

Visual Stimulus–Dependent Changes in Interhemispheric EEG Coherence in Ferrets

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Visual stimulus–dependent changes in interhemispheric EEG coherence in ferrets. *J. Neurophysiol.* 82: 3082–3094, 1999. In recent years, the analysis of the coherence between signals recorded from the scalp [electroencephalographic (EEG) coherence] has been used to assess the functional properties of cortico-cortical connections, both in animal models and in humans. However, the experimental validation of this technique is still scarce. Therefore we applied it to the study of the callosal connections between the visual areas of the two hemispheres, because this particular set of cortico-cortical connections can be activated in a selective way by visual stimuli. Indeed, in primary and in low-order secondary visual areas, callosal axons interconnect selectively regions, which represent a narrow portion of the visual field straddling the vertical meridian and, within these regions, neurons that prefer the same stimulus orientation. Thus only iso-oriented stimuli located near the vertical meridian are expected to change interhemispheric coherence by activating callosal connections. Finally, if such changes are found and are indeed mediated by callosal connections, they should disappear after transection of the corpus callosum. We performed experiments on seven paralyzed and anesthetized ferrets, recording their cortical activity with epidural electrodes on areas 17/18, 19, and lateral suprasylvian, during different forms of visual stimulation. As expected, we found that bilateral iso-oriented stimuli near the vertical meridian, or extending across it, caused a significant increase in interhemispheric coherence in the EEG beta-gamma band. Stimuli with different orientations, stimuli located far from the vertical meridian, as well as unilateral stimuli failed to affect interhemispheric EEG coherence. The stimulus-induced increase in coherence disappeared after surgical transection of the corpus callosum. The results suggest that the activation of cortico-cortical connections can indeed be revealed as a change in EEG coherence. The latter can therefore be validly used to investigate the functionality of cortico-cortical connections.

INTRODUCTION

Noninvasive electrophysiological methods are currently used for assessing developmental and compensatory changes in the connectivity of the human brain. In particular, the relatively new extension of the electroencephalographic (EEG) spectral analysis, EEG coherence analysis, has been used to reveal and localize the underlying changes in cortical connectivity during normal and abnormal development, while performing cognitive tasks, and in different pathologies (Besthorn et al. 1994; Fletcher et al. 1997; Knyazeva and Farber 1991; Kuks et al.

1987; Marosi et al. 1992; Merrin et al. 1989; Terstegge et al. 1993; Thatcher 1992).

The application of coherence analysis to the study of cortical connectivity is based on the assumption that coherence between two EEG signals reflects functional relations between the cortical regions underlying the recording electrodes. Because coherence values depend on the stability of both power and phase relations between the signals, any factors affecting the covariance of spatially distributed EEG signals must influence the coherence values. Among them, cortical connectivity is thought to be the most important factor.

Indeed, data on the spatial distribution of EEG coherence values both between and within the cerebral hemispheres are compatible with our current knowledge of cortical connectivity (Knyazeva and Farber 1996; Thatcher et al. 1986; Tucker et al. 1986). However, the empiric justification for ascribing EEG coherence to the activity of cortico-cortical connections in humans is limited to a few studies in which patients with agenesis, surgical section, or pathology of the corpus callosum showed decreased interhemispheric coherence compared with normals (Koeda et al. 1995; Kuks et al. 1987; Montplaisir et al. 1990; Nielsen et al. 1993; Nunez 1981; Pinkofsky et al. 1997; but see Corsi-Cabrera et al. 1995). These studies suggested that the integrity of the interhemispheric connections influences coherence level within the frequency range traditionally analyzed in human scalp EEG, being most pronounced in the alpha and beta bands. For reasons discussed below, they do not prove that coherence changes are mediated by callosal connections.

The experimental evidence that EEG coherence reflects the activity of cortico-cortical connections rests largely on the study of the alpha rhythm in dogs by Lopes da Silva et al. (1973, 1980) and Lopes da Silva and Storm van Leeuwen (1978). These studies showed that coherence mediated by cortico-cortical connections predominates over thalamocortical one within the alpha-range, implying cortico-cortical connectivity as the main substrate for the alpha synchronization. It should be mentioned that these studies did not try to relate coherence levels to the detailed structure of cortico-cortical connections, nor to any form of stimulation.

Recent studies in cats and monkeys showed stimulus-induced cortical activity in the gamma range (Brosch et al. 1995, 1997; Engel et al. 1990, 1991; Gray et al. 1989, 1990). This activity could be synchronized within distributed neuronal assemblies via cortico-cortical connections (Engel et al. 1991; Munk et al. 1995; Ts'o et al. 1986). Other studies emphasized the role of the thalamic input (or of cortico-thalamic loops) in

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synchronizing cortical activity in the gamma band (Barth and MacDonald 1996; Ribary et al. 1991; Steriade 1997; Steriade and Amzica 1996).

The claim that interhemispheric cortico-cortical connections are involved in the gamma band synchronization rests on the finding that the synchronization of neuronal assemblies located in different hemispheres is abolished by interruption of callosal connections, or destruction of cortical areas in one hemisphere (Engel et al. 1991; Munk et al. 1995). Although this result is compatible with the possibility that callosal connections mediate interhemispheric synchronization, it does not bring conclusive evidence that this is indeed the case. First, callosal transections were performed several weeks before the recording sessions. Therefore the possibility that the loss of interhemispheric synchronization is due to local reorganizations of connections or to synaptic changes induced by the lesion cannot be excluded. Second, callosal connections have been shown to regulate the general level of cortical excitability (Berlucchi 1966; Bremer et al. 1956), and indeed, a significant loss of multiunit responses was reported after chronic callosotomy (Munk et al. 1995). Because the gamma band oscillations depend on the level of neuronal depolarization (Steriade et al. 1996a,b), they might be decreased by the loss of a tonic excitatory input to the hemisphere. Therefore callosal transection could interfere with the stimulus-dependent synchronization without causing it. Similar arguments weaken the interpretation of decreased interhemispheric coherence in the patients with callosotomy or callosal agenesis mentioned above.

The present study of interhemispheric EEG coherence during visual stimulation in ferrets has the following goals. First, we intend to determine whether stimulus-dependent changes in cortical synchronized activity can be detected using this electrophysiological technique. Second, we wish to determine whether such changes can be unequivocally ascribed to the activation of cortico-cortical connections. This is done with the purpose of using the EEG coherence analysis for assaying specific aspects of cortico-cortical connections in the normal

adult or developing human brain, and in pathological conditions.

The advantage of this animal model is that it allows precise predictions. Indeed, in ferrets as in other mammals, the corpus callosum interconnects selectively portions of the visual areas representing a narrow sector of the visual field near the vertical meridian (VM) (Colin et al. 1998; Grigonis et al. 1992; Rockland 1985). Thus if callosal connections are responsible for synchronizing activity in the two hemispheres, and, if such synchronization can be detected by studying changes in EEG coherence, these changes should occur only with stimuli presented near the VM. Also, the corpus callosum selectively interconnects neurons with identical orientation specificity (Antonini et al. 1983; Berlucchi and Rizzolatti 1968; Houzel et al. 1994; Lepore and Guillemot 1982; Milleret et al. 1994; Schmidt et al. 1997). Therefore changes in EEG coherence should occur only for stimuli that activate iso-oriented neurons in the two hemispheres. Finally, stimulus-induced changes in interhemispheric EEG coherence should be abolished by acutely severing the part of the corpus callosum traversed by the fibers that interconnect the visual areas.

The results of the present study met all the above conditions and thus encourage the use of EEG coherence analysis as a way to investigate the involvement of cortico-cortical connections in normal brain operations (Knyazeva et al. 1999), and for assaying their function in pathological conditions (Kiper et al. 1998a).

Preliminary results were presented in abstract form (Kiper et al. 1998b; Knyazeva et al. 1998).

METHODS

Subjects

Seven adult female sable ferrets were used. In six animals (all but animal *FEEG.10*), the same protocol of visual stimulation was performed. *FEEG.10* is therefore not present in Table 1, but its results are described in the section *Effects of corpus callosum transection*. The animals were obtained from Marshall Europe and were maintained on

TABLE 1. Individual interhemispheric coherence levels, averaged within the reactive frequency band

Close Stimuli	Electrode Pairs	Ferret												
		<i>FEEG.2</i>		<i>EEG.3</i>		<i>FEEG.4</i>			<i>FEEG.5</i>		<i>FEEG.7</i>		<i>FEEG.8</i>	
		Block 1	Block 2	Block 1	Block 1	Block 2	Block 3	Block 1	Block 1	Block 2	Block 1	Block 2		
Bilateral identical	17/18	0.41*	0.47*	0.29†	0.21†	0.33*	0.36	0.41‡	0.21	0.25§	0.26	0.28*		
	19	0.38*	0.40*	0.24*	0.15	0.26*	0.27*	0.31‡	0.18	0.21§	0.18	0.27†		
	S. Sylvian	<i>0.18§</i>	0.14	0.13	0.11	0.18*	0.13	0.19	0.07	0.13	0.13	0.18		
Bilateral different	17/18	0.39	<i>0.40*</i>	0.28*	0.21†	0.32	0.35	0.38	0.25	0.22	0.27	0.26		
	19	0.36	0.33	0.24*	0.16	0.24	0.24	0.28	0.29	0.18	0.19	0.23§		
	S. Sylvian	0.18	0.11	0.15	0.11§	0.16	0.09	0.18	0.11	0.12	0.13	0.16		
Left visual field	17/18	0.34	0.42	0.27	0.23†	0.31	0.37	0.38	0.22	0.22	0.29	0.23		
	19	0.36	0.36	0.22	0.14	0.24	0.26§	0.28	0.19	0.20	0.21	0.23		
	S. Sylvian	0.20	0.14	0.15§	0.10	0.17§	0.12	0.16	0.09	0.17†	0.16	0.16		
Right visual field	17/18	0.39	0.42	0.27	0.17	0.31	<i>0.29†</i>	0.36	0.25	0.22	0.26	0.22		
	19	0.37	0.36	0.21	0.12	0.24	0.20	0.26	0.18	0.18	0.21	0.23		
	S. Sylvian	0.19	0.16	0.16§	0.10	0.16	0.12	0.16	0.09	0.13	0.16	0.16		
Background	17/18	0.35	0.43	0.22	0.16	0.29	0.35	0.34	0.23	0.22	0.26	0.22		
	19	0.33	0.37	0.18	0.13	0.22	0.21	0.24	0.19	0.18	0.19	0.20		
	S. Sylvian	0.22	0.14	0.13	0.09	0.14	0.11	0.15	0.09	0.11	0.13	0.16		

Bold numbers represent ICoh levels significantly higher than that associated with the background stimulus (* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.005$; § $P < 0.1$). Italics show ICoh decreases relative to the background level. For other details, see text.

a 14 h light/10 h dark cycle in the animal facility of the Institute of Cell Biology and Morphology. Animal maintenance and experimental procedures conformed to Swiss regulations, European Community directives (1997), Guidelines of the American Physiological Society (1991), and under the supervision of the Cantonal Veterinary Commission.

Surgical preparation

Before an experiment, each animal was food deprived for 12–14 h. Initial anesthesia was induced by intramuscular injections of ketamine hydrochloride (Ketalar, Parke-Davis, 10 mg/kg) and medetomidin hydrochloride (Domitor, Orion, 0.08 mg/kg) and followed by an injection of atropine sulfate (Sintectica S. A., 0.1 mg im). The femoral vein and trachea were cannulated, and the animal was placed in a stereotaxic apparatus. Anesthesia was continuously maintained by inhalation of isoflurane (Forene, Abbott Laboratory) 0.5% in a gas mixture of 50% O₂-50% N₂O. After installation in the stereotaxic apparatus, the scalp was incised along the midline, the skin and temporal muscles were retracted, and holes were drilled through the skull to position the recording electrodes. At this point, the animal was paralyzed with a continuous intravenous injection of gallamine triethiodide (Flaxedil, Rhône-Poulenc Rorer, 6 mg · kg⁻¹ · h⁻¹) diluted in lactated Ringer, and supplemented with 5% sucrose (5.4 ml/h). The animal's temperature was monitored by a rectal probe and maintained around 37°C with a thermostatically controlled heating pad. We continuously monitored the animal's electrocardiogram (EKG) and EEG (see *EEG recording*). The animal was artificially ventilated with a small-animal respirator (Harvard Apparatus), and expired CO₂ was maintained around 4% by adjusting tidal volume or respiration rate.

Corpus callosum transection

In four animals (*FEEG.4*, *-5*, *-8*, and *-10*), the corpus callosum (CC) was sectioned by lowering in the interhemispheric scissure a surgical thread passed through two parallel sewing needles, spaced anteroposteriorly ~5 mm and mounted on a micromanipulator. In the first two animals, the interhemispheric fissure was exposed by removing the bone on one hemisphere, over the whole anteroposterior extent of the CC and by incising the dura all along. Because this procedure required coagulating venous branches terminating in the sagittal sinus, in the last two animals two openings ~3 mm diam were performed at anteroposterior locations corresponding to the CC splenium and the rostrum. The surgical thread was then passed under the dura through one of the openings, recovered through the other opening, and then passed through the sewing needles. The needles were advanced to the depth of ~10 mm from the surface and then retracted. The surgical opening was then covered with agar. The location and extent of the section was controlled histologically.

Optics and visual stimulation

Each animal was fitted with ferret contact lenses, with a curvature of 2.6–2.9 mm, and a diameter of 4 mm, plano (Ocular Contact Lenses). The pupils were dilated by topical application of Atropine 1% (Dispersa) and the nictitating membranes retracted by application of Phenylephrin 5% (Lab. Chauvin). The optic disks were plotted on a tangent screen placed in front of the animal using a reversible ophthalmoscope (Eldridge 1979), and the locations of the foveas were estimated from these landmarks (Price and Morgan 1987; Zahs and Stryker 1985). To superimpose the foveal projections on the screen, paralysis-induced misalignments of the optical axes were corrected with the use of appropriate prisms.

The stimuli were presented on an Eizo T-560 i monitor, driven by an AT Truevision Vista graphics board, with a refresh rate of 120 Hz, interlaced. The stimuli were vertical rectangular patches of black-and-white sinusoidal gratings, with a space-averaged luminance of 32

cd/m², presented on a uniform background of equal luminance. At the viewing distance we used (14.5 cm), the screen subtended 67 by 95° of visual angle, and the patches 31.5 by 57.5°. In all animals, the stimulus set included a reference condition consisting of a uniform gray field filling the whole screen, with a luminance of 32 cd/m². This condition is referred to as the “background” in the remainder of the paper. In all but one animal, we used the following stimulation conditions (Fig. 1):

1) *Left hemifield stimulus*. A single patch was presented to the left of the foveas' projection on the screen. The grating's orientation was horizontal, the spatial frequency 0.13 c/deg, and contrast 98%. It was drifting downward with a temporal frequency of 2 Hz. The center of the patch was located 17° from the foveas.

2) *Right hemifield stimulus*. Identical to 1), except that the grating was presented to the right of the foveas.

3) *Bilateral identical stimuli*. Gratings 1) and 2) were simultaneously presented. Therefore a 1.3° wide, vertical strip on each side of the 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” stimuli, we presented the same gratings located further away from the fixation point. In that case, the patch centers were located 31.5° to the side of the fixation point. Therefore the gratings did not stimulate a vertical strip of 15.8° on each side of the VM, but were still within the binocular representation of the visual field in the known visual areas of the ferret (Law et al. 1988; our own unpublished observations). We refer to these as the “far” conditions.

In animals *FEEG.5* and *FEEG.7* we also used a stimulus condition

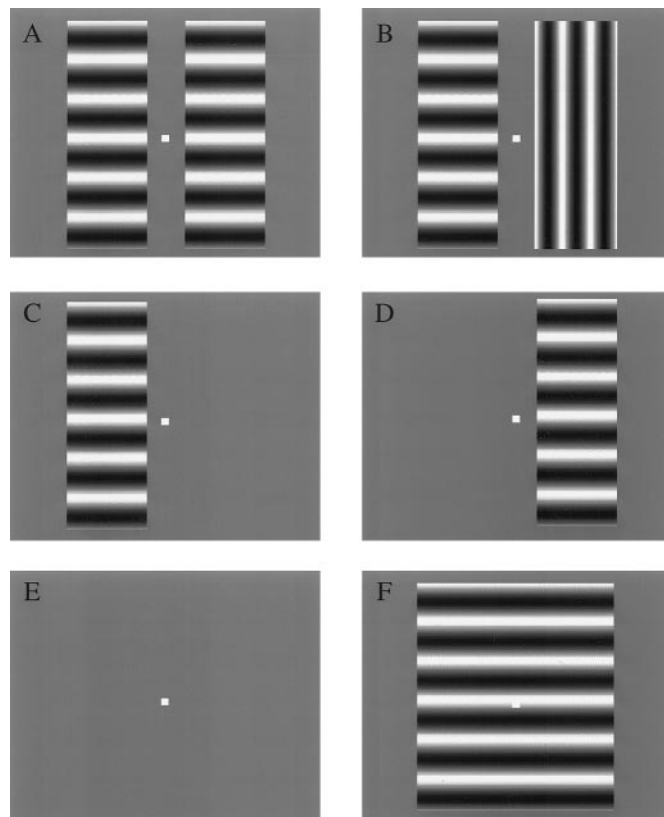


FIG. 1. Schematic representation of the stimuli used in our experiments. The white square in the center of the screen represents the ferrets' center of gaze. A: identical close stimulus. B: different close. C: unilateral left, i.e., presented in the ferret's left visual hemifield. D: unilateral right. E: background. F: whole screen. All horizontal gratings were drifting downward, and the vertical grating, rightward.

where the whole screen was filled with a downward drifting grating (spatial frequency 0.13 c/deg, contrast 98%, temporal frequency 2 Hz). In *animal FEEG.10*, only the whole screen stimulus was compared with the background.

EEG recording

Three active electrodes were positioned over each hemisphere. Their locations and an EEG sample are shown in Fig. 2. The first electrode was located ~1 mm anterior to the occipital pole, over a region corresponding to the 17/18 border (Colin et al. 1998; Law et al. 1988; Rockland 1985). The second electrode was positioned anterior to the first, and slightly more laterally, over a region corresponding to area 19, as determined by other experiments performed in our laboratory (Colin et al. 1998). A third electrode was placed more anteriorly and laterally, over the upper bank of the suprasylvian sulcus. Another three active electrodes were then stereotaxically placed at symmetrical locations on the other hemisphere.

The electrodes consisted of a thin (0.1 mm diam) silver wire terminated by a small ball (0.5 mm diam). The wire was insulated by a Teflon coating up to 5 mm from the ball. Electrodes were passed through the holes in the skull, positioned over the dura mater, and maintained in place with a few drops of melted bone wax. Two symmetrical reference electrodes were screwed into the bone over the frontal sinuses. We used separate reference electrodes to avoid artificially high interhemispheric coherence due to shared activity under a common reference electrode (Fein et al. 1988; Nunez 1995). In addition, the size and remote location of the reference electrodes minimized the probability that they could be affected by signals originating in the visual cortex. The EEG signals derived as voltage differences between the active electrodes, and the corresponding same-hemisphere reference were amplified, band-pass filtered (0.1–100 Hz), and stored in a personal computer after 12-bit A/D conversion at a sampling rate of 204.8 Hz.

Data collection

Each set of stimuli consisted of the sequence of four gratings (either far or close) and of a blank stimulus (uniform gray screen with a luminance of 32 cd/m²), each presented for 5 s, with interstimulus intervals between 2 and 3 s. The order of presentation was randomized between animals. The set of five stimuli was repeated in blocks for a minimum of 20 times. To ensure the reproducibility of our results within an experiment, blocks of visual stimuli were repeated in five of the seven animals. Before each block, the animal was presented with the blank screen to monitor the background EEG for dominant slow rhythms indicat-

ing excessively deep anesthesia, and to detect potential artifacts due to poor electrical contacts.

EEG processing

The “EEG Lab” software (Metrica, Moscow, Russia) was used for data processing. For each animal and experimental condition, a total of 1.5–2 min of artifact-free EEG in 5-s epochs was selected for analysis. The absence of artifacts resulting from pulsatory and respiratory movements of the brain, poor electrode contact, or other sources, was the only criterion for selection.

The EEGs were subjected to fast Fourier transform (FFT) (Otnes and Enochson 1978). Primary auto- and cross-spectra estimates were averaged over the epochs (not <20), and smoothed by Parsen’s window. Based on primary spectral estimates, the spectral power density (SPD) for every channel and interhemispheric coherence (ICoh) functions for symmetric and asymmetric electrode pairs were calculated. Interhemispheric coherence was computed with the formula

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

where S_{xx} , S_{yy} , and S_{xy} are auto- and cross-spectrum estimates of the x and y signals, respectively. In addition to the SPD and ICoh obtained via FFT of 5-s epochs, the first and second halves of every epoch were processed separately using the above-described algorithm. To evaluate the effects of visual stimulation on EEG parameters, the reactive frequency band was selected for each animal by visual inspection of the power and coherence spectra. In nearly all cases, the reactive band was between 15 and 40 Hz (see RESULTS). Although the band comprises both beta and gamma frequencies, which, in behaving animals, may display different dynamics under certain experimental conditions, we observed homogenous response for all except two animals. In these animals, the reactive EEG band was in the same range, but narrower (15–26 Hz for *FEEG.2* in the 1st block and 30–40 Hz for *FEEG.7*). Such homogeneous responses over the wide beta-gamma band could have resulted from anesthesia effects on EEG (see *Anesthesia effects on stimulus-dependent EEG coherence*). Statistical analysis confirmed the significance of the responses induced in this band by the stimuli.

Because our aim is to use EEG coherence analysis to study the cortico-cortical connectivity of individual cases (Kiper et al. 1998a), we first performed an analysis of each individual subject. For each animal, the significance of the changes induced by different visual stimuli in either power or coherence spectra was assessed by applying the Wilcoxon test to their mean band values for each block of stimuli separately. Comparisons across blocks were usually not possible,

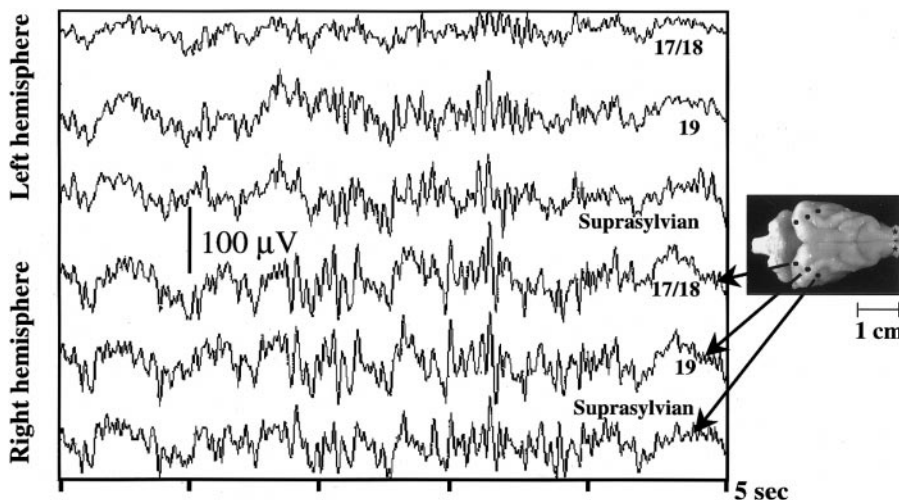


FIG. 2. Example of a ferret electroencephalogram (EEG) traces recorded for a 5-s period. Black dots positioned on the ferret’s brain (right) show the locations of the epidural recording electrodes. Stars show the locations of the reference electrodes.

because of the EEG changes between blocks (see further *Anesthesia effects on stimulus-dependent EEG coherence*).

To assess the significance of our results for the whole sample, we applied the nonparametric Friedman test for several related samples. To analyze the temporal stability of the ICoh responses, we used the Wilcoxon test for two related samples (1st vs. 2nd halves of the 5-s epochs). For pairwise comparisons (identical close vs. each of the other stimuli), we applied the Wilcoxon test. The tests were performed on the ICoh responses computed as differences in mean band ICoh values between any given stimulus and the background conditions.

Anesthesia effects on stimulus-dependent EEG coherence

The consequences of changing the levels of anesthesia on EEG responsiveness were studied in two animals. Increasing isoflurane concentration from 0.5 to 1% or from 1 to 1.5% caused a progressive reduction of spectral power density in the gamma band, consistent with the anesthesia effects on EEG observed in dogs (Katznelson 1981), cats (Kral et al. 1999), and humans (Nunez 1981). Stimulus-induced increases in the gamma band coherence also diminished progressively with increasing anesthesia levels. This finding supplements clinical observations that evoked gamma oscillations decrease their frequency and amplitude to the point of disappearance, being indicative of suppression of sensory information processing with increased anesthesia levels (Madler et al. 1991; Schwender et al. 1994). We therefore maintained the animals on 50% O₂-50% N₂O, and 0.5% of isoflurane in all our subsequent experiments. However, it should be mentioned that the necessary maintenance of general anesthesia using a minimum, constant concentration of 0.5% of isoflurane reduced the spectral power within the beta-gamma bands gradually and clearly. It also caused a simultaneous increase in the lower frequencies, and progressively reduced coherence responsiveness within the gamma band.

Histological procedures

At the end of each experiment, recording locations were marked by inserting needles coated with Procion Brown (Imperial Chemical Industries) in the electrode holes. The animal was then killed with an overdose of pentobarbital sodium (50 mg iv), rinsed transcardially with phosphate buffer (0.01 M, pH 7.35), and fixed with 4% paraformaldehyde in phosphate-buffered saline (0.06 M, pH 7.35). The brain was then extracted and soaked in 4% paraformaldehyde for 8–12 h. Before cutting, the brain was allowed to equilibrate in a 30% sucrose solution, and photographed to document the location of the electrodes. Sections (45 μ m thick) were cut with a cryostat, and alternate sections were stained with toluidine blue, cytochrome-oxidase, and for myelin (Gallyas 1979). On these sections the cytoarchitectonic borders of areas 17, 18, and 19 were identified on the basis of criteria established in the literature (Rockland 1985) and by ourselves (Colin et al. 1998).

RESULTS

EEG spectral power changes under visual stimulation

The spectral analysis of EEG signals in the presence of the background stimulus (reference condition) revealed a progressive decrease in power with increasing frequency, in most cases with a more or less clear-cut hump in the beta-gamma range. Within those power spectra, three components could be identified. Low-frequency activity within the 1- to 6-Hz band was the most powerful. Spindles occupied frequencies roughly from 6 to 14 Hz, were most pronounced in the suprasylvian derivations, and were lacking

from the primary visual areas derivations in two of the animals. Higher frequency activity was contained within a broadband in the beta/gamma range, whose limits were set between 15 and 40 Hz. No consistent changes in SPD were induced by visual stimulation. In particular, in the 15- to 40-Hz band, in which coherence changes were observed (see following text), no changes related to the stimulation condition were found in most of the animals (*FEEG.2*, -3 , -5 , and -7). In one of the animals (*FEEG.4*), all stimuli increased and, in another one (*FEEG.8*), decreased the SPD.

Individual analysis of EEG coherence changes induced by visual stimulation

The background interhemispheric coherence ranged between 0.80 and 90 (maximum values in the low-frequency range) and 0.13–20 (minimum values for the gamma band). Consistent stimulus-related changes in interhemispheric coherence were observed only in the 15- to 40-Hz band. Averaged ICoh within this band for the 17/18, 19, and suprasylvian electrodes are shown in Table 1. For the statistical analysis of the data, all stimulation conditions were compared with the background.

Bilateral stimulation with identical gratings located close to the VM in both hemifields systematically caused a significant coherence increase for the 17/18 and 19 electrode pairs. At each location, interhemispheric coherence increased significantly in 8 of 11 stimulation blocks. Bilateral stimulation with different gratings close to the VM resulted in an ICoh increase only in *animals FEEG.3* and *FEEG.4* (the 1st block).

Different results were obtained for EEG signals recorded from the suprasylvian areas, as shown in Table 1. In all conditions, the ICoh levels in the 15- to 40-Hz band were generally lower for these electrode locations than for the others. Furthermore, bilateral stimulation with identical gratings near the VM, which gave reproducible ICoh increases in the other visual areas, had no effect except in one block (*animal FEEG.4*). All other stimulation conditions were also ineffective.

A representative example (*FEEG.2*) of the ICoh spectra obtained during these stimulation conditions is shown in Fig. 3, along with their associated power spectra. Note that, although there were no changes in power spectra between these stimulation conditions and the background, the identical stimuli significantly increased ICoh for the 17/18 and 19, but not for the suprasylvian electrode pairs. In addition, it is important to note that in all the cases where the whole screen stimulus was presented (*FEEG.5*, -7 , and -8), it affected ICoh levels in the same way as the identical stimuli located near the VM (Fig. 7).

Figure 4 shows the results of the unilateral stimulations compared with the background for the same animal shown in Fig. 3. Unilateral stimulations did not increase ICoh levels in any of the electrode pairs (suprasylvian pair is not shown). Across all animals (see Table 1), unilateral stimulation with horizontal gratings in either the right or the left hemifield was not accompanied by a significant ICoh growth except in one stimulation block ($P < 0.05$).

Similarly, we found no significant ICoh increase with any of the stimuli located far from the VM. An example of this result is shown in Fig. 5.

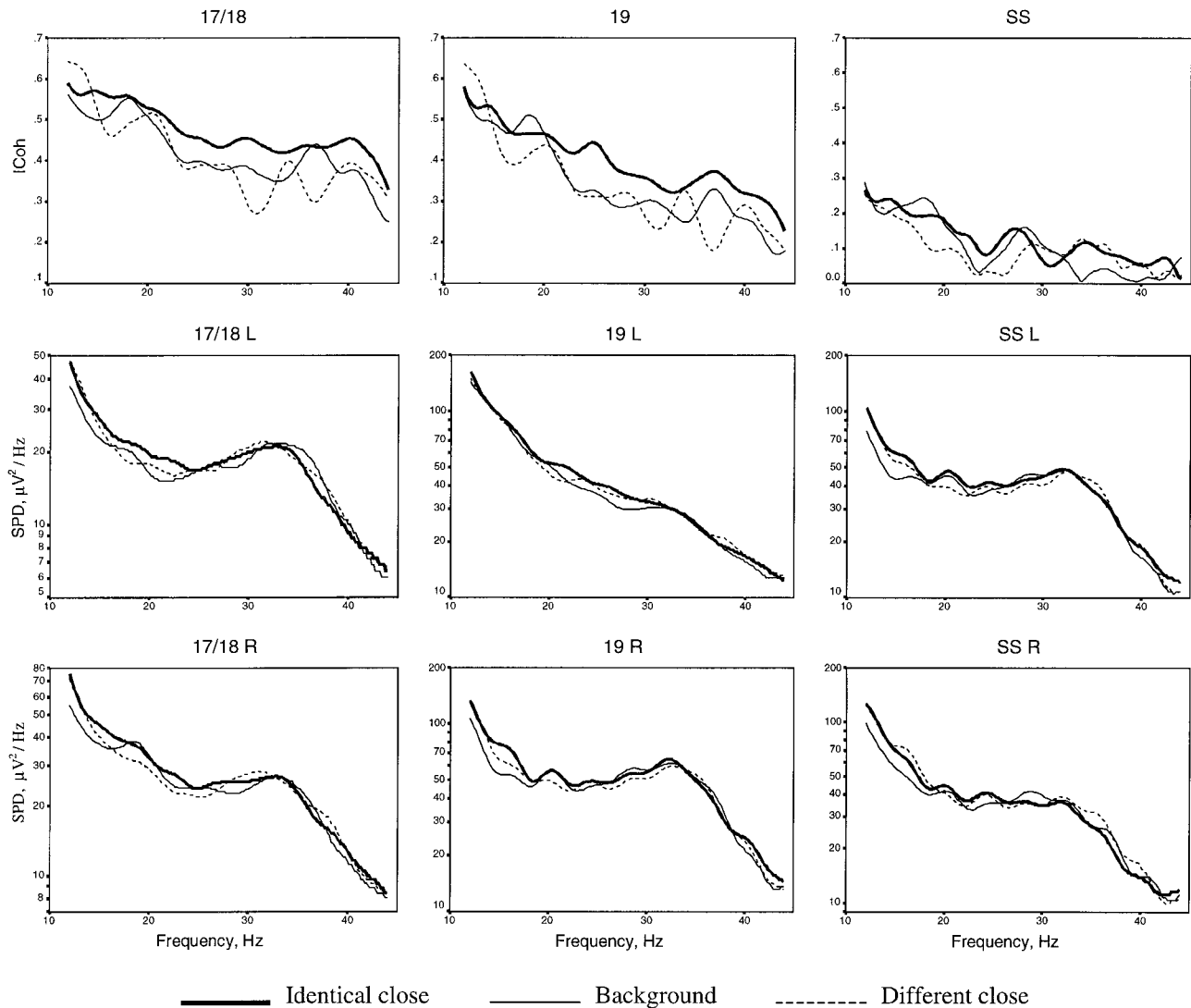


FIG. 3. Interhemispheric coherence (ICoh) and power spectra from *animal FEEG.2*. *Top row*: the ICoh between each electrode pair in response to the identical close (thick line), background (thin line), and different close (dashed line) stimuli. *Middle and bottom rows*: the corresponding power spectra for the electrodes on the left and the right hemisphere, respectively.

To further assess the specificity of the ICoh increase produced by the identical stimuli close to the VM, we statistically analyzed the relationships between this and each of the other stimulation conditions. These comparisons showed that, as expected, coherence values were significantly higher for the bilateral stimulation with identical gratings near the VM than for any of the other stimulus conditions, both for the 17/18 and for the 19 electrodes. Indeed, in nearly all the cases where a statistically significant ICoh increase was observed for the identical close condition compared with the background, it was also higher than any of the other stimulation conditions (44 of 45 comparisons).

Group data analysis of EEG coherence changes induced by visual stimulation

The above analysis of the individual results showed that in most cases, the various stimuli affected ICoh in the way we expected. To be able to generalize these results to the whole population, we performed a statistical analysis of the

whole sample. We used the nonparametric Friedman test to determine whether our ICoh responses (as defined in METHODS) were significantly different across our stimulation conditions. The responses to the close stimulation conditions varied significantly ($P = 0.035$ for the 17/18 pair, and $P = 0.033$ for the 19 pair). As expected from the examination of the individual cases, no significant changes were obtained in the suprasylvian electrode pair. Subsequent pairwise comparisons of the stimulation conditions (using the 1-tailed Wilcoxon test) showed that the identical close stimulus resulted in a significantly larger ICoh response than each of the other stimulation conditions, in both the 17/18 and 19 electrode pairs. The only exception was for the comparison between identical and different close stimuli, which failed to reach significance in the 19 electrode pair ($P = 0.17$). Specifically, the response to the identical stimulus was significantly higher than that to the different stimulus at the $P = 0.029$ level in the 17/18 pair. It was also higher than the responses to the left ($P = 0.014$ for the 17/18 pair, $P = 0.021$ for the 19 pair), and right ($P = 0.023$ for the 17/18

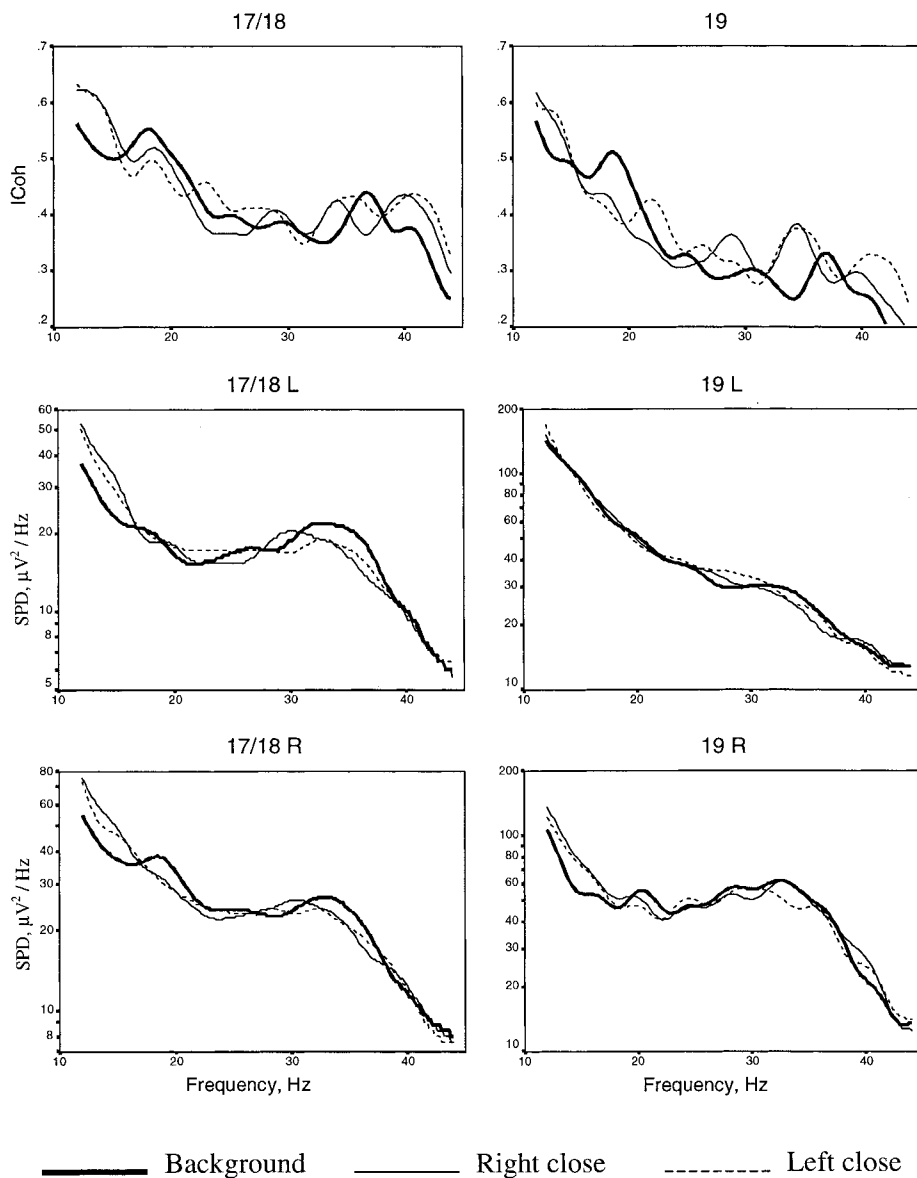


FIG. 4. Interhemispheric coherence (top row) and power spectra (2 bottom rows) for the unilateral stimuli close to the vertical meridian (VM), compared with the background (thick line) from animal *FEEG.2*. The denominations right close (thin line) and left close (dashed line) refer to stimuli located in the right and the left hemifield, respectively.

pair, $P = 0.014$ for the 19 pair) stimuli. There were no significant differences between ICoh responses to the far stimuli ($P = 0.237$ for the 17/18 pair; $P = 0.647$ for the 19; $P = 0.675$ for the suprasylvian; Friedman test).

Stability of the ICoh response

To investigate the stability of the ICoh increase for the whole sample, we compared the band ICoh values of the first versus second halves (2.5 s each) of our stimulation period. The two-tailed Wilcoxon test did not show any difference in the background or the bilateral identical condition (for 17/18 and 19 electrode locations P values ranged from 0.213 to 0.594). Analysis of individual data confirmed that, in most blocks, the response induced by visual stimulation was stable over 5 s (Fig. 6). But in two blocks (animals *FEEG.4* and *FEEG.5*), the increase in EEG coherence was larger for epochs of analysis restricted to 2.5 s after stimulus onset, and attenuated over the following 2.5 s of stimulation. An example of this effect is also shown in Fig. 6, for animal *FEEG.4* (block 3).

Stimulation-induced ICoh changes in heterotopic electrode pairs

Stimulation-dependent interhemispheric changes in ICoh were not restricted to the activity recorded at homotopic points in the two hemispheres. The Friedman test performed on the ICoh responses to unilateral and bilateral close stimuli showed significant differences in the 17/18 and contralateral 19 ($P < 0.021$) pairs, but not in the 17/18 and contralateral suprasylvian electrode pairs. Subsequent Wilcoxon pairwise comparisons revealed that the ICoh increase to bilateral identical stimuli was greater than to any of the other stimuli ($P < 0.038$). The robustness of the responses was revealed by the individual analysis. Indeed, in all but one animal (*FEEG.7*), identical stimuli presented near the VM significantly increased the ICoh between the 17/18 and the contralateral 19 electrodes ($P < 0.05$, the Wilcoxon test). These increases are likely due to heterotopic callosal connections that were demonstrated anatomically (Bressoud and Innocenti 1999; Innocenti 1986). Because we never

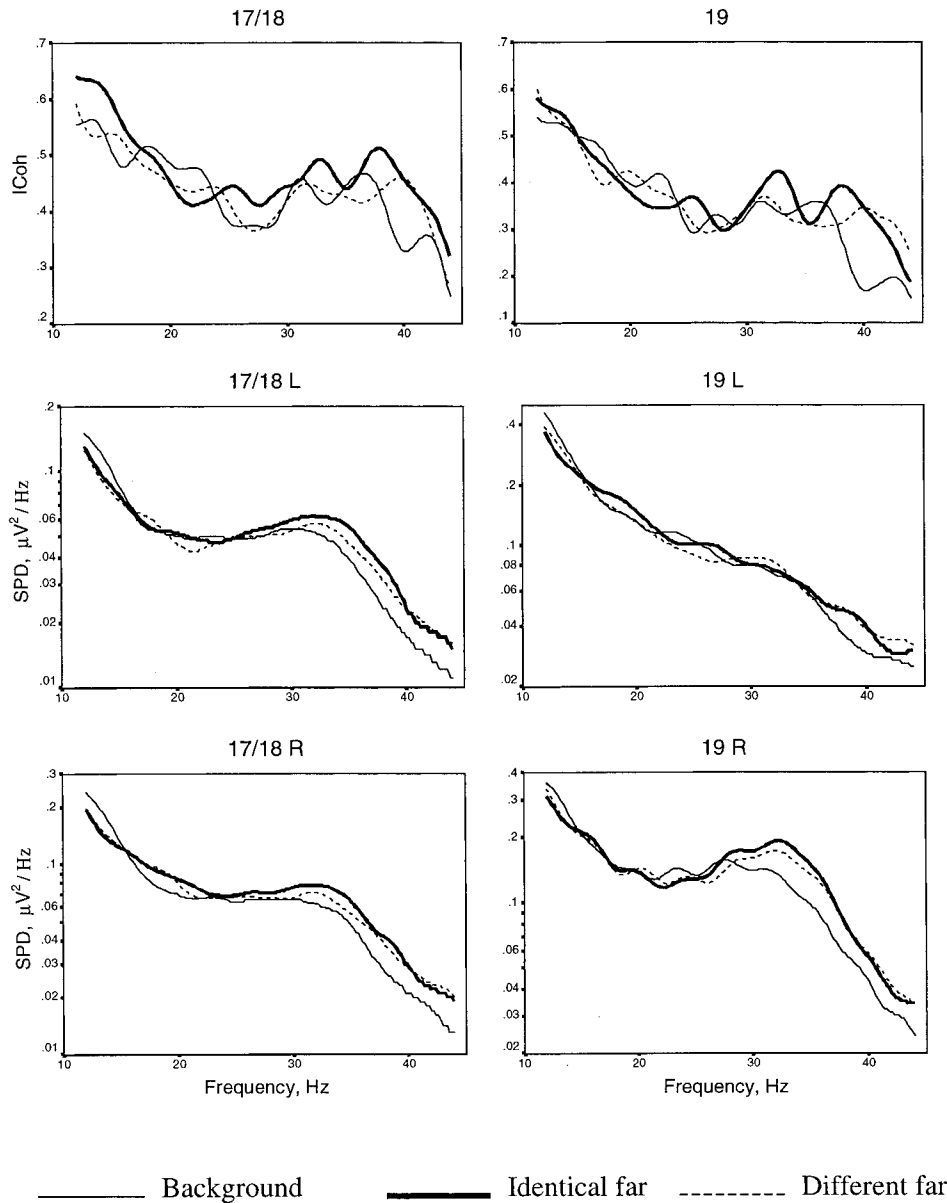


FIG. 5. ICoh and spectral power density (SPD) for the stimuli located far from the VM. Responses to the different far (dashed line) and identical far (thick line) stimuli are compared with the background (thin line).

observed any consistent stimulus-dependent coherence changes *within* a single hemisphere, the possibility that these coherence changes might instead be provided by the intrahemispheric connectivity is not supported by our data.

Effects of CC transection

Our postmortem histological analysis showed that the CC was cut in three of the four animals in which this had been attempted (*FEEG.4*, -5 , -8 , and -10). In two of the three animals (*FEEG.5* and *FEEG.8*), the transection included the splenium and part of the body of the CC, for a total length of 2.5–3 mm (corrected for 40% shrinkage). In *animal FEEG.4*, the caudal 1.5 mm of the splenium appeared intact. In *FEEG.5*, the mesencephalic tegmentum under the transected portion of the CC, and in *FEEG.8*, the cingulate gyrus on the left hemisphere above the transected part of the CC were also sectioned.

In *FEEG.10*, the callosal transection failed, but the lesion involved the medial part of the left hemisphere and, as in *FEEG.8*, the cingulate cortex above the CC. Therefore this animal provided a control for nonspecific EEG changes induced by the surgical trauma involved in accessing the CC, and will be referred to as “sham operated.”

The outcomes of the CC transections were assessed by applying the Wilcoxon test to individual animals. The ICoh increase due to stimulation with the whole screen grating was abolished in both animals where the transection included the splenium ($P > 0.29$ for 17 and 18/19 electrode locations), but not in the sham-operated animal (the difference was still significant at $P < 0.1$). In the animal with the incomplete CC transection (*FEEG.4*), the ICoh response to the identical-close stimulus as well disappeared after the transection ($P > 0.14$). Examples of these results are shown in Fig. 7 (*FEEG.5*: complete transection of the CC; *FEEG.10*: sham-operated animal),

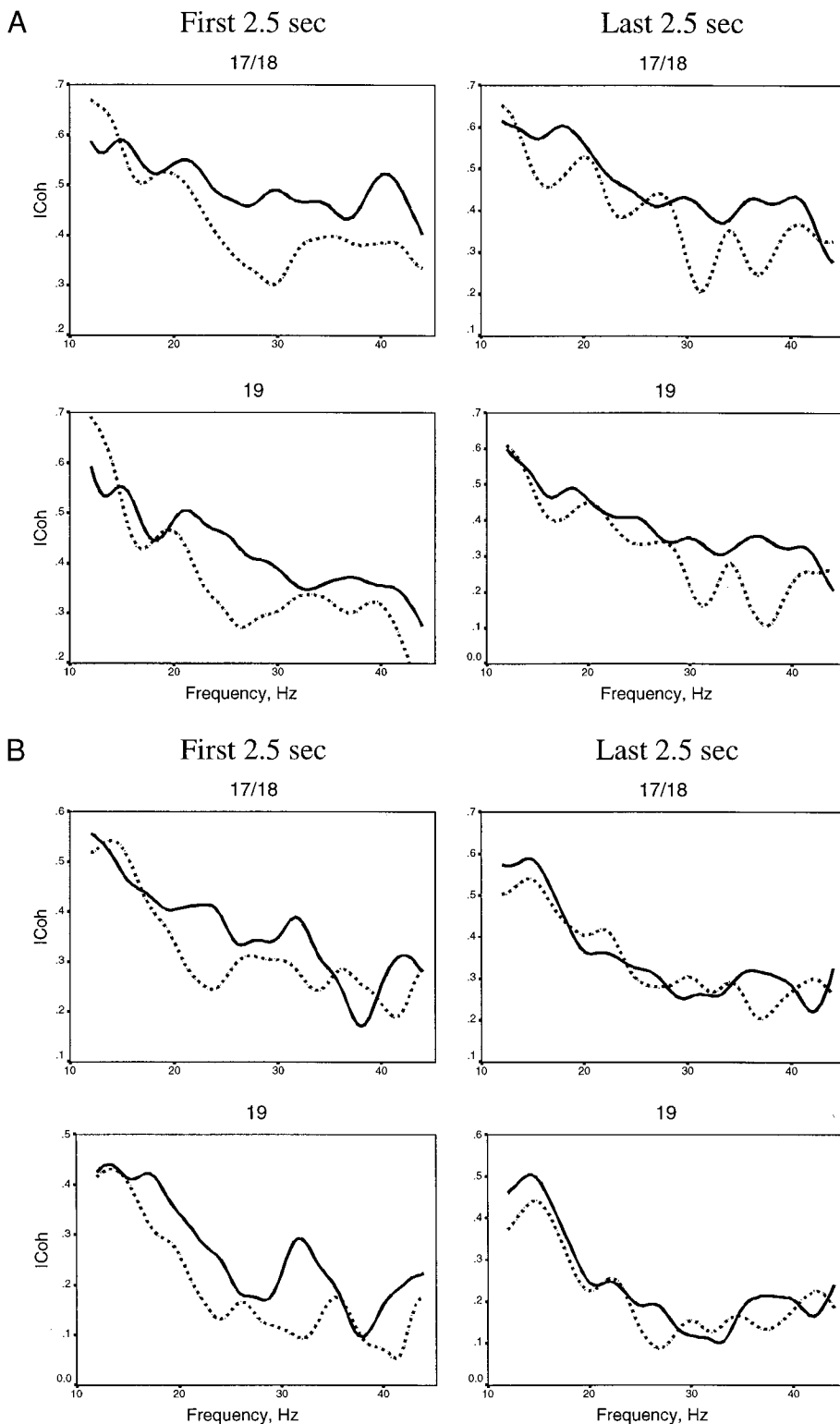


FIG. 6. Comparison of the ICoH levels obtained during the 1st and 2nd halves of the stimulation period. *A*: responses of ferret FEEG.2 to the bilateral identical stimulus (thick line) compared with the background (dotted line) during the 1st (left panels) and the last (right panels) 2.5 s of stimulation. In this animal, the responses attenuated only slightly during the 5 s of stimulation. *B*: responses to the bilateral identical stimulus of another ferret (FEEG.4, block 3), who showed a clear attenuation of the ICoH responses during the stimulation period (note the different scales on the coherence axes).

which shows the ICoH spectra for the whole screen stimulus and the background conditions, both before and after the CC transection.

DISCUSSION

In the present study, we intended to determine whether changes in cortical synchronized activity that can be ascribed

to the activation of cortico-cortical connections could be detected using EEG coherence analysis. This was done to validate the use of this technique as a way of assaying cortico-cortical connectivity in humans (see accompanying paper, Knyazeva et al. 1999).

We decided to use the callosal connections between visual cortical areas as our experimental system because they have

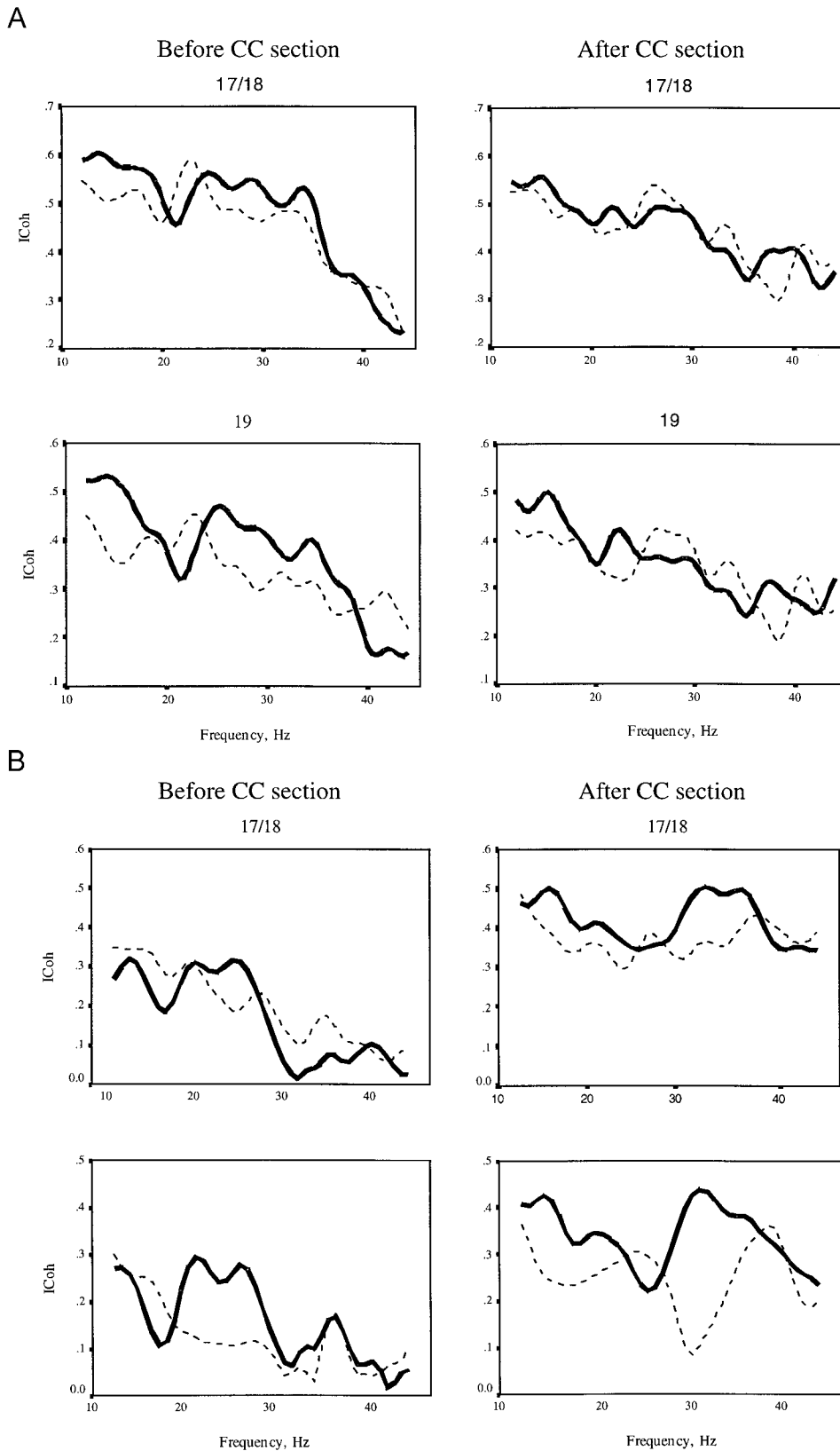


FIG. 7. Effects of corpus callosum (CC) transection on ICoh levels during 2.5-s stimulations. *A*: responses of one animal (*FEEG.5*) to the whole screen stimulus (thick line) compared with the background (dashed line), before and after transection of the CC. The successful CC section completely abolished the ICoh responses in the 17/18 and 19 electrode pairs. Note differently scaled ordinates in the plots presenting coherence spectra before and after the CC section. *B*: in this sham-operated animal (*FEEG.10*, see text), the responses to the identical close (thick line) compared with the background (dashed line) were still significant after the surgical procedure, although they probably changed their frequency characteristics within the reactive gamma band against the background of overall ICoh increase.

been well characterized in several species. In particular, the sites of origin and termination, as well as several electrophysiological properties of the callosal fibers are known in detail in the cat (reviewed in Innocenti 1986; see also Houzel et al.

1994; Innocenti and Bressoud 1999). The organization of visual areas in ferrets is in many respects similar to that of cats (Colin et al. 1998; Law et al. 1988; Redies et al. 1990; Rockland 1985), although their callosal connections are known in

fewer details (Colin et al. 1998; Grigonis et al. 1992; Rockland 1985).

EEG coherence as a method for assaying cortico-cortical connections

Our study was based on the assumption that if EEG coherence reflects the functional state of cortico-cortical connectivity, changes in EEG coherence should be found when cortico-cortical connections are activated. Among the many possible cortico-cortical connections, the callosal connections appeared to provide several advantages for testing this hypothesis. First, it is known that, as a rule, symmetrical points of the two hemispheres are directly interconnected by callosal axons. Second, in the visual areas, callosal connections are restricted to the border between areas 17 and 18 and to parts of area 19. This reflects the fact that in areas that are precisely retinotopically organized, it is the representations of the VM of the visual field that are connected by callosal axons (Innocenti 1986). Third, callosal connections originate almost exclusively from excitatory cortical neurons, mainly from the pyramidal cells, although some of the callosal axons probably terminate on inhibitory neurons (Innocenti 1986). Finally, anatomic and electrophysiological evidence converge in suggesting that callosal axons interconnect mainly or exclusively columns of cortical neurons with the same orientation specificity (Antonini et al. 1983; Berlucchi and Rizzolatti 1968; Houzel et al. 1994; Lepore and Guillemot 1982; Milleret et al. 1994; Schmidt et al. 1997), a rule that seems common to other cortico-cortical connections of the primary visual areas (Gilbert and Wiesel 1989; but see Kisvárdy and Eysel 1992).

On this basis, we predicted that if EEG coherence reflects the activity of cortico-cortical connectivity, an increase in EEG coherence should be found when the two hemifields are stimulated with identically oriented stimuli, presented close to, or crossing the VM. Indeed, in this condition, the thalamic input to the two hemispheres can be potentiated and time locked by the activation of callosal connections (Engel et al. 1991; Munk et al. 1995). We expected that stimuli presented far from the VM would not produce changes in interhemispheric coherence because the corresponding parts of the visual areas are not callosally connected. Finally, we also expected that nonidentically oriented stimuli presented to the two hemifields would fail to increase interhemispheric coherence. Our results show that all these expectations were met. In addition, we found that stimuli presented near the VM but restricted to one hemifield fail to synchronize the activity of the two hemispheres.

The fact that the stimulus-dependent increase in interhemispheric coherence is abolished by an acute callosal transection supports the hypothesis that the effects are due to the activation of callosal connections, but, for reasons explained in the introduction, it does not prove it unequivocally.

In conclusion, it appears that EEG coherence increases between two cortical sites when they are 1) interconnected and 2) simultaneously activated *both* through their direct connection *and* their thalamic input. We presently ignore if the second condition has always to be fulfilled, or if in some other condition coherence can be affected solely through activation of cortico-cortical connections. This uncertainty limits the interpretation of EEG coherence in terms of the underlying neural circuits as will be discussed elsewhere (Knyazeva et al. 1999).

Neural substrate and meaning of rhythmic cortical activities

Traditionally, three questions have been asked in relation with EEG activity. The first concerns the cellular correlates of EEG signals, the second, the organization of cortical and cortico-subcortical networks producing rhythmic activities, and the third, the functions of rhythms within the continuum of behavioral or mental states.

The first question was answered by Creutzfeldt and collaborators, by showing the high correlation between EEG signals and the postsynaptic potentials recorded from nearby cortical neurons (Creutzfeldt et al. 1966). Nevertheless, the question of the spatial origin of the EEG signal recorded by a skull electrode in humans remains a matter of discussion and of continuing methodological progress (see Knyazeva et al. 1999 for discussion). The spatial origin of the EEG signal is probably less questionable in the case of epidural electrodes for which it can be assumed, as we did, that the signal recorded is generated close to the electrode tip.

The question of the origin of the cortical rhythms is complex and goes beyond the scope of the present discussion. Suffice to say that consensus seems to emerge as to the fact that rhythms of thalamic, or possibly also of more distal origin, play an important part in the genesis of cortical rhythms (Ghose and Freeman 1992; Ribary et al. 1991; Steriade and Amzica 1996; Steriade et al. 1990). However, cortical neurons, even disconnected from their thalamic input can generate periodic rhythms (Llinas et al. 1991; Muramoto et al. 1993), and these can be propagated through cortico-cortical connections and, in particular, by callosally projecting neurons (Nunez et al. 1992).

It should be mentioned that the role of callosal connections in synchronizing the EEG activity of the two hemispheres has been a much-debated question in the 1960s and 1970s. The interest was probably evoked by Claes and Bremer's animal studies reporting that callosal transection decorrelates the EEG activity of the two hemispheres (reviewed in Bremer et al. 1956). Bremer and collaborators introduced the concept of "dynamogenèse réciproque" of symmetrical cortical areas, to indicate that symmetrical cortical areas coactivate each other during sensory stimulation as well as during resting activity. Unfortunately, the results of Bremer could not always be replicated (see, for example, Batini et al. 1967; Singer and Creutzfeldt 1969; Susic and Kovacevic 1974). In a review of this literature, Berlucchi (1990) concluded: "The corpus callosum has long been suspected to be involved in the fine bilateral synchronization of normal EEG activities but not in the gross bilateral signs of the sleep-wake cycle." Indeed, it appears from the present work that much of the disagreements may have been due to the fact that the studies of callosal transection were focused solely on spindles and alpha waves, and were performed in nonstimulated conditions.

In recent years, the synchronization of oscillations in the gamma band has been proposed as part of a mechanism for the binding of perceptual features (see reviews by Engel et al. 1997; Singer 1994; Singer and Gray 1995). In that view, known as the "synchronization hypothesis," cell populations coding different features of a given object would synchronize their rhythmic activity, thereby linking together the object's features and achieving a coherent perception of the world. Although the functional significance of the synchronous oscillations remains a matter of debate (Ghose and Freeman 1992;

Kiper et al. 1996), the hypothesis has received experimental support (reviewed in Engel et al. 1997; Roelfsema and Singer 1998; Singer and Gray 1995).

It should be noted that in most animal studies, synchronization was evaluated by cross-correlation analysis of spike trains, not by coherence analysis of EEG and local field potential signals. These two approaches have been shown to provide similar information (Guevara and Corsi-Cabrera 1996). Nevertheless, the oscillations' frequency band observed in the cross-correlograms between the activity of two cells or two groups of cells was usually narrower than the band of coherence increase found in our experiments. Broadband synchronization was also observed in a study that applied coherence analysis to local field potentials in the behaving monkey (Bressler et al. 1993). It has been shown that the frequency of oscillations can be quite variable over short periods of time, and across neuronal pairs (Nowak et al. 1995; Steriade 1997). Thus considering that we were recording from a large population of cells with each of our epidural electrodes, and that we had recording periods as long as 5 s, a broadband coherence change is not necessarily a surprise. Whether this broadband event really represents the sum over space and time of many narrowband oscillations, or whether it is of a different nature remains unclear.

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