statistical interaction ($F(1,9) = 8.18$; $p < 0.019$) among these factors, Duncan post-hoc testing results are indicated by the asterisk ($p < 0.02$).

These are crucial issues for the understanding of executive control functions [22], to be investigated with advanced whole-head magnetoencephalographic techniques combining high temporal and moderate spatial resolution.

5. Conclusions

The present EEG study investigated the functional fronto-parietal coupling during the long-term episodic memory (visuo-spatial contents), to test the predictions of the HERA model on the related inter-hemispherical functional asymmetry. In line with the HERA model, fronto-parietal functional coupling of gamma rhythms (about 40 Hz) prevailed in the left hemisphere during the encoding condition and in the right hemisphere during the retrieval condition. That coupling would show balanced bidirectional information flows between frontal and parietal areas, as opposed to dominant parietal-to-frontal information flow in the right hemisphere during the encoding condition and in the left hemisphere during the retrieval condition (i.e. hemisphere-condition combination not involved by the HERA model). In the light of this fronto-parietal coupling at gamma frequency, the previous evidence of increased parietal gamma rhythms during the encoding and retrieval processes [2] become fully compatible with the predictions of the HERA model. Even with all limitations of the studies carried out in small groups (here $N = 10$), the present results open promising perspectives to the study of fronto-parietal functional coupling during encoding and retrieval processes in humans.

Acknowledgments

References

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

[2] C. Babiloni, F. Babiloni, F. Carducci, S. Cappa, F. Cincotti, C. Del Percio, C. Miniussi, D.V. Moretti, P. Pasqualetti, S. Rossi, K. Sosta, P.M. Rossini, Human cortical EEG rhythms during long-term episodic memory task. A high-resolution EEG study of the HERA model, Neuroimage 21 (2004) 1576–1584.

[3] C. Babiloni, F. Vecchio, F. Babiloni, G.A. Brunelli, F. Carducci, F. Cincotti, V. Pizzella, G.L. Romani, F. Tecchio, P.M. Rossini, Coupling between "Hand" primary sensorimotor cortex and lower limb muscles after ulnar nerve surgical transfer in paraplegia, Behav. Neurosci. 118 (2004) 214–222.

[4] F. Babiloni, F. Carducci, C. Babiloni, A. Urbano, Improved realistic Laplacian estimate of highly-sampled EEG potentials by regularization techniques, Electroencephalogr. Clin. Neurophysiol. 106 (1998) 336–343.

[5] F. Babiloni, C. Babiloni, F. Carducci, L. Fattorini, P. Onorati, A. Urbano, Spline Laplacian estimate of EEG potentials over a realistic magnetic resonance-constructed scalp surface model, Electroencephalogr. Clin. Neurophysiol. 98 (1996) 363–373.

[6] E. Basar, C. Basar-Eroglu, S. Karakas, M. Schurmann, Brain oscillations in perception and memory, Int. J. Psychophysiol. 35 (2000) 95–124.

[7] A. Bechara, H. Damasio, A.R. Damasio, G.P. Lee, Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making, J. Neurosci. 19 (1999) 5473–5481.

[8] C.A. Biggins, G. Fein, J. Raz, A. Amir, Artifactually high coherences result from using spherical spline computation of scalp current density, Electroencephalogr. Clin. Neurophysiol. 79 (1991) 413–419.

[9] K.J. Blinowska, R. Kus, M. Kaminski, Related Granger causality and information flow in multivariate processes, Phys. Rev. E Stat. Nonlin. Soft Matter. Phys. 70 (2004) 050902.

[10] J.B. Brewer, Z. Zhao, J.E. Desmond, G.H. Glover, J.D. Gabrieli, Making memories: brain activity that predicts how well visual experience will be remembered, Science 281 (1998) 1185–1187.

[11] W.S. Brown, J.T. Marsh, J.C. Smith, Contextual meaning effects on speech-evoked potentials, Behav. Biol. 9 (1973) 755–761.

[12] R.L. Buckner, W.M. Kelley, S.E. Petersen, Frontal cortex contributes to human memory formation, Nat. Neurosci. 12 (1999) 311–314.

[13] K. Dujardin, J.L. Bourriez, J.D. Guieu, Event-related desynchronization (ERD) patterns during verbal memory tasks: effect of age, Int. J. Psychophysiol. 16 (1994) 17–27.

[14] K. Dujardin, J.L. Bourriez, J.D. Guieu, Event-related desynchronization (ERD) patterns during memory processes: effects of aging and task difficulty, Electroencephalogr. Clin. Neurophysiol. 96 (1995) 169–182.

[15] A.K. Engel, P. Fries, W. Singer, Dynamic predictions: oscillations and synchrony in top-down processing, Nat. Rev. Neurosci. 2 (2001) 704–716.

[16] A.K. Engel, W. Singer, Temporal binding and the neural correlates of sensory awareness, Trends Cogn. Sci. 5 (2001) 16–25.

[17] P.C. Fletcher, R.N.A. Henson, Frontal lobes and human memory. Insights from functional neuroimaging, Brain 124 (2001) 849–881.

[18] C. Gerloff, J. Richard, J. Hadley, A.E. Schulman, M. Honda, M. Hallet, Functional coupling and regional activation of human cortical motor areas during simple, internally paced and externally paced finger movements, Brain 121 (1998) 1513–1531.

[19] A. Gevins, M.E. Smith, H. Leong, L. McEvoy, S. Whitfield, R. Du, G. Rush, Monitoring working memory load during computer-based tasks with EEG pattern recognition methods, Hum. Factors 40 (1998) 79–91.

[20] J.A. Gonzalez-Hernandez, C. Pita-Alcorta, I. Cedeno, J. Bosch-Bayard, L. Galan-Garcia, W.A. Scherbaum, P. Figueredo-Rodriguez, Wisconsin Card Sorting Test synchronizes the prefrontal, temporal and posterior association cortex in different frequency ranges and extensions, Hum. Brain Mapp. 17 (2002) 37–47.

[21] M.H. Grosbras, A. Berthoz, Parieto-frontal networks and gaze shifts in humans: review of functional magnetic resonance imaging data, Adv. Neurol. 93 (2003) 269–280.

[22] O. Gruber, T. Goschke, Executive control emerging from dynamic interactions between brain systems mediating language, working memory and attentional processes, Acta Psychol. (Amst). 115 (2004) 105–121.

[23] R. Habib, L. Nyberg, E. Tulving, Hemispheric asymmetries of memory: the HERA model revisited, Trends Cogn. Sci. 7 (2003) 241–245.

[24] D.M. Halliday, J.R. Rosenberg, A.M. Amjad, P. Breeze, B.A. Conway, S.F. Farmer, A framework for the analysis of mixed time series/point process data—theory and application to the study of physiological tremor, single motor unit discharges and electromyograms, Prog. Biophys. Mol. Biol. 64 (1995) 237–278.

[25] M.W. Jones, A comparative review of rodent prefrontal cortex and working memory, Curr. Mol. Med. 2 (2002) 639–647.

[26] M. Kaminski, K. Blinowska, W. Szclenberger, Topographic analysis of coherence and propagation of EEG activity during sleep and wakefulness, Electroencephalogr. Clin. Neurophysiol. 102 (1997) 216–227.

[27] M.J. Kaminski, K.J. Blinowska, A new method of the description of the information flow in the brain structures, Biol. Cybern. 65 (1991) 203–210.

[28] A. Keil, M.M. Muller, W.J. Ray, T. Gruber, T. Elbert, Human gamma band activity and perception of a gestalt, J. Neurosci. 19 (1999) 7152–7161.

[29] A. Korzeniewska, S. Kasicki, M. Kaminski, K.J. Blinowska, Information flow between hippocampus and related structures during various types of rat's behavior, J. Neurosci. Methods 25 (1997) 49–60.

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

[31] L. Leocani, G. Comi, EEG coherence in pathological conditions, J. Clin. Neurophysiol. 16 (1999) 548–555.

[32] M. Lepage, O. Ghaffar, L. Nyberg, E. Tulving, Prefrontal cortex and episodic memory retrieval mode, Proc. Natl. Acad. Sci. 97 (2000) 506–511.

[33] T. Locatelli, M. Cursi, D. Liberati, M. Franceschi, G. Comif, EEG coherence in Alzheimer's disease, Electroencephalogr. Clin. Neurophysiol. 106 (1998) 229–237.

[34] T. Mima, T. Matsuoka, M. Hallett, Functional coupling of human right and left cortical motor areas demonstrated with partial coherence analysis, Neurosci. Lett. 23 (2000) 93–96.

[35] T. Mima, T. Matsuoka, M. Hallett, Information flow from the sensorimotor cortex to muscle in humans, Clin. Neurophysiol. 112 (2001) 122–126.

[36] P. Nunez, Neocortical dynamics and human EEG rhytms, Oxford University Press, New York, 1995.

[37] P.L. Nunez, R. Srinivasan, A.F. Westdorp, R.S. Wijesinghe, D.M. Tucker, R.B. Silberstein, P.J. Cadusch, EEG coherency. I: Statistics, reference electrode, volume conduction, Laplacians, cortical imaging, and interpretation at multiple scales, Electroencephalogr. Clin. Neurophysiol. 103 (1997) 499–515.

[38] P.L. Nunez, B.M. Wingeier, R.B. Silberstein, Spatial-temporal structures of human alpha rhythms: theory, microcurrent sources, multiscale measurements, and global binding of local networks, Hum. Brain Mapp. 13 (2001) 125–164.

[39] L. Nyberg, A.R. McIntosh, R. Cabeza, R. Habib, S. Houle, E. Tulving, General and specific brain regions involved in encoding and retrieval of events: what, where, and when, Proc. Natl. Acad. Sci. USA 93 (1996) 11280–11285.

[40] R.D. Pascual-Marqui, The spherical spline Laplacian does not produce artifactually high coherences: comments on two articles by Biggins et al., Electroencephalogr. Clin. Neurophysiol. 87 (1993) 62–64.

[41] F. Perrin, Comments on article by Biggins et al., Electroencephalogr. Clin. Neurophysiol. 83 (1992) 171–174.

[42] F. Perrin, J. Pernier, O. Bertrand, J.F. Echallier, Spherical splines for scalp potential and current density mapping, Electroencephalogr. Clin. Neurophysiol. 72 (1989) 184–187.

[43] G. Pfurtscheller, F.H. Lopes da Silva, Event-related EEG/MEG synchronization and desynchronization: basic principles, Clin. Neurophysiol. 110 (1999) 1842–1857.

[44] C. Ranganath, MK. Johnson, M. D'Esposito, Left anterior prefrontal activation increases with demands to recall specific perceptual information, J. Neurosci. 20 (2000) RC108.

[45] P. Rappelsberger, H. Petsche, Probability mapping: power and coherence analyses of cognitive processes, Brain Topogr. Fall 1 (1988) 46–54.

[46] P. Rappelsberger, The reference problem and mapping of coherence: a simulation study, Brain Topogr. Fall-Winter 2 (1989) 63–72.

[47] E. Rodriguez, N. George, J.P. Lachaux, J. Martinerie, B. Renault, F.J. Varela, Perception's shadow: long-distance synchronization of human brain activity, Nature 397 (1999) 430–433.

[48] S. Rossi, S.F. Cappa, C. Babiloni, P. Pasqualetti, C. Miniussi, F. Carducci, F. Babiloni, P.M. Rossini, Prefrontal cortex in long-term memory: an "interference" approach using magnetic stimulation, Nat. Neurosci. 4 (2001) 948–952.

[49] M. Sandrini, S.F. Cappa, S. Rossi, P.M. Rossini, C. Miniussi, The role of prefrontal cortex in verbal episodic memory: rTMS evidence, J. Cogn. Neurosci. 15 (2003) 855–861.

[50] J. Sarnthein, H. Petsche, P. Rappelsberger, G.L. Shaw, A. von Stein, Synchronization between prefrontal and posterior association cortex during human working memory, Proc. Natl. Acad. Sci. USA 9 (1998) 7092–7096.

[51] C. Tallon-Baudry, A. Kreiter, O. Bertrand, Sustained and transient oscillatory responses in the gamma and beta bands in a visual short-term memory task in humans, Vis. Neurosci. 16 (3) (1999) 449–459.

[52] C. Tallon-Baudry, O. Bertrand, C. Delpuech, J. Permier, Oscillatory gamma-band (30–70 Hz) activity induced by a visual search task in humans, J. Neurosci. 17 (1997) 722–734.

[53] R.W. Thatcher, P.J. Krause, M. Hrybyk, Cortico-cortical associations and EEG coherence: a two-compartmental model, Electroencephalogr. Clin. Neurophysiol. 64 (1986) 123–143.

[54] E. Tulving, S. Kapur, F.I. Craik, M. Moscovitch, S. Houle, Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings, Proc. Natl. Acad. Sci. USA 91 (1994) 2016–2020.

[55] A. von Stein, J. Sarnthein, Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization, Int. J. Psychophysiol. 1 (38 (3)) (2000) 301–313.

[56] A. von Stein, P. Rappelsberger, J. Sarnthein, H. Petsche, Synchronization between temporal and parietal cortex during multimodal object processing in man, Cereb Cortex. 9 (1999) 137–150.

[57] A.D. Wagner, W. Koutstaal, D.L. Schacter, Related articles links when encoding yields remembering: insights from event-related neuroimaging, Philos. Trans. R. Soc. Lond. B Biol. Sci. 354 (1999) 1307–1324.

[58] S.P. Wise, D. Boussaoud, P.B. Johnson, R. Caminiti, Premotor and parietal cortex: corticocortical connectivity and combinatorial computations, Annu. Rev. Neurosci. 20 (1997) 25–42.