

# Visual Stimulus–Dependent Changes in Interhemispheric EEG Coherence in Humans

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**Knyazeva, M. G., D. C. Kiper, V. Y. Vildavski, P. A. Despland, M. Maeder-Ingvar, and G. M. Innocenti.** Visual stimulus–dependent changes in interhemispheric EEG coherence in humans. *J. Neurophysiol.* 82: 3095–3107, 1999. We analyzed the coherence of electroencephalographic (EEG) signals recorded symmetrically from the two hemispheres, while subjects ( $n = 9$ ) were viewing visual stimuli. Considering the many common features of the callosal connectivity in mammals, we expected that, as in our animal studies, interhemispheric coherence (ICoh) would increase only with bilateral iso-oriented gratings located close to the vertical meridian of the visual field, or extending across it. Indeed, a single grating that extended across the vertical meridian significantly increased the EEG ICoh in normal adult subjects. These ICoh responses were obtained from occipital and parietal derivations and were restricted to the gamma frequency band. They were detectable with different EEG references and were robust across and within subjects. Other unilateral and bilateral stimuli, including identical gratings that were effective in anesthetized animals, did not affect ICoh in humans. This fact suggests the existence of regulatory influences, possibly of a top-down kind, on the pattern of callosal activation in conscious human subjects. In addition to establishing the validity of EEG coherence analysis for assaying cortico-cortical connectivity, this study extends to the human brain the finding that visual stimuli cause interhemispheric synchronization, particularly in frequencies of the gamma band. It also indicates that the synchronization is carried out by cortico-cortical connection and suggests similarities in the organization of visual callosal connections in animals and in man.

## INTRODUCTION

Over the last few years, animal studies of brain rhythms in the gamma band ( $>20$  Hz) revealed two correlates of alert states during sensory stimulation or active behavior: local synchronization of activity, reflected in a power increase, and/or distant synchronization between remote cortical areas, shown by cross-correlation or coherence analyses (Bressler et al. 1993; Eckhorn 1994; Engel et al. 1991; Kreiter and Singer 1992). The importance of these findings is twofold. First, the synchronization of cortical activity might represent the neural substrate for Gestalt-type perceptual operations (reviewed in Singer and Gray 1995; von der Malsburg 1995). Second, to the

extent that the distant synchronization of fast cortical activity depends on cortico-cortical connections (Engel et al. 1991; Munk et al. 1995; for other references see Kiper et al. 1999), its analysis might provide a way of assessing the functional connectivity between cortical areas. This would be particularly desirable in human studies, for which reliable methods for analyzing cortico-cortical connections are scarce.

In animal studies, activity changes in the gamma frequency band were detected by intracortical recordings, an invasive technique mostly unusable in humans. On the other hand, the mere possibility of recording gamma activity from the human scalp recently was a debated topic (Lutzenberger et al. 1997; Menon et al. 1996). Thus it is important to determine whether stimulus- and connectivity-dependent changes of fast brain rhythms can be reliably identified by electroencephalographic (EEG) techniques in humans. This study was designed to replicate in humans the essential features of the animal experiments reported by Kiper et al. (1999). In that paper, we showed that in ferrets, stimulus-induced distant synchronization of cortical activity similar to that reported in cats and monkeys could be detected using epidural EEG recording and analysis of the interhemispheric coherence. An increased coherence in the gamma band was obtained for visual stimuli that activate callosally connected neuronal pools in the two hemispheres, suggesting that coherence changes can indeed be used to assay cortico-cortical connectivity.

A few noninvasive EEG and magnetoencephalography (MEG) studies in humans described gamma band responses to stimuli of different modalities (Desmedt and Tomberg 1994; Joliot et al. 1994; Kristeva-Feige et al. 1993; Lutzenberger et al. 1995; Makeig 1993; Müller et al. 1996; Pantev et al. 1991; Pullvermüller et al. 1995; Sannita 1994; Sannita et al. 1995; Tallon et al. 1995; Tallon-Baudry et al. 1997; Tiitinen et al. 1993). In the visual domain, Müller et al. (1996) observed a gamma power increase in occipital and parietal regions in humans viewing a single moving bar but not two bars moving in opposite directions. Similarly, Lutzenberger et al. (1995) found that gamma band power increased in the occipital region in response to coherently moving bars. Recently, Tallon-Baudry et al. (1997) reported a wide-spread transient power increase in the gamma band when human subjects were able to detect a figure hidden in a background. The results of these experiments are considered to support the hypothesis that the

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binding of perceptual features is achieved by synchronization of activity in the gamma band. However, it remains unclear which specific neural circuits are responsible for the synchronization.

In conclusion, it remains to be proven that cortico-cortical connections participate in synchronizing cortical activity in humans, as it appears to be the case in animals. This motivated the present study of stimulus induced power and coherence changes of EEG signals. The rationale for analyzing specifically the interhemispheric coherence dynamics induced by visual stimuli is identical to that discussed in relation to the animal work (Kiper et al. 1999), under the assumption that the relevant features of callosal connections between the visual areas are preserved across species, including man.

## METHODS

### *Subjects and experimental procedures*

Nine adult volunteers (5 women, 4 men), 19–37 years of age and without neurological history, participated in this study. All subjects but one were right-handed and had normal or corrected to normal vision. The EEGs were recorded in the resting state (both with closed and open eyes) and during visual stimulation. The ongoing EEG tracings were constantly monitored during the experiment to keep the subject's wakefulness level and the quality of recording under steady watch. To check the within-subject reliability of our data, the EEGs of two subjects were recorded twice at the 4- to 5-mo interval. All the procedures conformed to the Declaration of Helsinki (1964) by the World Medical Association concerning human experimentation.

### *Visual stimulation*

The stimuli were presented on a Eizo T-560 i monitor, driven by an AT Truevision Vista graphics board, with a refresh rate of 104 Hz, interlaced. A small white square in the center of the screen served as fixation point and was alternated with stimulus frames. The subjects were instructed to maintain their gaze on the fixation point. Adequate fixation was monitored by on-line video recordings. The stimuli were vertical rectangular patches of black-and-white sinusoidal gratings, with a space-averaged luminance of 32 cd/m<sup>2</sup>, presented on a uniform background of equal luminance. At the viewing distance we used (42 cm), the screen subtended 39 by 28° of visual angle, and the patches 13 by 24°. All the sinusoidal gratings had a spatial frequency of 0.5 c/deg, a contrast of 50%, and drifted with a temporal frequency of 2 Hz. The stimuli described below were presented in individual sequences repeated for a minimum of 50 times and randomized across subjects. Each stimulus was presented for 2 s (a duration shown to be appropriate by our animal experiments, Kiper et al. 1999). The inter-stimulus interval was variable, and averaged ~1.5 s. Longer intervals (breaks) were introduced when the subjects showed signs of fatigue or discomfort.

1) *Left hemifield stimulus*. A single patch of horizontally oriented, downward drifting gratings was presented to the left of the fixation point. The center of the patch was located 7° from the fixation point.

2) *Right hemifield stimulus*. Identical to 1), but presented to the right of the fixation point.

3) *Bilateral identical stimuli*. Gratings 1) and 2) were simultaneously presented. Therefore a vertical strip of visual field of 0.5° on each side of the vertical meridian (VM) was not stimulated.

4) *Bilateral different stimuli*. The grating to the left of the fixation point was as described above, but that on the right was vertically oriented and drifted to the right.

In addition to these four "close" conditions, we ran the same stimulations with gratings located further away from the fixation point. In that case, the patch centers were located 13° to the side of the

fixation point. Therefore the gratings did not stimulate a vertical strip of 6.5° on each side of the VM. We refer to these as the "far" conditions.

5) *Whole screen identical stimulus*. This consisted of a single patch of downward drifting horizontal grating (27 by 24°) centered on the fixation point.

6) *Whole screen different stimuli*. In this case, we presented a patch equal in extent to the whole screen identical stimulus consisting of a horizontal downward drifting grating on the left, and of a vertical rightward drifting grating on the right.

7) *Background*. As a reference condition, we used a uniform gray screen with same space-averaged luminance as the other stimuli.

The stimulation protocol for humans was, thus similar to that of our animal experiments (Kiper et al. 1999).

### *EEG recording and processing*

The EEGs were recorded according to the 10–20 system (Jasper 1958; Nuwer et al. 1994) from Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, T3, T4, T5, and T6 referenced to Fpz using a Neurofax encephalograph (Deltamed, France). Electrode sites determined by conventional measurements were treated with abrasive paste, and Ag-AgCl cup electrodes were affixed with collodion and filled with conductive electrode paste. This procedure allowed us to keep all electrode impedance below 5 k $\Omega$  for extended periods of time. The signals were filtered by an analogue band-pass filter (time constant of 1 s, upper cutoff at 100 Hz), a 50-Hz notch filter, and sampled at a frequency of 256 Hz to avoid contamination of the band under study ( $\leq 46$  Hz) from undersampled higher frequency components. We used the PC-based "EEG Lab" software package (Metrica, Moscow, Russia) for spectral processing.

Several methodological issues should be taken into account while analyzing gamma activity by means of noninvasive EEG techniques (Jürgens et al. 1995; Lutzenberger et al. 1997; Pulvermüller et al. 1997). Because coherence data depend on the derivation type (Andrew and Pfurtscheller 1996) and, in particular, are highly sensitive to signal variations at the common reference (Fein et al. 1988), we checked the reproducibility of our results under different montage schemes. Because there exists no universally accepted reference electrode, we digitally converted our initial Fpz reference into common average, bipolar, and ipsilateral earlobe reference montages, which all emphasize different properties of the EEG signals. In general, the common average reference acts like a spatial high-pass filter removing the DC component from the recorded signal (Lehmann 1986). However, if relatively few electrodes are used, the signal recorded from each active electrode can have a significant impact on the reference level, and this can lead to the emergence of spurious coherence changes over brain areas that are not really reactive (Gibbs and Gibbs 1984; Reilly 1993). Bipolar derivation potentially gives information on local voltage gradients but is highly dependent on the choice of electrode pairs and on the spacing between the electrodes. Electrode pairs located above co-active brain areas can thus fail to detect significant voltage differences (Osselton 1966, 1969). Under our experimental conditions, ipsilateral earlobe reference electrodes represent a good approximation of an ideal remote reference point, not contaminated by visual cortex activity, which is the focus of our study. In this case, any observed visual stimulus-dependent changes in interhemispheric coherence cannot be ascribed to the influence of a common reference, each hemisphere having its own independent reference electrode.

To obtain statistically reliable spectral parameters, 36–70 artifact-free EEG epochs, each of 2-s duration, were selected and processed in each experimental condition for every subject. Subsequently, to test the stability of the changes, the first and the second halves of the 2-s epochs were extracted and processed separately.

The EEG segments containing artifacts, including those due to eye

movements and excessive muscle activity, were identified on visual inspection and eliminated from further analysis.

To avoid a potential contamination of the data with muscle artifacts, the individually averaged spectral functions were carefully inspected within the frequency range 1–100 Hz. All subjects' responsive EEG frequencies were lower than 50 Hz, below the range of frequencies that is typical of muscle activity (Cacioppo et al. 1990). Thus a significant impact of muscle activity was highly improbable.

Spectral power density (SPD) for every channel and coherence functions for symmetrical interhemispheric pairs of leads (ICoh) were calculated by averaging the primary spectral estimates (computed by fast Fourier transformation) over all epochs and smoothing the averages by Parsen's window. Coherence function (Coh) between two signals  $x$  and  $y$  at each frequency  $f$  was then calculated as

$$\text{Coh}_{xy}(f) = |S_{xy}(f)|^2 / [S_{xx}(f) * S_{yy}(f)]$$

where  $S_{xy}(f)$ ,  $S_{xx}(f)$ , and  $S_{yy}(f)$  are cross-spectrum and autospectrum estimates of the  $x$  and  $y$  signals, respectively. Resulting spectral estimates had effective frequency resolution of 2 Hz for the data obtained from 2- and 1-s epochs.

### Statistical analysis

Preliminary visual inspection suggested that stimulus-specific responses were elicited within the beta-gamma band, i.e., at frequencies between the alpha range and 50 Hz. However, in some subjects, the beta1-frequencies (14–25 Hz) appeared to be contaminated by harmonics of the alpha rhythm and, therefore could not be used in all subjects. Thus the resulting gamma band was determined as 25–46 Hz. Because alpha band also seemed to be responsive, it was quantified for the standard range of 8–12 Hz, which well fitted all our subjects. For group data analysis, the individual ICoh and SPD responses for the bands defined above were computed as the differences between the band averages in stimulus and background conditions. Then, the ICoh responses were analyzed as a dependent variable with ANOVA (SPSS, version 7.5). Although their distribution was not normal, we performed ANOVA, because it is robust against deviations from normality, provided that there is the same number of cases in all the groups under comparison, and that their dispersions are not grossly inhomogeneous (Kelly et al. 1997; Morrison 1990). These conditions being satisfied, we assessed the effects of stimulation (factor Stimulus), electrode pair location (factor Location), and EEG frequency band (factor Band) on ICoh responses in the group of nine subjects. The Stimulus factor included three levels (stimuli): whole-screen, identical-close, and different-close. The Location factor had levels corresponding to interhemispheric pairs O1/O2, P3/P4, T5/T6, T3/T4, C3/C4, F3/F4, and Fp1/Fp2 with ipsilateral earlobe or common average references; or to bipolar pairs O1-P3/O2-P4, O1-T5/O2-T6, P3-C3/P4-C4, P3-T5/P4-T6, C3-F3/C4-F4, F3-Fp1/F4-Fp2. The Band factor had two levels: the alpha (8–12 Hz) and the gamma (25–46 Hz) ranges. Analyses of variance for different EEG montages (with ipsilateral earlobe reference, common average, and bipolar) were performed separately. For the analysis of SPD, where application of ANOVA was questionable because of significant inhomogeneity of the data, we used the Friedman test for several related samples, which does not assume a normal distribution of the data. Multiple comparisons were performed using the conservative Tamhane's T2 test for samples with unequal variances.

Having in mind to use EEG coherence analysis in future studies of individual cases, we gave special consideration to the reproducibility of the data both within and between subjects. To this end, we applied the nonparametric Wilcoxon's test to mean band values of the SPD and ICoh for single epochs of 2 s using built-in routines of the "EEG Lab."

## RESULTS

### Group data analysis of ICoh changes under visual stimulation

A three-way ANOVA with the following fixed factors: Band (alpha vs. gamma), Stimulus (whole-screen, identical-close, different-close) and Location (symmetrical electrode pairs; see METHODS) was performed on the individual ICoh responses, separately for each of the three montage schemes. For *ipsilateral earlobe* referenced data, the Band and Stimulus factors were highly significant ( $F_{1,349} = 131.21$ ,  $P < 0.0005$  for Band and  $F_{2,349} = 11.74$ ,  $P < 0.0005$  for Stimulus). Their interaction ( $F_{2,349} = 11.48$ ,  $P < 0.0005$ ) indicates that the ICoh responses to the various stimuli were clearly different in the two frequency bands under consideration. Location failed to reach statistical significance ( $F_{6,349} = 1.99$ ,  $P = 0.066$ ) but significantly interacted with Band ( $F_{6,349} = 6.84$ ,  $P < 0.0005$ ). This suggests that the topographical variations of the ICoh responses were band-specific. Figure 1, A–C, illustrates these results.

Indeed, responses in the alpha band consisted in a decreased ICoh in all the derivation pairs and stimulus conditions (Fig. 1A) in contrast to the gamma band location- and stimulus-specific coherence increases (Fig. 1B). Thus the next step was to analyze variance in the gamma band alone.

A two-way ANOVA with Stimulus and Location as factors and ICoh response as a dependent variable confirmed the main effects of both factors at a significance level of  $P < 0.0005$  ( $F_{2,174} = 23.14$  for Stimulus and  $F_{6,174} = 6.20$  for Location). The interaction between them was also significant ( $F_{12,174} = 1.99$ ,  $P = 0.029$ ).

Multiple comparisons showed that the ICoh response to the whole screen stimulation was higher than to any of the other two stimuli (identical-close or different-close;  $P < 0.05$ ) in occipital, parietal, posterior temporal, and central pairs. The ICoh responses associated with the whole screen stimulation depended on the location of the electrode pair. Parietal and occipital responses were similar ( $P = 0.927$ ); both were larger than the frontal (Fp1/Fp2 and F3/F4) and anterior temporal (T3/T4) pairs ( $P < 0.001$ ), and marginally larger than central (C3/C4) and posterior temporal (T5/T6) responses ( $P \leq 0.1$ ). No other stimulation condition resulted in such a location-specific pattern of responses.

Similar results were obtained with *common average reference* (Fig. 1C), except for a significant ICoh increase during the whole screen condition in the Fp1/Fp2 pair. However, the latter was not confirmed with bipolar derivations (see following text), suggesting that this frontal response is an artifact inherent to the common average montage, and due to activity in the occipital and parietal regions.

The same two-way ANOVA applied to *bipolar* EEG coherence data showed that the Stimulus and Location factors were significant ( $F_{2,149} = 24.80$ ,  $P < 0.0005$ , and  $F_{5,149} = 2.32$ ,  $P < 0.05$ , respectively). Multiple comparisons revealed that ICoh responses in posterior pairs of electrodes only changed as a function of stimulation condition. In summary, for posterior electrode locations all the montage schemes gave consistent results. Therefore we will restrict further descriptions to the ICoh responses computed with ipsilateral earlobe referenced EEG signals.



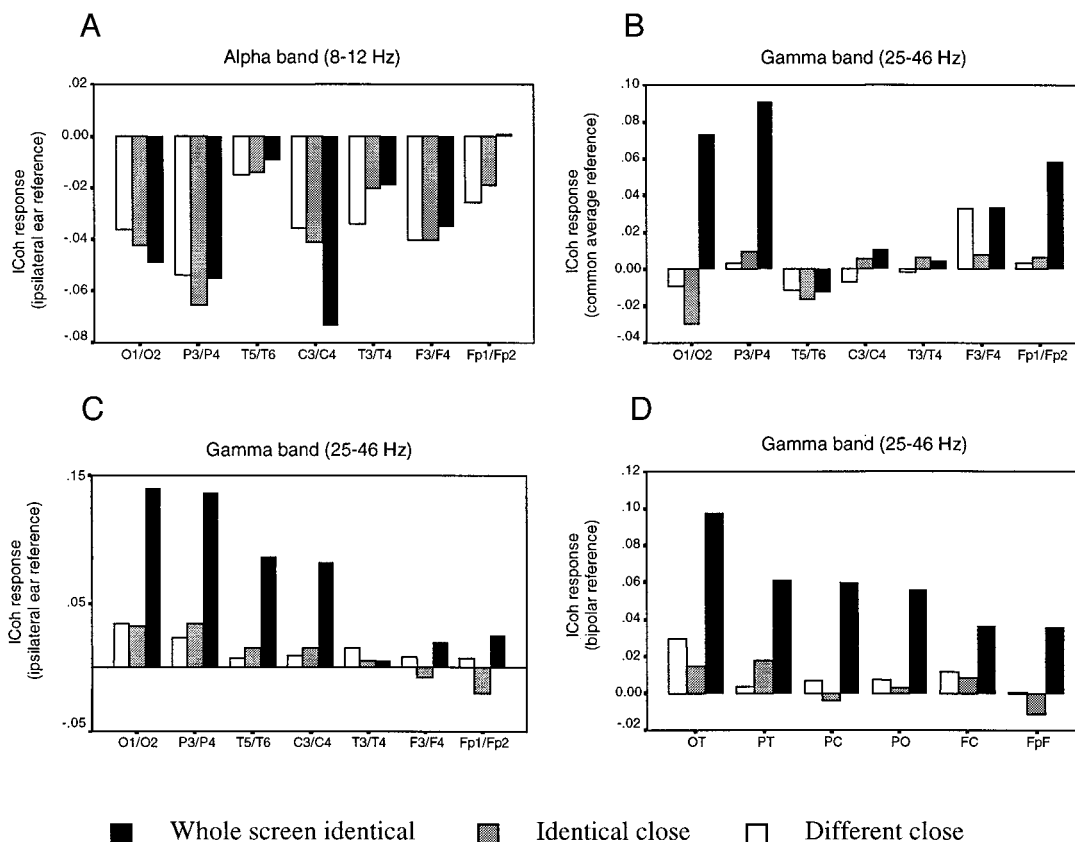


FIG. 1. Group averaged electroencephalogram (EEG) interhemispheric coherence (ICoh) responses in the alpha (A) and gamma (B–D) bands with ipsilateral ear (A and B), common average (C), and bipolar (D) references. In all graphs, the ICoh responses computed as the differences between the mean band values in stimulus (whole screen identical, different close, and identical close) and background conditions are shown. ANOVA showed stimulus- and location-specific ICoh changes for the gamma band only. For O1/O2 and P3/P4, the changes were independent of the montage scheme (see text).

#### Individual ICoh changes under visual stimulation

The above group statistics are confined to the whole-screen, different-close, and identical-close stimulus conditions, which were presented to nearly all subjects. Systematic ICoh changes were revealed in the gamma band in the occipital and parietal regions. Analysis of the individual data (Table 1) indicated that the gamma band ICoh increase in response to the whole screen stimulation is highly reproducible between subjects.

Indeed, compared with the background condition, it was significant in all but one of the subjects and restricted to the occipital and parietal electrode pairs (Fig. 2).

Individually, some moderate increase was occasionally obtained for the identical-close (3 subjects) and different-close (4 subjects) stimulus conditions. A between-conditions comparison showed that ICoh levels were always greater for the whole screen gratings compared with the other stimuli (Table 2), including the whole-screen-different stimulus, which was presented in three experiments.

In five subjects, we used *unilateral* stimuli close to the VM, as well as a set of *far* stimuli. These were analyzed by means of individual statistics only. No reproducible ICoh responses were found either for the unilateral-close stimuli (Tables 1 and 2), or for any of the far stimuli. Individual examples of spectral curves obtained during the unilateral and the far stimulation are shown in Figs. 3 and 4, respectively.

To determine whether the ICoh changes were reproducible

over long time intervals in the same individual, we recorded the EEGs of two subjects (*IC* and *NB*) twice, at a several month interval. In both cases, significantly larger responses were obtained with the whole-screen than with other stimuli (Tables 1 and 2).

#### Temporal stability of the gamma band coherence response

The data presented so far are based on the analysis of 2-s EEG segments. To study the temporal stability of the ICoh responses during stimulation, we performed a MANOVA with Epoch of analysis as a factor (1st vs. 2nd second), and ICoh values for the O1/O2 and P3/P4 pairs as dependent variables, for the background and whole screen conditions separately. This analysis showed no significant changes between the first and second halves of exposure to the stimuli ( $F_{1,17} = 0.580$ ,  $P = 0.682$  for background, and  $F_{1,17} = 0.085$ ,  $P = 0.986$  for the whole screen). In addition, individual statistics also revealed no significant ICoh differences between the first and last seconds in any of the stimulus conditions. The group results and a representative individual example are shown in Fig. 5.

#### EEG spectral power response to visual stimulation and its relation to the ICoh response in the gamma band

To reveal possible relations between local and distant synchronization, we analyzed stimulus-induced SPD changes of

TABLE 1. Individual ICoh values in the gamma band during visual stimulation with close and whole screen gratings, compared to background

Stimuli	IC, Experiment 1	IC, Experiment 2	NG	DK	LM	LT	NB, Experiment 1	NB, Experiment 2	KL	MG	TR
<i>O1/O2</i>											
Whole screen	<b>0.575<sup>a</sup></b>	<b>0.433<sup>b</sup></b>	<b>0.595<sup>a</sup></b>	<b>0.381<sup>c</sup></b>	<b>0.381<sup>d</sup></b>	0.581	<b>0.765<sup>a</sup></b>	<b>0.587<sup>a</sup></b>	<b>0.701<sup>a</sup></b>	<b>0.599<sup>a</sup></b>	<b>0.423<sup>a</sup></b>
Bilateral identical	0.432	0.381/0.376	0.457	0.315	0.294	0.559	<b>0.678<sup>a</sup></b>	<b>0.568<sup>a</sup></b>	0.415	No data	0.338
Bilateral different	<b>0.486<sup>d</sup></b>	0.382	0.455	<b>0.352<sup>b</sup></b>	0.313	0.545	<b>0.605<sup>a</sup></b>	<b>0.481<sup>c</sup>/0.501<sup>c</sup></b>	<b>0.438<sup>c</sup>/0.479<sup>b</sup></b>	0.523	No data
Left	<b>0.458<sup>c</sup></b>	No data	0.476	0.321	0.289	0.540	No data	No data	No data	No data	No data
Right	<b>0.458<sup>c</sup></b>	No data	0.429	0.329	0.293	0.550	No data	No data	No data	No data	No data
Background	0.406	0.371	0.451	0.288	0.299	0.582	0.466	0.355	0.389	0.488	0.328
<i>P3/P4</i>											
Whole screen	<b>0.522<sup>a</sup></b>	<b>0.404<sup>b</sup></b>	<b>0.520<sup>a</sup></b>	<b>0.358<sup>c</sup></b>	<b>0.346<sup>b</sup></b>	0.432	<b>0.636<sup>a</sup></b>	<b>0.648<sup>a</sup></b>	<b>0.612<sup>a</sup></b>	<b>0.485<sup>f</sup></b>	<b>0.305<sup>c</sup></b>
Bilateral identical	<b>0.414<sup>c</sup></b>	0.331	0.307	<b>0.281<sup>b</sup></b>	0.274	0.387	<b>0.565<sup>a</sup></b>	<b>0.627<sup>a</sup></b>	0.412	No data	0.242
Bilateral different	<b>0.435<sup>b</sup></b>	0.330/0.355	<i>0.279<sup>c</sup></i>	<b>0.284<sup>b</sup></b>	0.286	0.363	<b>0.496<sup>a</sup></b>	<b>0.525<sup>a</sup>/0.572<sup>a</sup></b>	0.391/0.419	0.390	No data
Left	<b>0.416<sup>c</sup></b>	No data	0.332	<b>0.275<sup>b</sup></b>	0.284	0.398	No data	No data	No data	No data	No data
Right	<b>0.406<sup>c</sup></b>	No data	0.296	<b>0.298<sup>f</sup></b>	0.267	0.398	No data	No data	No data	No data	No data
Background	0.365	0.345	0.326	0.221	0.280	0.395	0.367	0.332	0.398	0.393	0.228
<i>T5/T6</i>											
Whole screen	<b>0.278<sup>d</sup></b>	<b>0.221<sup>c</sup></b>	<b>0.338<sup>a</sup></b>	0.213	0.219	0.331	<b>0.376<sup>a</sup></b>	<b>0.376<sup>a</sup></b>	<b>0.451<sup>a</sup></b>	<b>0.348<sup>c</sup></b>	0.194
Bilateral identical	0.184	0.184	0.204	0.206	0.184	0.243	<b>0.320<sup>a</sup></b>	<b>0.342<sup>a</sup></b>	0.171	No data	0.164
Bilateral different	0.206	0.183/0.167	0.220	0.215	0.199	0.295	0.264	0.289/0.291	0.163/0.211 <sup>b</sup>	0.294	No data
Left	0.209	No data	0.200	0.194	0.198	0.304	No data	No data	No data	No data	No data
Right	0.221	No data	0.165	0.215	0.178	0.300	No data	No data	No data	No data	No data
Background	0.212	0.192	0.203	0.183	0.187	0.333	0.228	0.236	0.157	0.293	0.178

The data are based on 2-s epochs of analysis. Significance levels are given compared to background values for the frequency band 25–46 Hz. <sup>a</sup>  $P < 0.0000$ . <sup>b</sup>  $P < 0.01$ . <sup>c</sup>  $P < 0.0005$ . <sup>d</sup>  $P < 0.005$ . <sup>e</sup>  $P < 0.05$ . <sup>f</sup>  $P < 0.001$ . The slash is used to separate values for the 2 bilateral different conditions, if applied. Left and right stand for stimuli presented in the left and right hemifields, respectively. ICoh, interhemispheric coherence.

the EEG signal in the alpha and gamma bands. To determine whether the spectral power was affected by the stimulation condition (whole screen, identical-close and different-close), we applied the nonparametric Friedman test (see METHODS, *Statistical analysis*) separately to the group data from each EEG derivation and band. Figure 6 shows that the decrease in the alpha power was similar for all the conditions in all derivations, whereas the increase in the gamma SPD was stimulus-specific in the occipital ( $P = 0.040$  for O1 and 0.028 for O2) and parietal ( $P = 0.054$  for P3 and 0.069 for P4) derivations.

Pairwise comparisons of the responses confirmed that, in the gamma band, the whole-screen stimulus was accompanied by a significantly larger SPD response than any of the other stimulation conditions ( $P$  ranged from 0.006 to 0.035 for O1, O2, and P4, and increased up to 0.08 for P3, Wilcoxon test).

As mentioned above, both ICoh and SPD in the gamma band increased specifically with whole screen stimulation. In principle, the power spectra of two EEG signals do not determine their coherence spectrum, which depends also on their phase relations (Nunez 1995), and one can thus expect these two measures to vary independently. However, if the processing of a stimulus involves both locally and distantly distributed synchronizations at the same frequencies, an increase in both local power and in distant coherence should be observable. The scatterplots from Fig. 7 show that the association in question may be expected for the whole screen stimulus. Indeed, Pearson's correlations between SPD and ICoh responses appeared to be significant (at the  $P = 0.01$  level; 2-tailed) for the whole screen condition only (0.915 for O1, 0.936 for O2, 0.845 for P3, and 0.944 for P4).

## DISCUSSION

This study was designed to determine whether functional aspects of the cortico-cortical connectivity could be analyzed in humans with EEG coherence techniques. Our results show that in humans, as in animals (Kiper et al. 1999), the EEG ICoh responses are location, frequency, and stimulus specific. Comparison with animal data suggests that, in humans, callosal fibers can synchronize the activity in the two hemispheres, and, possibly, within the hemisphere. Indeed, we found that the gamma activity of visual areas in the two hemispheres becomes synchronized only when a subject views a stimulus that presumably activates callosal connectivity.

### *Topography and frequency characteristics of the EEG ICoh response to visual stimulation*

Pronounced and reproducible ICoh responses, consistent across montage schemes, were restricted to occipital and parietal derivations (or parieto-occipital for bipolar EEG signals). This suggests that the responses resulted from the activity of the neural circuits underlying the posterior scalp electrodes. In addition, the observed changes in ICoh were visual stimulus dependent, and these changes conformed to predictions (see Kiper et al. 1999) based on the properties of the callosal connections between the visual areas of the two hemispheres. This points to the visual cortex as the main source of the activity we recorded in these experiments.

The surface electrode locations can be only roughly correlated with underlying cortical areas (Binnie et al. 1982; Myslobodsky and Bar-Ziv 1989). In particular, occipital electrodes O1 and O2, which are located lateral and superior to the occipital pole and overlapping the calcarine sulcus, might be either over Brodmann's area 17/V1, or 18/V2 (Homan et al. 1987). They might also record

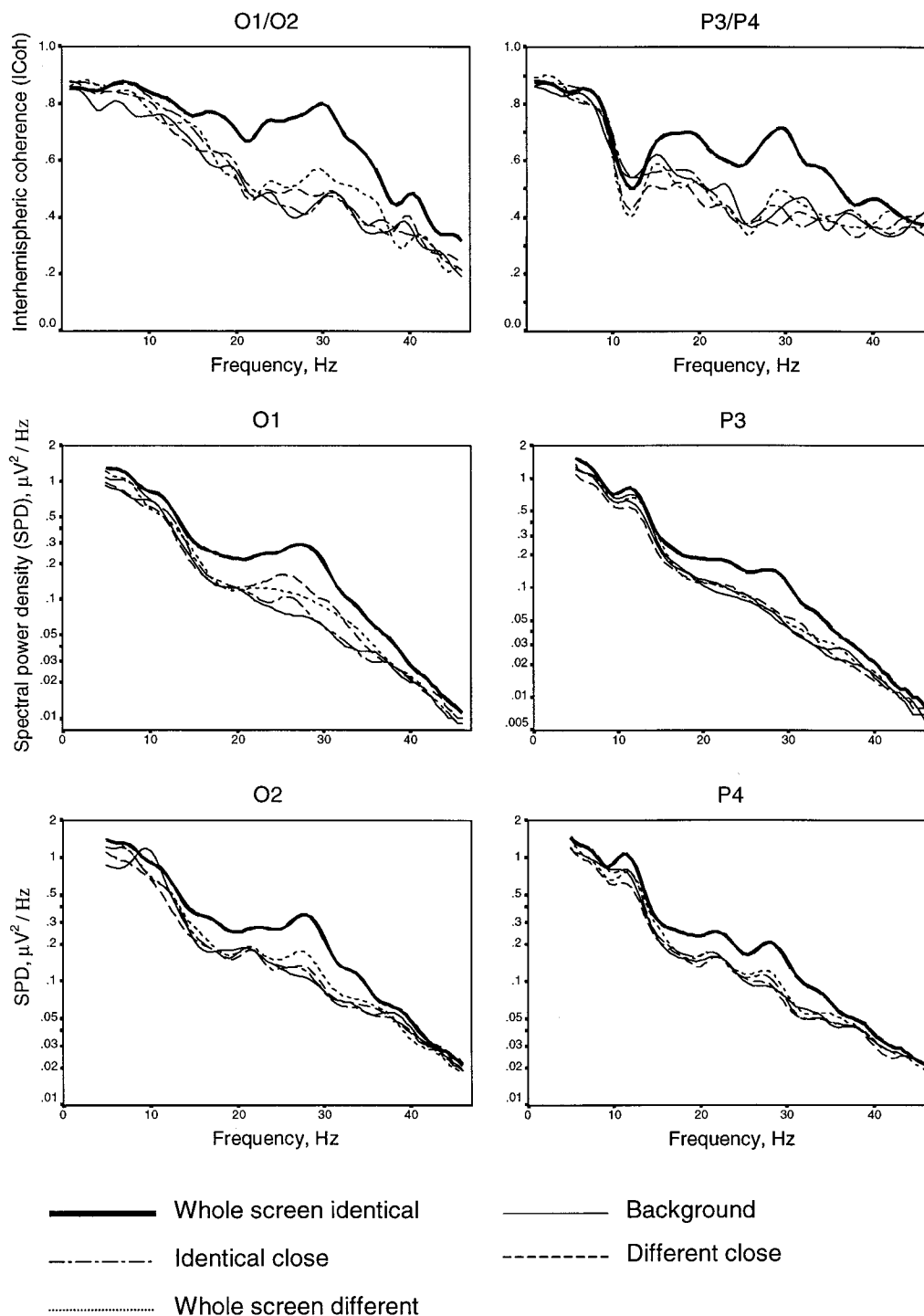


FIG. 2. Individual ICoh (top 2 panels) and power spectra (bottom 4 panels) for subject KL during various stimulation conditions: background (thin line), whole screen identical (thick line), whole screen different (dotted line), different close (dashed line), and identical close (dashed and dotted line).

the activity of other occipital extrastriate areas, because neuroimaging studies have shown that regions activated by coherently moving stimuli are considerably larger than primary visual areas (Van Essen and Drury 1997; Zeki 1993), and, in humans, callosal fibers connect both primary and secondary visual areas (Innocenti 1986; Zilles and Clarke 1997).

The P3 and P4 electrodes are localized over the parietal cortex, which is known to be concerned with visual functions

(for reviews see Cavada and Goldman-Rakic 1993; Gulyás 1997). In particular, these locations were shown to occupy a portion of the superior parietal lobule (Brodmann's area 7), in the vicinity of the intraparietal sulcus (Homan et al. 1987). In primates, portions of area 7 are visually responsive (Johnson et al. 1993; Mouncastle et al. 1975; Steinmetz et al. 1987), and, in humans, this region may partially include the motion-selective area V3A (Tootell et al. 1997).

TABLE 2. Individual ICoh values in the gamma band during visual stimulation with close gratings compared to the whole screen stimulus

Stimuli	IC, Experiment 1	IC, Experiment 2	NG	DK	LM	LT	NB, Experiment 1	NB, Experiment 2	KL	MG	TR
<i>O1/O2</i>											
Bilateral identical	0.432 <sup>a</sup>	0.381 <sup>b</sup>	0.457 <sup>a</sup>	0.315 <sup>c</sup>	0.294 <sup>d</sup>	0.559	0.678 <sup>a</sup>	0.568	0.415 <sup>a</sup>	No data	0.338 <sup>a</sup>
Bilateral different	0.486 <sup>d</sup>	0.382 <sup>b</sup> /0.386 <sup>e</sup>	0.455 <sup>a</sup>	0.352	0.313 <sup>c</sup>	0.545	0.605 <sup>a</sup>	0.481 <sup>a</sup> /0.501 <sup>a</sup>	0.438 <sup>b</sup> /0.479 <sup>a</sup>	0.523 <sup>d</sup>	No data
Left	0.458 <sup>a</sup>	No data	0.476 <sup>a</sup>	0.321 <sup>b</sup>	0.289 <sup>d</sup>	0.540	No data	No data	No data	No data	No data
Right	0.458 <sup>a</sup>	No data	0.429 <sup>a</sup>	0.329 <sup>b</sup>	0.293 <sup>c</sup>	0.550	No data	No data	No data	No data	No data
Whole screen	0.575	0.433	0.595	0.381	0.381	0.581	0.765	0.587	0.701	0.599	0.423
<i>P3/P4</i>											
Bilateral identical	0.414 <sup>a</sup>	0.331 <sup>c</sup>	0.307 <sup>a</sup>	0.281 <sup>c</sup>	0.274 <sup>c</sup>	0.387	0.565 <sup>d</sup>	0.627	0.412	No data	0.242 <sup>d</sup>
Bilateral different	0.435 <sup>d</sup>	0.330 <sup>c</sup> /0.355 <sup>e</sup>	0.279 <sup>a</sup>	0.284 <sup>c</sup>	0.286 <sup>c</sup>	0.363 <sup>b</sup>	0.496 <sup>a</sup>	0.525 <sup>a</sup> /0.572 <sup>a</sup>	0.391 <sup>a</sup> /0.419 <sup>a</sup>	0.390 <sup>d</sup>	No data
Left	0.416 <sup>a</sup>	No data	0.332 <sup>a</sup>	0.275 <sup>d</sup>	0.284 <sup>b</sup>	0.398	No data	No data	No data	No data	No data
Right	0.406 <sup>a</sup>	No data	0.296 <sup>a</sup>	0.298 <sup>c</sup>	0.267 <sup>f</sup>	0.398	No data	No data	No data	No data	No data
Whole screen	0.522	0.404	0.520	0.358	0.346	0.432	0.636	0.648	0.612	0.485	0.305
<i>T5/T6</i>											
Bilateral identical	0.184 <sup>a</sup>	0.184 <sup>b</sup>	0.204 <sup>a</sup>	0.206	0.184 <sup>b</sup>	0.343	0.320 <sup>e</sup>	0.342	0.171 <sup>a</sup>	No data	0.164 <sup>b</sup>
Bilateral different	0.206 <sup>d</sup>	0.183 <sup>b</sup>	0.220 <sup>a</sup>	0.215	0.199	0.295	0.264 <sup>a</sup>	0.289 <sup>d</sup> /0.291 <sup>a</sup>	0.163 <sup>a</sup> /0.211 <sup>a</sup>	0.294 <sup>e</sup>	No data
Left	0.209 <sup>d</sup>	No data	0.200 <sup>a</sup>	0.194	0.198	0.304	No data	No data	No data	No data	No data
Right	0.221 <sup>c</sup>	No data	0.165 <sup>a</sup>	0.215	0.178 <sup>b</sup>	0.300	No data	No data	No data	No data	No data
Whole screen <i>t</i>	0.278	0.221	0.338	0.213	0.219	0.331	0.376	0.376	0.451	0.348	0.194

<sup>a</sup>  $P < 0.0000$ . <sup>b</sup>  $P < 0.05$ . <sup>c</sup>  $P < 0.005$ . <sup>d</sup>  $P < 0.0005$ . <sup>e</sup>  $P < 0.01$ . <sup>f</sup>  $P < 0.001$ .

In five subjects, the response extended to posterior temporal derivations. The posterior temporal electrode over the left hemisphere (T5) falls on Brodmann's area 37, whereas on the right side (T6), it may be either over areas 19, 37, or 39 (Homan et al. 1987). Because we used moving stimuli, a more consistent response at T5 and T6 electrodes could have been expected because they are the closest to the presumptive motion associated visual area MT (Kaas 1995; Roland 1993; Tootell 1995; Van Essen and Drury 1997). However, considering the small size of this area, and inevitable differences in area and electrode location between subjects, the instability of the ICoh response in these electrodes is not surprising.

Of all the EEG rhythmic components, the alpha (8–12 Hz) and higher frequencies are considered mainly of cortical origin (Lopes da Silva 1991; Steriade et al. 1990). The alpha rhythms are viewed as a reflection of a "resting" state of the cortical areas (for review see Niedermeyer 1993; Pfurtscheller et al. 1996). Active states, such as the perception of visual stimuli, are accompanied by a desynchronization in the alpha-range (Lehtonen and Lehtinen 1972; Pfurtscheller et al. 1994; Ray and Cole 1985; Vanni et al. 1997). Consistent with this view, we observed a decreased power in the alpha band during visual stimulation with gratings, compared with the uniformly illuminated screen. In humans, interhemispheric synchronization in the alpha band was shown to be dependent on the integrity of the corpus callosum (CC) in the resting state (Koeda et al. 1995; Pinkofsky et al. 1997). In our experiments, ICoh in the alpha band tended to decrease or remained unchanged with visual stimulation. When an occasional increase was present, it appeared to be a component of a broadband response that involved the gamma frequencies as well. In addition, all changes in ICoh within this band were not stimulus specific.

Several human EEG studies revealed early-onset responses to visual stimuli in the gamma band. Lutzenberger et al. (1995) found an increase in the power of the 35- to 45-Hz band within the first 500 ms of stimulation. It was obtained with horizontal bars moving coherently in the right and left quadrants of the upper or lower hemifield. A significant increase in the power at

40–96 Hz was obtained by Müller et al. (1996), in response to a single vertical moving bar in the left hemifield, but not to two incoherently moving bars. The responses were predominantly from within the right hemisphere (O2, P4, T6 locations) and were most pronounced between 400 and 900 ms after the motion onset. Finally, recent studies using static visual stimuli (Tallon et al. 1995; Tallon-Baudry et al. 1997) revealed a short-lived gamma response to a real or illusory object. The gamma response was widely distributed over the cortex, covering both postcentral and precentral areas. These studies support the notion that the gamma band dynamics is associated with perception in humans, as it was originally suggested in animal studies (reviewed in Pulvermüller et al. 1997), but they cannot be interpreted in terms of cortical circuitry.

#### *Activation of callosal connections increases interhemispheric and, possibly, intrahemispheric synchronization*

Results presented in the companion paper (Kiper et al. 1999) suggested that callosal connections between areas 17, 18, and, possibly, 19 of the two hemispheres, when activated by a visual stimulus, synchronized the gamma band activity of these areas. These conclusions were based on three aspects of the results. First, the activation was obtained by stimuli located close to the VM of the visual field, whose representations are selectively connected by the CC, not for more peripheral stimuli. Second, the activation was obtained with bilateral iso-oriented gratings, but not with gratings of different orientation. Finally, the effects were eliminated by transection of the CC, as is also the case for the correlated activity of single neurons (Engel et al. 1991).

In humans, as in other species (reviewed in Innocenti 1986; Kennedy et al. 1991), the representations of the VM of the visual field are selectively interconnected by callosal axons in the primary and in some of the secondary visual areas (Clarke and Miklossy 1990). Therefore by comparison with the animal work, the present results suggest that the increased coherence in the gamma band is due to activation of callosal connections,

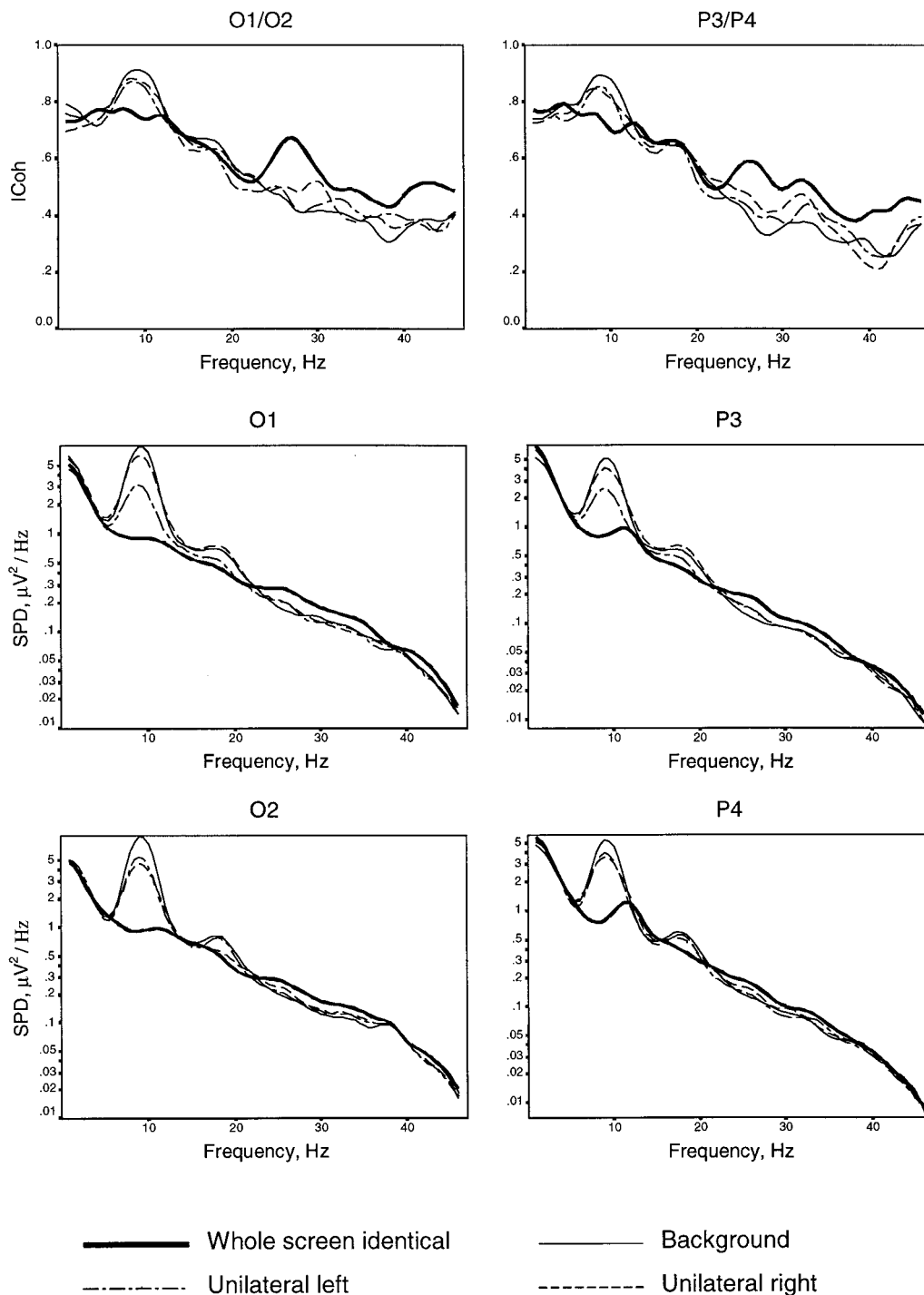


FIG. 3. Individual ICoh and power spectra (*subject IC*) associated with the unilateral visual stimuli: left, i.e., with the stimulus located in the left visual hemifield (dashed and dotted line), and right (dashed line). Results for the whole screen identical (thick line) and background (thin line) stimuli are shown for comparison.

which probably interconnect exclusively or preferentially iso-orientation columns (Gilbert and Wiesel 1989; discussed in Houzel et al. 1994). Whether callosal axons selectively interconnect iso-orientation columns in primates is not known, although a columnar organization of callosal connections was demonstrated in monkeys (Kennedy et al. 1986). It is tempting to assume that callosal axons do selectively interconnect iso-orientation columns in man. This might be a general trait of

cortico-cortical connectivity implementing “collinearity,” a fundamental principle of “Gestalt” perception (Bosking et al. 1997; Schmidt et al. 1997). Unlike in our animal study, we do not know whether the transection of the CC would eliminate the stimulus-dependent interhemispheric synchronization of gamma activity in humans. This is likely, however, because recent studies support a role of callosal connections in synchronizing the activity of the two hemispheres in humans



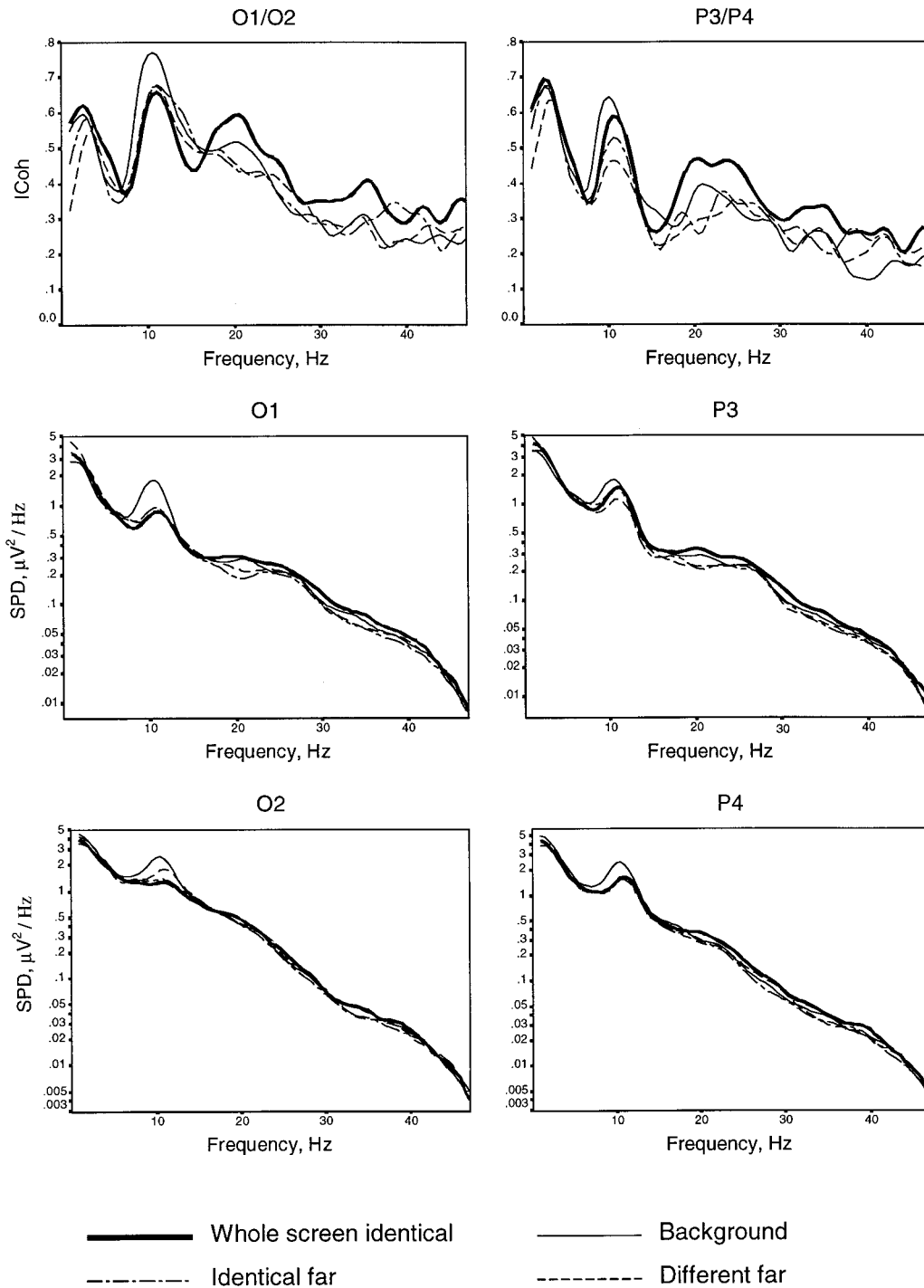


FIG. 4. Individual ICoherence and power spectra (*subject LM*) associated with visual stimuli presented far from the vertical meridian: identical far (dashed and dotted line), and different far (dashed line) stimuli. The background (thin line) and whole screen identical (thick line) conditions are shown for comparison.

(Koeda et al. 1995). A study in split-brain patients could help to rule out the possibility that, in spite of our precautions, volume conduction could contribute to the stimulus-dependent ICoherence dynamics.

There is one important difference between our animal and human results. In the animal experiments, EEG coherence increased with stimuli separated  $2.6^\circ$  from the VM. In humans, instead, it increased only with stimuli extending across the VM. One possible explanation of these differences is that the

callosal connections cover a narrower strip of visual field representation in man than in ferret. Furthermore, a complete activation of the region of bilateral representation in the cortex might be required. This region was estimated to extend  $\sim 1^\circ$  on either side of the VM (Fendrich et al. 1996), and therefore only half of it was stimulated by the bilateral identical stimuli. Alternatively, in awake humans, ICoherence might increase only when the stimuli are perceived as a whole, rather than two separate gratings (Kiper et al. 1998; Knyazeva et al. 1998).

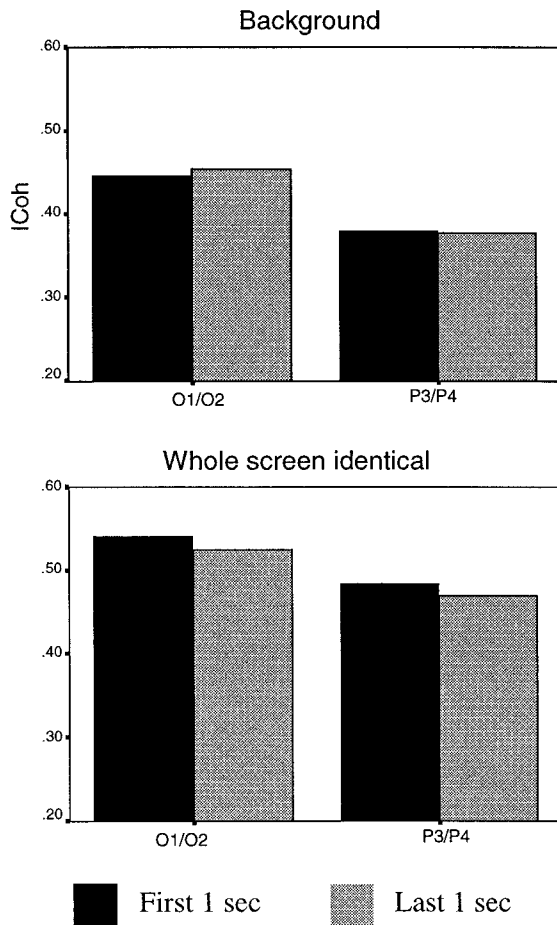


FIG. 5. Bars represent group ICoh values for the 1st and 2nd second of stimulation period.

The same explanation relates to the question of the functional significance of the increased coherence in the gamma band. Assuming that the synchronicity of activity serves as a "tag" for perceived "connectedness" across cortical networks, the occurrence of oscillations in the gamma band is currently interpreted as a way of the temporal tag spreading (Roelfsema and Singer 1998). If this is true, and, if the callosal connections are critical in propagating the tag, one would predict errors in perceiving connectedness when callosal connections are interrupted. The rich literature on split-brain and acallosal subjects provides evidence in favor of such a conclusion. Indeed, each hemisphere of a split-brain patient can erroneously complete its own version of incomplete or chimeric figures flashed along the VM (Levy et al. 1972; reviewed in Trevarthen 1990). Furthermore, a patient's performance in judging the alignment of two lines is degraded when these are flashed to separate hemispheres. Also, the patients cannot perform lexical decision on letters divided between the two hemifields and perform poorly on other tasks requiring interactions between the two hemispheres (reviewed in Corballis 1995). In addition, split brain or acallosal patients are impaired in the stereoscopic vision along the VM (Lassonde et al. 1995; Mitchell and Blakemore 1970), a low level type of cortical binding, for which the role of the CC is debated (reviewed in Berlucchi and Antonini 1990).

With the limitations mentioned, it appears that changes in

interhemispheric EEG coherence can probably be used to assay electrophysiologically the functionality of callosal connections. Therefore this method complements others such as the psychophysical study of the interference between gratings presented near the VM (Berardi et al. 1989), the analysis of ipsilaterally evoked responses (Brown et al. 1994), and transcranial magnetic stimulation (Paus et al. 1997).

It should be mentioned that anatomic studies in the cat and computer simulations predicted that callosal connections would play a role not only in the synchronization of activity between the two hemispheres, but also on the local activity within each hemisphere (Innocenti et al. 1994). The prediction seems to be borne out in the present study because the whole screen condition not only increased the distant interhemispheric synchronization, but also the EEG power in the gamma band. It was previously shown that an increase in the EEG power is indicative of local synchronization of the postsynaptic potentials in the vicinity of the recording electrode (Creutzfeldt et al. 1966). However, a comparable increase in the EEG power was not obtained in our animals study (Kiper et al. 1999). The reasons for this difference are not known. It may be due to the effect of anesthesia in the animal work, or to

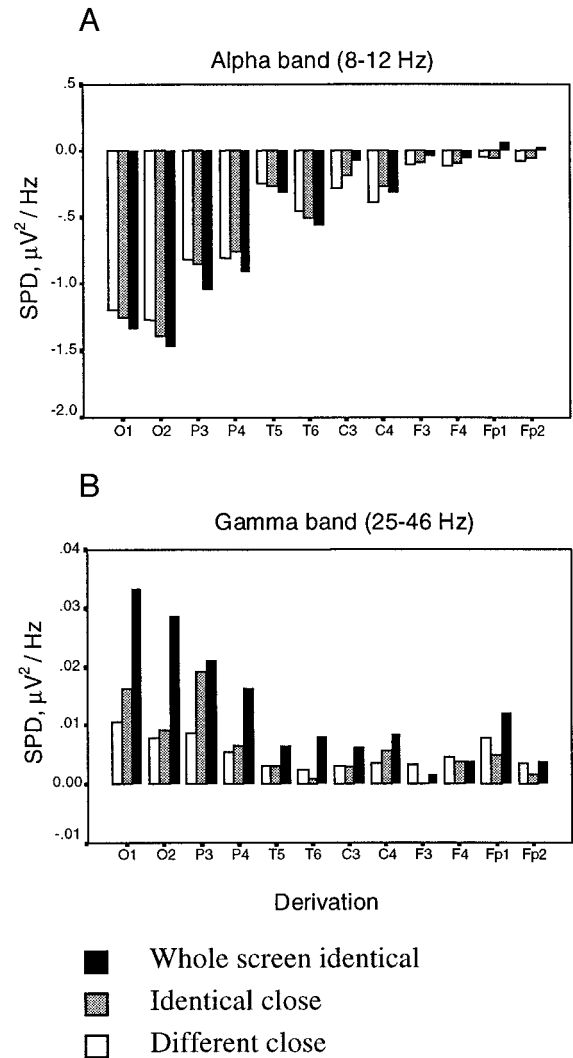


FIG. 6. Group averaged power spectra in the alpha (A) and gamma (B) bands to the whole screen identical, different close, and identical close stimuli.

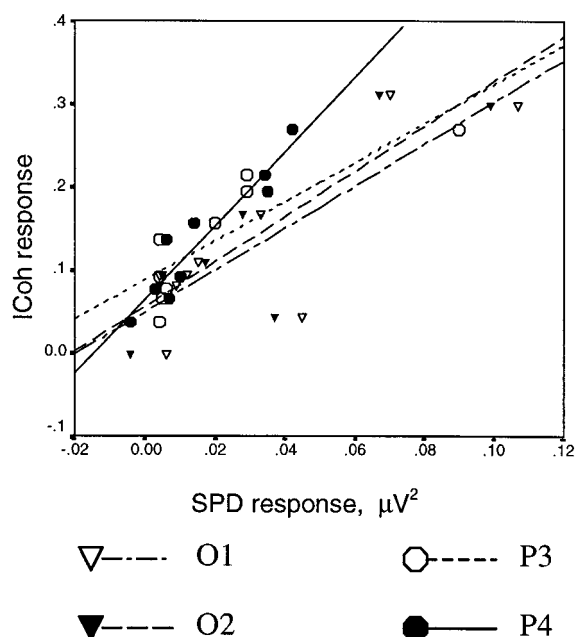


FIG. 7. Scatterplot of ICoh and spectral power density (SPD) responses in the gamma band obtained from the occipital ( $\nabla$  and  $\blacktriangledown$ ) and parietal ( $\circ$  and  $\bullet$ ) EEG derivations. Each data point represents a single subject's response to the whole screen identical stimulus.

differences in the functional callosal connectivity between ferrets and man.

#### Possible mechanisms of callosal action

How activation of callosal connections modifies the synchronous activity in the hemispheres remains unclear. One obvious possibility is that the activity in callosal axons can, on its own, control the activity of the postsynaptic targets. This is consistent with observations in split-chiasm cats (Berlucchi and Rizzolatti 1968; Milleret et al. 1994; Tardif et al. 1997), and with the fact that callosally projecting neurons can display oscillatory activity (Nunez et al. 1992). However, in our experimental conditions, the stimulation of one hemifield, with gratings extending near the VM, and, therefore presumably activating the callosally projecting neurons, was insufficient to modify the interhemispheric coherence and to increase the local power in the gamma band. This relative weakness of the callosal input is compatible with recent morphometric observations, stressed relative inadequacy of the callosal compared with thalamocortical axons to drive the postsynaptic targets (Tettoni et al. 1998). As an alternative to the direct drive explanation, it could be suggested that the activity of the two hemispheres synchronizes when two conditions are present: 1) direct thalamic input to the two hemispheres and 2) reverberating activation between the hemispheres. A neural network embodying such features did in fact generate synchronous oscillations in the two hemispheres, albeit in the theta rhythm (Innocenti et al. 1995). Gamma oscillations might be generated when callosal input, adding to the thalamocortical input, brings the depolarization of the callosally projecting neurons and/or their targets to a sufficient level of depolarization to trigger their intrinsic rhythm (Gray and McCormick 1996; Steriade 1997). This interpretation is compatible with the many electrophysiological observations demonstrating that the CC in-

creases cortical excitability (Berlucchi 1966; Bremer et al. 1956; Innocenti 1986). In particular, Bremer (1967) showed that evoked potentials in the cat visual cortex increased in amplitude if preceded by stimulation of the homotopic area in the contralateral hemisphere. Creutzfeldt et al. (1969) reported synchronous excitation of the neurons in superficial cortical layers in the case of contralaterally evoked callosal potential. This effect disappeared after section of the CC. Obviously, the fact that the activity of callosal connections may be limited to facilitatory influences in certain conditions does not imply that it is, by itself, never sufficient to drive the postsynaptic targets. One appealing possibility is that the callosal and other cortico-cortical connections can switch from a feed-forward mode to an assembly creating mode, the latter revealed by the appearance of gamma oscillations.

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