

Synchronization of Neurons During Local Field Potential Oscillations in Sensorimotor Cortex of Awake Monkeys

VENKATESH N. MURTHY AND EBERHARD E. FETZ

Department of Physiology and Biophysics and Regional Primate Research Center, University of Washington, Seattle, Washington 98195

SUMMARY AND CONCLUSIONS

1. The neural activity associated with 20- to 40-Hz oscillations in sensorimotor cortex of awake monkeys was investigated by recording action potentials of single and multiple units. At a given site, activity of many units became synchronized with local field potential (LFP) oscillations. Cycle-triggered histograms (CTHs) of unit spikes aligned on cycles of LFP oscillations indicated that about two thirds of the recorded units ($n = 268$) were entrained with LFP oscillations. On average, units had the highest probability of spiking 2.7 ms before peak LFP negativity, corresponding to a -27.6° phase shift relative to the negative peak of the LFP.

2. The average relative modulation amplitude (RMA), defined as the ratio of amplitude of oscillatory component of CTH and the baseline multiplied by 100, was $45 \pm 27\%$ (mean \pm SD). The RMAs of single units did not differ significantly from those of multiple units.

3. Phase shifts and RMAs did not vary systematically with the cortical depth of recorded units.

4. Autocorrelation histograms (ACHs) of entrained units exhibited clear 20- to 40-Hz periodicity if they were compiled with spikes that occurred during oscillatory episodes in LFPs. ACHs of spikes outside oscillatory episodes usually did not show periodicity. Global ACHs of all spikes typically showed weak or no evidence of periodic activity.

5. Cross-correlation histograms (CCHs) between pairs of units compiled with all spikes, whether they occurred during or outside LFP oscillations, seldom revealed significant features (19 of 134 pairs or 14%). However, CCHs compiled with spikes that occurred during oscillatory episodes (OS-CCHs) had significant features in 67 of 134 pairs recorded ipsilaterally; in these 67 cases, units at both sites showed modulation in CTHs.

6. The latencies of the OS-CCH peaks (taking the medial unit as reference) were normally distributed about a mean of -0.5 ± 13 ms. Normalized peak height of CCHs (peak/baseline*100) was, on average, $14.3 \pm 11.2\%$. Peak latency and normalized peak amplitude did not change significantly with horizontal separation of recorded precentral pairs up to 14 mm.

7. Units in the left and right hemispheres could become synchronized during oscillations. Significant features in OS-CCH were detected in 22 of 42 pairs of units recorded bilaterally. The average peak latency was 0.2 ± 8.0 ms and the average normalized peak amplitude was $10 \pm 8\%$. These parameters did not differ significantly from those for ipsilateral OS-CCHs.

8. Oscillations tended to affect both the temporal structure and net rate of unit firing. For each unit, the firing rate was clamped to a narrow range of frequencies during oscillatory episodes. The coefficient of variation (SD/mean) of firing rates was significantly reduced during oscillatory episodes compared with prior rates ($P < 0.001$, paired t -test). However, the overall mean firing rate of each unit during all oscillatory episodes did not differ from its average rate immediately before the episodes. Thus oscillatory episodes

tended to clamp mean firing rates to the cells' average rates outside episodes.

9. The strength of synchronization between units during oscillatory episodes was unrelated to their involvement in the task. For pairs of precentral units recorded ipsilaterally, the probability of occurrence of significant features in the OS-CCH was slightly larger when both units of the pair were task related (33 of 56 pairs or 59%) than when only one unit was task related (20 of 39 pairs or 51%) or neither unit was task related (7 of 16 or 44%). However, these differences were not statistically significant. The magnitude of the correlation peak and the latency to peak were also not significantly different for the three cases.

10. These results suggest that units across wide regions can become transiently synchronized specifically during LFP oscillations, even if their spikes are uncorrelated during nonoscillatory periods. Synchronization did not occur preferentially for coactivated, task-related neurons, suggesting that synchronous oscillations may not play an obvious role in sensorimotor association or binding. However, they could reflect an attention- or arousal-related mechanism that facilitates associations between larger populations.

INTRODUCTION

In the companion paper (Murthy and Fetz 1996), we documented the occurrence of episodic widespread synchrony in cortical neural activity as revealed by local field potentials (LFPs). Although LFPs represent a robust and convenient measure of activity in neural populations, the spike trains of neurons provide a more specific measure of the extent of synchronization of individual neurons, whose relation to behavior can be characterized. In this paper, we document the degree of synchronization of sensorimotor cortex neurons during LFP oscillations.

The synchronization of units in the visual cortex during high-frequency oscillations has been amply demonstrated (for reviews see Engel et al. 1992; Gray 1994; Singer 1994). Multiunit activity recorded at sites separated by ≤ 7 mm in area 17 of cats can become synchronized in a stimulus-specific manner (Eckhorn et al. 1988; Gray and Singer 1989; Gray et al. 1989). In addition, oscillatory multiunit activity can become synchronized between different visual areas ipsilaterally (Engel et al. 1991b) and between homologous areas bilaterally (Engel et al. 1991a). Nonperiodic synchronization has also been documented by central peaks in the cross correlogram in visual cortex units (Krüger and Aiple 1988; Nelson et al. 1992; Nowak et al. 1995; Toyama et al. 1981; Ts'o et al. 1986) and lateral geniculate relay cells

(Sillito et al. 1995) as well as in the frontal cortex (Vaadia et al. 1995) and motor cortex (Allum et al. 1982; Fetz et al. 1991; Kwan et al. 1987; Murphy et al. 1985; Smith 1989; Smith and Fetz 1989). Nonperiodic synchrony tends to decrease with increasing separation of recording sites and has been attributed to common synaptic input. Oscillatory activity may serve to propagate synchrony beyond the range of direct connections (König et al. 1995).

In a previous report (Murthy and Fetz 1992) we provided preliminary evidence for synchronization of units with LFP oscillations, as revealed by cycle-triggered averages. In the present study we document the features of cycle-triggered histograms (CTHs) and the cross-correlation histograms (CCHs) between neurons recorded at different sites to quantify the occurrence and strength of synchronized activity. CCHs compiled during periods of LFP oscillations were compared with those compiled outside oscillatory episodes. CCHs were also compiled for units recorded bilaterally in left and right motor cortex when the monkey performed bimanual manipulatory movements.

It has been hypothesized that the oscillations in sensorimotor cortex could facilitate associations between cells involved in the same task (Murthy and Fetz 1992). This "association" hypothesis is the sensorimotor analogue of the binding hypothesis in the visual system (Singer 1994); it predicts that synchronization would tend to occur preferentially when neurons become functionally related, as for instance during a sensorimotor task involving coordinated activation. To test this hypothesis, we compared CCHs of unit pairs in which both units were task modulated with those in which one or neither of the units was task modulated. Another aspect of this hypothesis is the suggestion that synchronization could operate as a temporal code to transiently bind a behaviorally related population of neurons that individually continue to code specific response features in their firing rates. Such a synchrony code for representation of gestalt events could operate orthogonally to the rate code, in which case the cells' average firing rates should not change during oscillations. To determine whether oscillatory episodes altered the temporal structure of spikes without affecting the ongoing average firing rate, we compared mean firing rates just before and during oscillations.

METHODS

Animal training, surgical procedures, and general recording techniques are described in the companion paper (Murthy and Fetz 1996). Using pairs of glass-coated tungsten microelectrodes (1–2 M Ω impedance), we recorded from the sensorimotor cortices of three monkeys (2 *Macaca mulatta* and 1 *Macaca nemestrina*) while they made reaching movements to retrieve food pieces offered at the side of their heads or from the slots of a Klüver board facing them. The signal from each electrode was filtered at two band-pass settings to record LFPs (10–100 Hz) and unit activity (0.3–3 kHz). Single units or multiunit activity consisting of a few neurons were isolated on each electrode by means of time-amplitude window discriminators (Bak Electronics). Single units were identified by their reproducible waveforms and the presence of a refractory period in their autocorrelation histograms (ACHs). Multiunits were also isolated by the use of time-amplitude window discriminators (and were not merely derived from threshold cross-

ings); thus multiunits included several biphasic waveforms. Action potentials and LFPs were recorded as analog signals on frequency-modulated tape (XR-7000, TEAC; bandwidth DC 2.5 kHz) for off-line analysis.

Units were tested for their relation to the task and their responses to passive manipulations. The relation between firing rate and wrist movements in a trained flexion-extension task was determined for some neurons. In most cases, the arm and hand contralateral to the recording site were passively manipulated to determine whether the firing rates of recorded units were modulated by proprioceptive or cutaneous stimulation. Changes in firing rate during active movements were also noted. If the firing rates were modulated during reaching and manipulatory movements, the units were classified as task related. The cortical location of the recording site was also determined in relation to the microstimulation map of the sensorimotor cortex for each monkey. Biphasic current pulses (5–50 mA, 0.2-ms pulse duration, 10 pulses at 300 Hz) were applied through microelectrodes at different depths of the cortex to evoke movements. Recording sites were characterized by the movement (e.g., "wrist extension," "digit 2 flexion," etc.) that was evoked at minimal stimulation (<25 mA, usually 5–10 mA).

Data analysis

The LFP and unit data recorded on frequency-modulated tape were analyzed off-line. ACHs, CCHs, CTHs, and spike-triggered averages (STAs) were calculated with custom-written software for a PDP-11/73 computer.

CTHs. To document modulations in unit activity associated with oscillatory LFPs, we calculated CTHs of units aligned on the cycles of LFP oscillations. LFP signals were low-pass filtered through an audio equalizer (Radio Shack, 0–63 Hz) and passed through a time-amplitude window discriminator (Bak Electronics) to generate trigger pulses. The threshold and window were adjusted so that triggers were generated when the LFP signal had an oscillatory cycle with a period between 20 and 60 ms (17–50 Hz). These narrow window settings rarely generated a trigger pulse from transients or artifacts in LFP. Moreover, a software criterion was set to reject CTA trigger pulses unless three or more appropriately timed pulses occurred together. Using the accepted pulses as reference, we compiled histograms of unit spikes at 0.5- or 1-ms bin resolution for 125-ms periods preceding and following the reference trigger, and averages of unfiltered LFPs. The CTH provided an estimate of the probability of occurrence of spikes at different phases of LFP oscillations. As noted previously (Murthy and Fetz 1996), the error in estimating the phase of the cycle triggers was <2.4 ms. However, the uncertainty in the latency of CTH features measured relative to the average LFP peaks would be less, because of the mean limit theorem.

CTH FEATURES. To quantify the degree to which the unit was modulated with LFP oscillations, we fit histograms with a Gabor function (damped sinusoid) of the form

$$g(t) = ae^{-[b(t-c)]^2} \cos [d(t - e)] + f \quad (1)$$

using the Levenberg-Marquardt algorithm (Press et al. 1990). In this equation, $g(t)$ is the Gabor estimate of the count in time bin t in the histogram, and a – f are parameters estimated from the data. Goodness of fit was assessed with the χ^2 measure. Gabor functions could describe nonoscillatory as well as oscillatory features (that is, histograms with only single clear peaks or with multiple peaks). Single peaks resulted in Gabor function fits that had a large damping factor and the resulting best fit function resembled a Gaussian. The best fit Gabor functions provided several useful measures: (1) relative modulation amplitude (RMA), defined as the amplitude of modulation divided by the offset multiplied by 100 ($a/f * 100$)

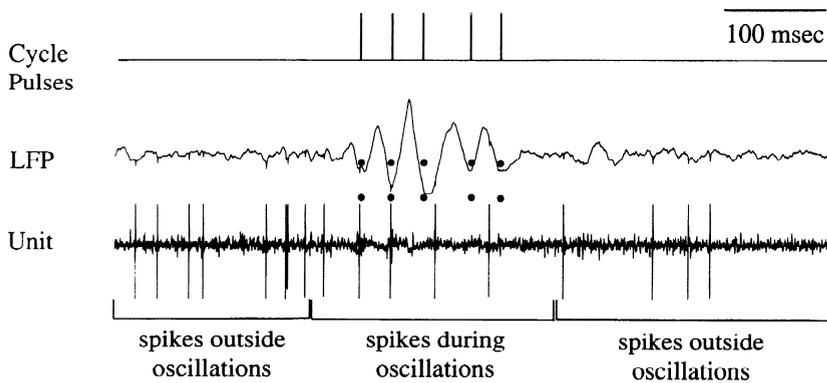


FIG. 1. Method of identifying spikes that occurred during oscillations. Local field potential (LFP) signal was passed through a window discriminator to generate cycle pulses. Three or more such pulses occurring together with intertrigger interval of <50 ms were defined as an oscillatory episode. All unit spikes that occurred in the interval from 50 ms before to 50 ms after the episode were designated as spikes "inside" oscillations; others were designated outside oscillations.

and 2) the time difference between the peak and the closest LFP negativity; and, when histograms had multiple peaks, 3) frequency of oscillation ($d/2\pi$) and 4) decay constant of Gabor function divided by the period of oscillation ($d/2\pi b$), which measured the degree of periodic oscillations in the histograms.

CROSS-CORRELATIONS. The CCHs were calculated with a binwidth of 0.5 or 1 ms, for 125-ms periods before and after the reference spikes from one of the electrodes. To determine the correlation between units specifically during the oscillatory episodes, we compiled "oscillation-selected CCHs" (OS-CCHs) using only spikes that occurred during LFP oscillations (Fig. 1). If at least three cycle pulses occurred with an interpulse interval of <50 ms, the first and last trigger defined the onset and offset of an oscillatory episode. Unit spikes that occurred within a period from 50 ms before the onset to 50 ms after the offset were considered to be spikes "during" the oscillatory episode. Spikes that failed to satisfy this criterion were considered to be spikes "outside" oscillations. Note that the selected spikes could have occurred at any phase of the LFP oscillations. STAs of LFPs recorded from both electrodes and ACHs of the reference units were also compiled simultaneously with CCHs.

CCH FEATURES. The presence of significant features in the correlogram was initially judged by visual inspection. The statistical significance of correlogram features was determined by comparing the counts in the feature (usually a peak) with the counts in the baseline. To characterize both single and multiple correlogram peaks by a common method, we used Gabor functions for all CCHs. From the best fit Gabor function for each correlogram, we estimated four parameters: 1) location of the peak with respect to the origin of CCH, 2) RMA, 3) area under the peak divided by the area of baseline under the peak, expressed as mean percent increase (MPI) (Cope et al. 1987), and 4) frequency of oscillations when there were multiple peaks. As a control, we sometimes compiled a modified version of the standard shift predictor (Perkel et al. 1967). The target spike train was shifted by an arbitrary time period (usually 1 s) greater than the average duration of oscillatory episodes and a CCH was compiled between the shifted spikes and the unshifted reference spikes. None of the shifted correlations exhibited significant features.

FIRING FREQUENCIES DURING AND OUTSIDE OSCILLATIONS. Onsets and offsets of oscillations (as defined above) were used to calculate the average frequency of each unit during individual oscillatory episodes. First the average of interspike intervals fully contained within the episode, and of the interpolated 50-ms intervals when they straddled the onset and offset of oscillatory episodes, was calculated. Then the average interspike intervals were converted to frequencies. The average frequency in a standard period of 100 or 200 ms before the defined onset of each oscillatory

episode was calculated in a similar manner, as was the average frequency following the oscillatory episode.

RESULTS

We recorded 134 pairs of units unilaterally (84, 41, and 9 pairs from *monkeys 1-3*, respectively) and 42 pairs bilaterally (all from *monkey 1*). The large sample from *monkey 1*, which exhibited particularly robust oscillations, also allowed us to compare synchronization between different cortical areas of the same monkey. The recorded pairs were often selected on the basis of their modulation in CTHs calculated on-line. CTHs, ACHs, and CCHs were then compiled off-line for the recorded pairs.

ACHs

In sensorimotor cortex, ACHs of spike activity compiled for recording periods of 2–30 min rarely revealed clear periodicity, even if robust oscillations occurred in the LFPs recorded simultaneously and when CTAs showed modulated unit activity (Fig. 2A). There are two possible explanations. First, cycle frequency of the oscillations could vary substantially over the recording period, which would smooth out the secondary ACH peaks. Second, in the awake, behaving monkey, oscillatory periods comprised only a small fraction of the total recording period (usually $<10\%$) (Murthy and Fetz 1996) and long periods of nonoscillatory activity tended to dilute any periodicity in the ACH. However, gated ACHs compiled specifically for spikes that occurred during LFP oscillations did exhibit periodicity (Fig. 2B). In contrast, ACHs of unit spikes outside LFP oscillations showed no periodicity (Fig. 2C). STAs of LFPs indicated that the spikes tended to occur during the negativity of LFPs (Fig. 2E). Calculating STAs for long recording periods that included both oscillatory and nonoscillatory activity also diluted oscillatory features. Because we were interested primarily in the relation between units and LFPs specifically during oscillatory episodes, we used CTHs extensively to quantify associated modulations in unit activity.

CTHs

A typical CTH of two units recorded simultaneously at sites in the hand and arm area of the motor cortex is shown in Fig. 3. Such histograms exhibited periodic peaks near the

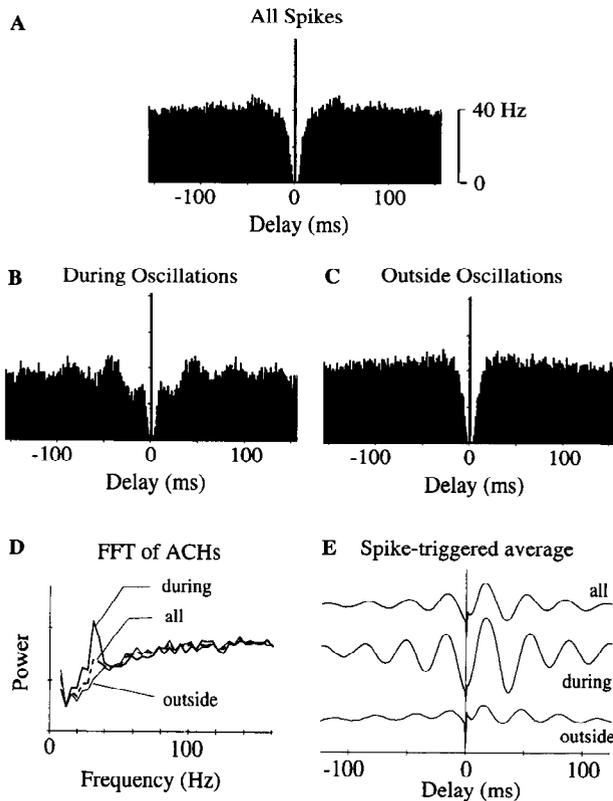


FIG. 2. Autocorrelation histograms (ACHs) of a single precentral unit. *A*: ACH compiled with all spikes showed negligible periodicity. *B*: ACH of the same unit compiled with spikes selected during oscillations showed periodicity around 30 Hz. *C*: ACH compiled with spikes outside oscillations. *D*: Fourier transforms (FFT) of the ACHs. *E*: spike-triggered averages (STAs) of LFPs from triggers selected during and outside oscillations and for all triggers. Averages in *E* are displayed with offsets for clarity. Calibration in *A* also applies for *B* and *C*.

negative phase of the LFPs. The best fit Gabor functions are also shown for each histogram. The largest peaks in the histograms sometimes occurred one cycle ahead of the largest peak in the corresponding LFP, indicating that the units were more strongly synchronized with LFP cycles in the early part of an oscillatory episode than later in an episode. This could also be seen in single traces. Of the 268 units examined, 202 (75%) had significant features in CTHs. Parameters of CTHs for precentral and postcentral sites and for well-isolated single units and multiunits from the three monkeys (168, 82, and 18 unit-LFP pairs from *monkeys 1–3*, respectively) did not differ significantly, and therefore were pooled for analysis.

FREQUENCY DISTRIBUTION. The distribution of frequencies of LFP and unit oscillations determined from the CTHs is shown in Fig. 4. Units were classified as oscillatory on the basis of the Gabor fit, if the ratio of the decay constant to the period of oscillations ($d/2\pi b$) was >0.8 . By this criterion, only 176 of 268 units (66%) were classified as oscillatory. The mean frequency of LFP oscillations (27.9 ± 2.0 Hz, mean \pm SD) was slightly lower than the mean frequency for unit modulation (28.9 ± 2.8 Hz) ($P < 0.001$). The oscillatory frequency obtained from CTHs does not necessarily reflect the overall firing frequency of the unit, because a

variable number of spikes could occur per cycle. Rather it represents the frequency of periodic unit modulation with LFPs during oscillatory episodes. The frequency of LFPs and units obtained from CTHs for 176 recordings is shown in Fig. 4C, along with the least-squares regression line. Pairwise correlation of LFP frequency and unit frequency indicated a strong correlation between the two ($r^2 = 0.46$, $P < 0.0001$, F test). LFP frequency was, on average, lower than the corresponding unit frequency ($P < 0.001$; paired t -test).

PHASE SHIFT. For each CTH, we calculated the difference in the time of peak firing probability in the unit histogram and the nearest negativity of LFP (referred to as the “time shift”). Time shifts were taken to be negative when unit firing preceded LFP negativity. The distribution of time shifts for 202 recording sites is shown in Fig. 5A. No systematic differences were seen across tasks (F-Ex, Klüver, and Side), so data from recordings during different tasks were combined. The mean time shift was -2.72 ± 7.29 ms ($n = 202$). Because different units could have different frequencies of oscillations, we also calculated the phase shifts using the frequency of LFP oscillations obtained from CTHs (Fig. 5B). The mean phase shift was $-27.6 \pm 69.5^\circ$. Thus, on average, units fired with the highest probability just before the negative peak of the LFPs.

RMA. The extent to which the unit histograms were modulated with LFP oscillations was quantified as follows. The amplitude of the modulation factor in the Gabor function (a in Eq. 1) divided by the baseline offset (f in Eq. 1) multiplied by 100 provided a measure of the RMA. Parameter a was considered to be significant if it was >2 SD of the baseline noise as estimated from the flat portion of CTH (>100 ms from the center). Units that were strongly modulated with the LFP oscillations would have a large RMA value. The distribution of the RMA values for data from 202 sites is shown in Fig. 6. There were no systematic differences between data from the three monkeys in the various tasks, so the data were pooled. The overall mean value of RMA was $44.6 \pm 27.3\%$ ($n = 202$), and values for single and multiunit activity were not statistically different ($44.9 \pm 26.5\%$ vs. $43.9 \pm 28.1\%$). Units with phase shifts between -90 and 90° were more numerous and had a greater RMA than those outside this range (Fig. 7). The mean RMA for precentral units ($44.6 \pm 26.8\%$) was not different from that for postcentral units ($45.1 \pm 37.4\%$).

To determine whether the variance in RMA and other CTH parameters reflected variability owing to nonstationarity at individual sites, we computed these parameters for different epochs of data recorded at a given site. In 18 cases analyzed this way, the variance at individual sites was $<10\%$ of the overall variance across sites. Therefore nonstationarity was probably not the primary cause of variation in the CTH parameters reported.

CORTICAL DEPTH. In the companion paper we show that the phase of LFP oscillations changed with depth in the superficial layers of the cortex, reversing from the surface to $\sim 1,000 \mu\text{m}$ (Murthy and Fetz 1996). We wanted to determine whether the units recorded at different depths in the cortex had different phase shifts when referenced to LFP oscillations recorded by the same electrode. If units at all

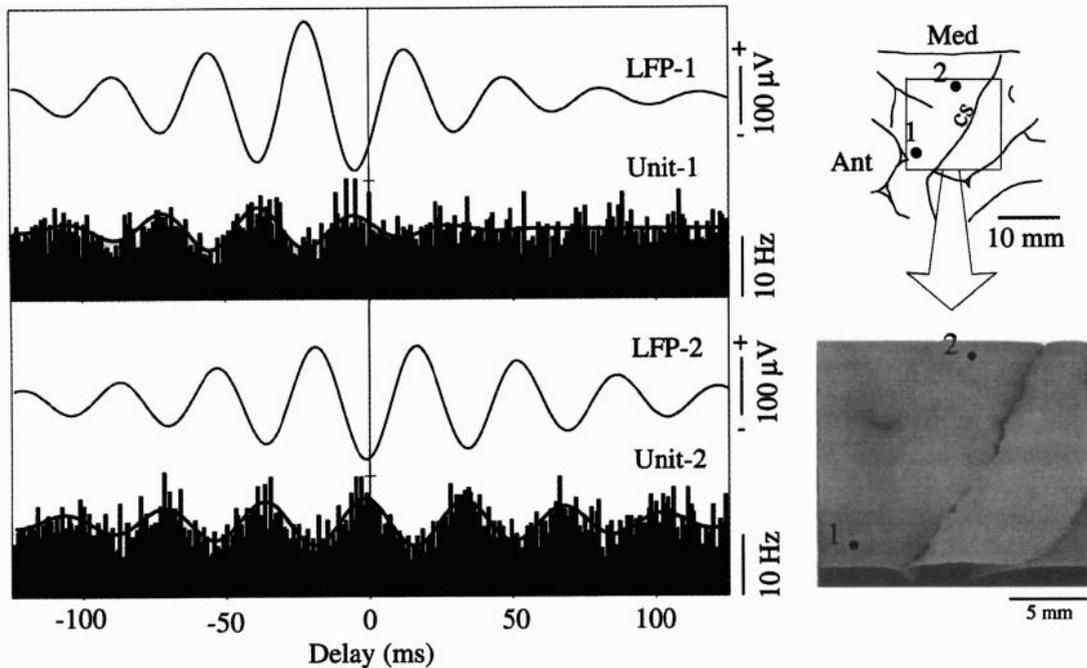


FIG. 3. CTA for activity at 2 precentral sites. Cycles of oscillations from LFP-2 were used as reference to compile averages of LFP-1 and LFP-2, and histograms of *single units 1* and *2*. Gabor function fits for the histograms are shown superimposed. Recording sites are indicated at *right*.

depths were synchronized with each other, with minimal time shifts, they would be expected to have systematically different phase relations with LFPs recorded at different depths. As shown in Fig. 8, there was no significant change in phase shift of units relative to LFP as a function of cortical depth.

Changes in firing rates during oscillations

It has been suggested that synchronous oscillations could provide a mechanism for coding the binding of functionally related cells that could operate independently of rate coding (Engel et al. 1992; Singer 1994). In this context, it would be interesting to determine whether the occurrence of oscillations affects the average firing rates of neurons (clearly, the instantaneous firing rates will be altered by the temporal entrainment with oscillations). Therefore we averaged the firing rates during each oscillatory episode and compared this with the mean firing rate just before the episode. In Fig. 9 is plotted a typical example of the average frequencies before and during oscillatory episodes for a precentral cortex unit that was well synchronized with LFP oscillations (RMA value of 36% in the CTH). The unit exhibited a wide range of frequencies in the times just preceding oscillatory episodes, but a more restricted range of firing rates during the oscillations. The SD of the values was reduced by 100% during oscillations. Interestingly, the overall mean rate during all oscillatory episodes (53.3 ± 26.4 Hz) was similar to the mean rate before oscillation (57.0 ± 13.2 Hz).

Thirty-one single units from precentral cortex were selected for detailed analysis on the basis of clear isolation of spike waveforms for long recording periods. Multiunits were not analyzed because different component units could

change in opposite directions, leading to an unknown degree of cancellation in the average. (Nevertheless, results from many multiunit records were similar to those from single units.) For each unit, overall average firing rate was the same both before and during oscillation (Fig. 10). This relation held for all the units, which exhibited a 10-fold range of rates. The coefficient of variation (SD/mean) during oscillatory episodes was significantly lower than the corresponding coefficient of variation before oscillations ($P < 0.001$, paired *t*-test). A comparison of the pre- and postoscillatory activity revealed no significant difference in average rates or in variance (Fig. 10).

CCHs

For a given pair of units, comprehensive CCHs compiled for the entire recording period usually exhibited no significant features; only 19 of 134 pairs (14%) had such features. However, when spikes were selected preferentially during oscillatory episodes, features often became evident in the CCHs (67 of 134 or 50%). Conversely, CCHs compiled with spikes outside oscillatory episodes usually exhibited no significant features; only 13 of 134 pairs (9%) had significant features. An example of CCHs compiled with reference spikes within oscillatory episodes and outside oscillations for the same pair of single units is shown in Fig. 11. The absence of features in the comprehensive correlograms is perhaps not surprising, because previous studies found that the probability of finding cross-correlation features is negligible beyond a horizontal separation of 1 mm (Kwan et al. 1987; Smith 1989). In our recordings, only 12% of the pairs had a horizontal separation of <1 mm and none showed CCH features indicative of direct synaptic interactions.

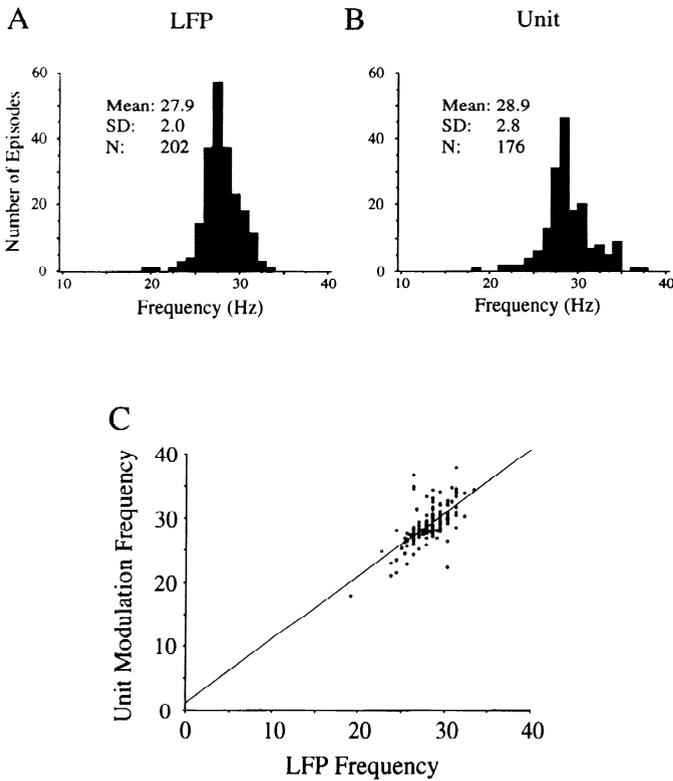


FIG. 4. Distribution of oscillation frequencies for LFP and units estimated from cycle-triggered histograms (CTHs). *A*: frequencies for LFPs were obtained directly from the averages as the inverse of the period. *B*: unit frequencies were obtained from Gabor function fits. Units were accepted as oscillatory only if the ratio of the decay constant to the cycle period was >0.8 , resulting in fewer units in the final distribution ($n = 176$) compared with LFPs ($n = 202$). *C*: LFP frequency and the corresponding unit frequency were strongly correlated ($r^2 = 0.46$, $P < 0.0001$, F test).

A peak in the OS-CCH was determined initially by visual inspection. The statistical significance of the peak was assessed by comparing the average counts in the peak with the counts in a comparable length of baseline period. We determined the significance using the raw counts rather than any function obtained by curve fitting to minimize model dependencies of statistical tests. Best fit Gabor functions were then obtained for OS-CCHs with significant peaks (single or multiple). OS-CCH parameters such as latency to peak and magnitude of correlation were obtained from the Gabor functions. The parameters of single- and multiunit correlations were not statistically different, and therefore were grouped together.

PEAK LATENCY The principal peak in the OS-CCH was usually located close to the origin. For a given pair of units, the peak latency from the origin could be negative or positive, depending on which unit was chosen as reference. Because this choice was arbitrary, all latencies could be converted to positive values; the mean value of the absolute peak latency was 8.7 ± 9.6 ms ($n = 67$). However, when units recorded at the more medial site were taken as the reference for each ipsilateral pair, a more symmetrical distribution of peak latency of the OS-CCH emerged (Fig. 12A).

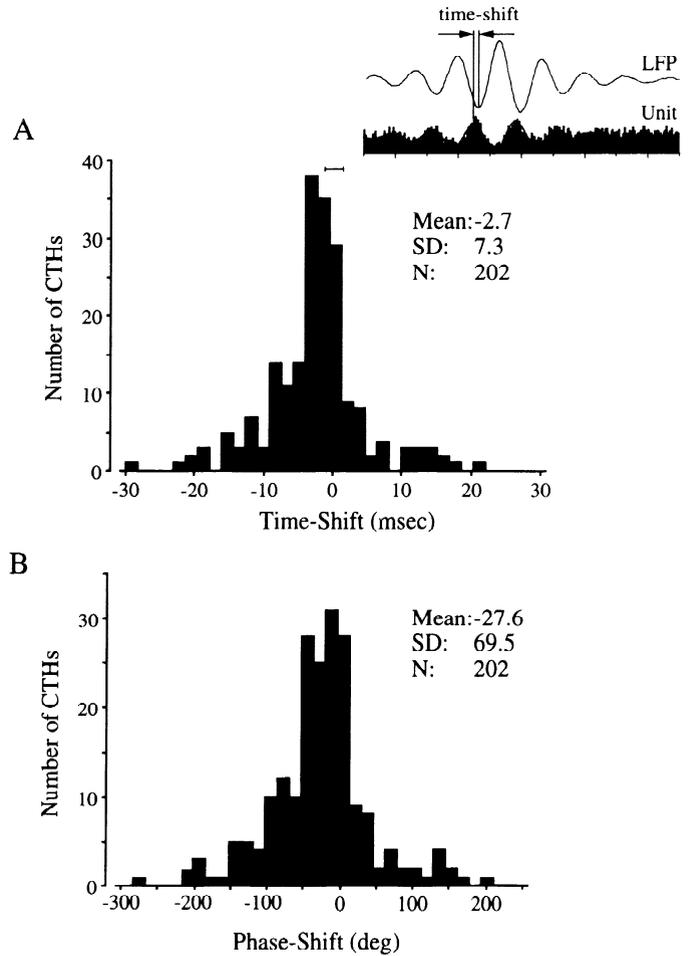


FIG. 5. Distribution of time shifts and the corresponding phase shifts of unit modulation relative to LFP. Time shifts, calculated as shown in the inset, were converted to phase shifts with the use of the frequency of LFP oscillations.

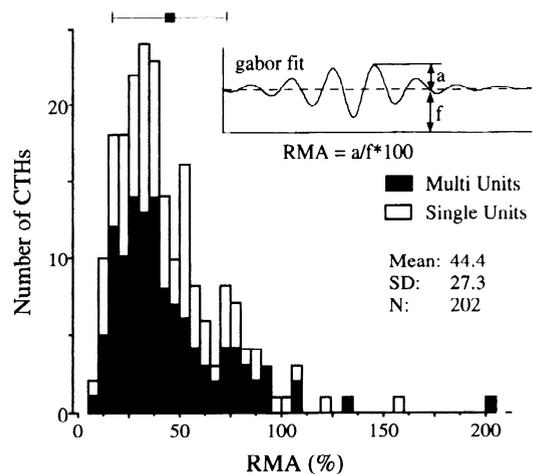


FIG. 6. Distribution of relative modulation amplitude (RMA) for single units (open bars) and multiunits (solid bars). Mean values for single and multiple units were not significantly different from each other. Data from different monkeys during different behaviors were pooled because no systematic differences were found.

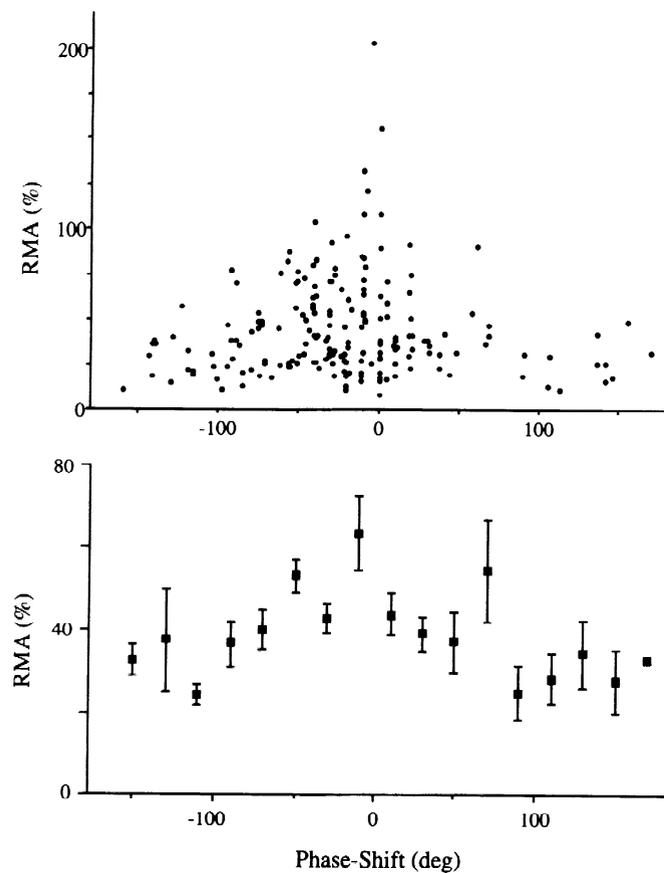


FIG. 7. RMA vs. phase shift. Most of the points were clustered between -90° and 0° phase shift. RMAs corresponding to low phase shifts were larger. Averages for 20° bins (*bottom*) confirm this general trend. Error bars: mean \pm SE.

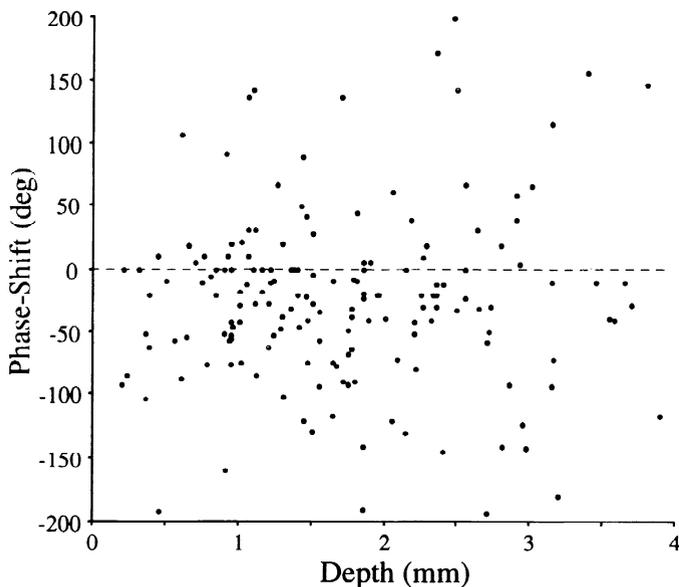


FIG. 8. Relation between phase shift of units and cortical depth. For each unit, the phase shift with respect to LFP recorded at the same site was calculated from CTHs. Phase shift was independent of the cortical depth at which the neuron was recorded. By convention, negative phase shifts were related to peaks in unit histograms preceding negative LFP peaks.

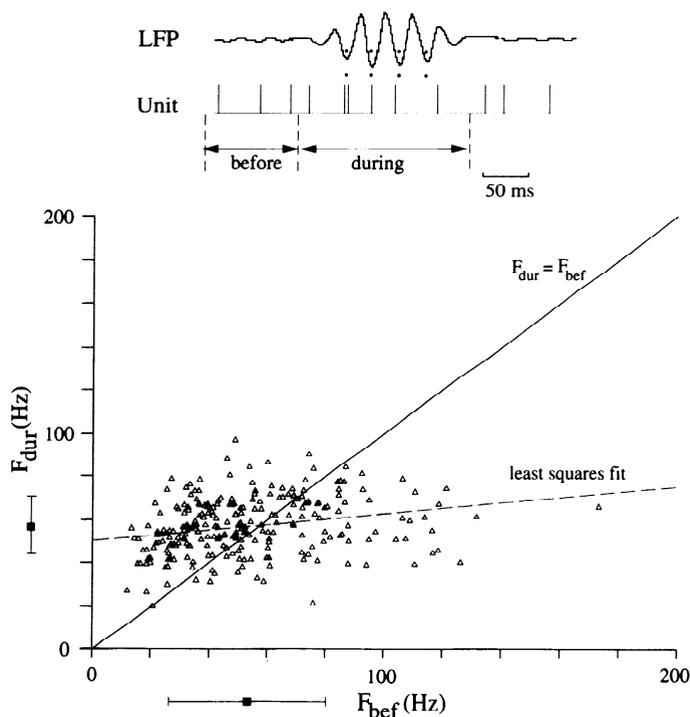


FIG. 9. Effect of oscillations on firing rates of a single precentral cortex unit. Firing rates during oscillatory episodes (F_{dur}) and in a 100-ms period before the episode (F_{bef}) were calculated for multiple episodes. Scatterplots of F_{dur} vs. F_{bef} indicate that the firing rate had significantly less variance during oscillations than in the period preceding them. However, the overall average frequency in both periods was not significantly different (53.3 ± 26.4 vs. 57.0 ± 13.2 Hz; indicated on the respective axes). The unit was significantly modulated with LFP oscillations (RMA = 36%).

The mean peak latency of the lateral relative to the medial unit was -0.52 ± 12.96 ms ($n = 67$), which was not significantly different from zero. This suggests that, on average, units could become synchronized with each other with negligible delays.

CCH MAGNITUDE. Several measures of the magnitude of correlogram peaks have been used previously. These include the k statistic (Kirkwood and Sears 1982), synaptic efficacy and contribution (Abeles 1982; Aertsen et al. 1989), correlation strength (Mastrorade 1983), and normalized area (Smith 1989). In this study, we used normalized peak amplitude and MPI (Cope et al. 1987) as noted in the METHODS section.

The distributions of normalized peak magnitudes for OS-CCHs from all three monkeys are shown in Fig. 12B. The mean value of peak amplitude as a percentage of baseline was $14.3 \pm 11.2\%$, $n = 67$ (single-single: $14.9 \pm 9.1\%$, $n = 20$; multi-multi: $12.6 \pm 9.9\%$, $n = 37$; single-multi: $19.2 \pm 17.8\%$, $n = 10$). There were no statistically significant differences between the means of the three distributions. The distributions of MPI for OS-CCHs are shown in Fig. 12C. MPI had an average value of $8.3 \pm 6.3\%$ ($n = 67$).

ELECTRODE SEPARATION AND CCH PARAMETERS. In the motor cortex the probability of finding cross-correlation features decreases with increasing horizontal separation of the recorded neurons (Kwan et al. 1987; Smith 1989). In these cases the correlogram features were usually nonperiodic and were attributed to direct synaptic interactions (monosynaptic

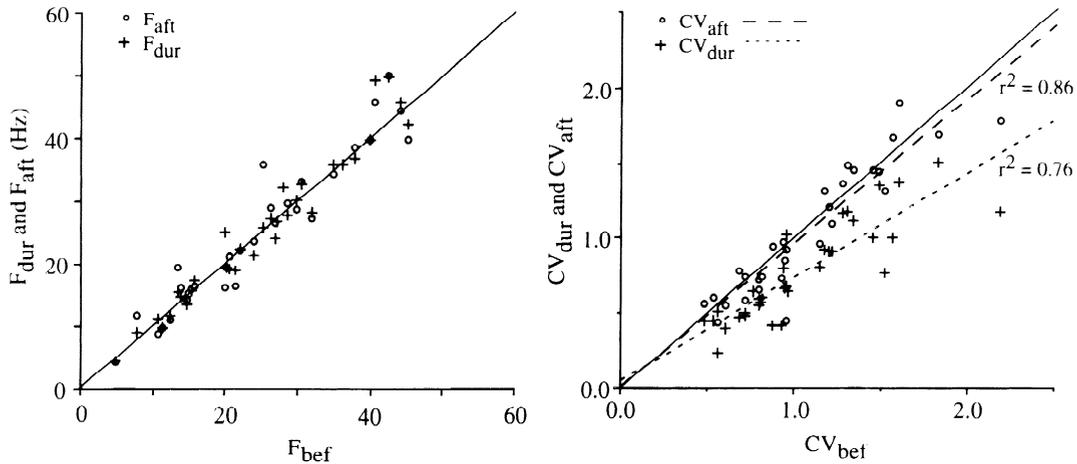


FIG. 10. Changes in firing rate associated with oscillations. Average firing rates before, during, and after all oscillatory episodes were calculated as described in METHODS and in Fig. 15. *Left*: plot of mean firing rate during (F_{dur}) and after (F_{aft}) all oscillatory episodes against firing rate before oscillations (F_{bef}) for 31 single precentral units; overall average rates were the same before, during, and after oscillatory episodes. Solid line has a slope of 1. *Right*: for the same data, the coefficient of variation of firing rates during oscillatory episodes (CV_{dur}) was significantly smaller ($P < 0.001$, paired t -test) than that before oscillations (CV_{bef}). The coefficient of variation after oscillatory episodes (CV_{aft}) did not differ significantly from the values before. Regression lines for the 2 variables are shown as solid and dashed lines; unity gain line is a solid line. Coefficient of variation tended to be inversely related to firing rate (not shown).

serial connections or common synaptic inputs). In the present study, correlations most likely reflect a general synchronous activation of large groups of neurons. Figure 13 shows the probability of finding significant features in the OS-CCH as a function of distance between the recorded pairs. No clear trend in probability was seen as the electrode separation increased. The probability of finding a correlation feature was lower for precentral-postcentral pairs (9 of 23 or 39%) than for precentral-precentral pairs (60 of 111 or 54%); no postcentral-postcentral pairs were recorded. These probabilities were likely to have been biased by the preferential selection of units that showed modulation in CTH. For pairs that had significant correlation features, peak latency and normalized peak height did not vary with electrode separation (Fig. 14).

IS THE PRESENCE OF FEATURES IN THE OS-CCH PREDICTED FROM CTHs? For pairs of units, we determined whether the presence of modulation in the CTHs could predict the presence of a significant feature in the OS-CCH. That is, if both units were modulated with LFP oscillations, are they likely to also exhibit a feature in OS-CCH? Of 82 pairs of ipsilaterally recorded units for which units at both sites had CTH modulation, 46 (56%) had significant features in OS-CCHs. In comparison, when only one or neither site showed CTH modulation, 15 of 38 pairs (40%) and 6 of 14 pairs (43%), respectively, had features in OS-CCHs. Although these two latter proportions were smaller than the first, the differences were not statistically significant ($P > 0.1$) when tested with a 2×2 contingency table.

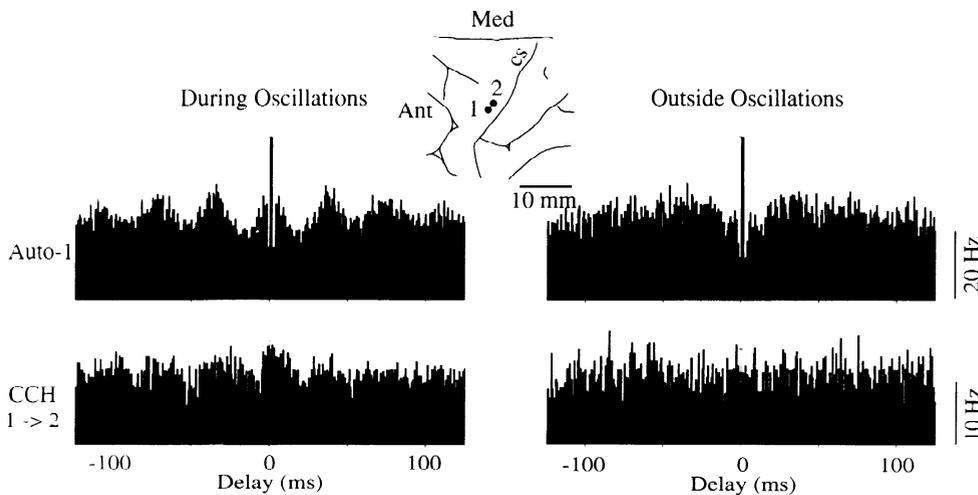


FIG. 11. ACHs and cross-correlation histograms (CCHs) of units recorded simultaneously from the hand area of the motor cortex. ACH compiled during LFP oscillations (Auto-1, *left*) showed clear oscillations, whereas that compiled outside oscillations (*right*) did not. CCHs with unit 1 as reference (CCH 1 \rightarrow 2) had multiple peaks only during oscillations (*left*), indicating that synchronization was confined to periods of LFP oscillations. Monkey was retrieving raisins from the experimenter's hand at the side of its head.

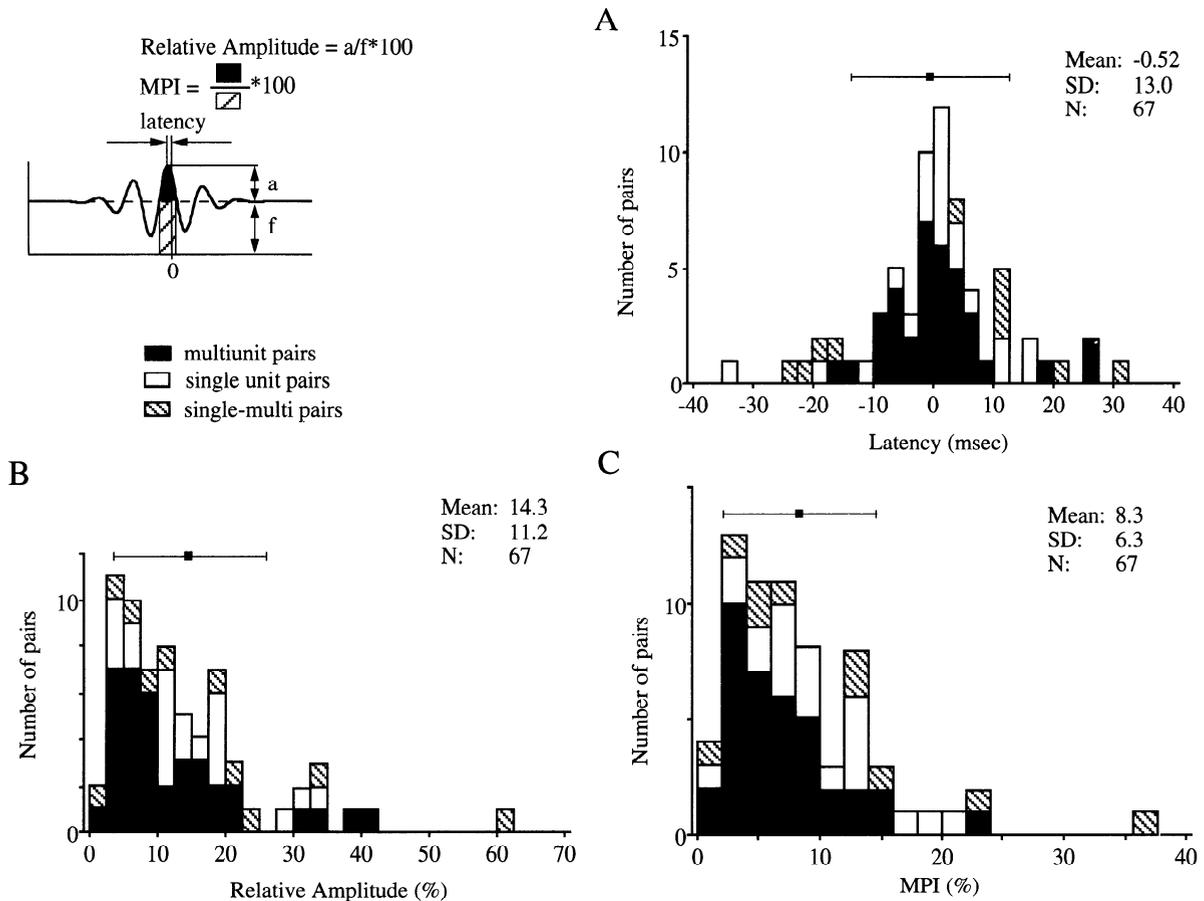


FIG. 12. Parameters of oscillation-selected CCHs (OS-CCHs) obtained from the Gabor function fit for each OS-CCH, with the use of the medial unit as reference. The distributions of latency of cross-correlation peak (A), relative amplitude (B), and mean % increase (MPI) (C) were obtained for pairs of single units (open bars), for paired multiunit recordings (black bars), and for single-multiunit pairs (hatched bars). The parameters for single, multiunit, and combined pairs were not statistically different.

Bilateral recordings

LFP oscillations in the precentral areas of the two hemispheres could become synchronized when the monkey made bimanual manipulatory movements. To determine whether

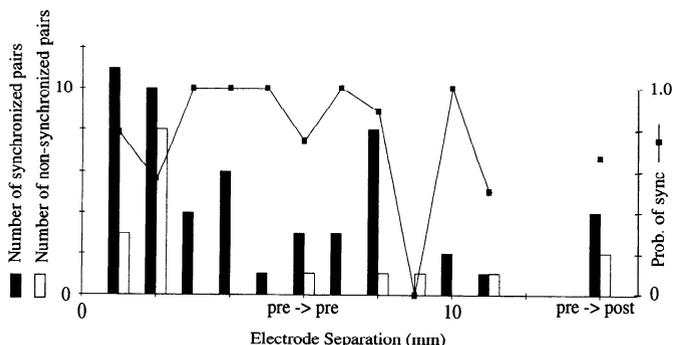


FIG. 13. Number of pairs that had a significant feature in the OS-CCH (solid bars), pairs that did not have a significant feature (open bars), and the probability of observing an OS-CCH feature (squares joined by solid line), as a function of horizontal separation. Solid line: distribution for recordings in which both electrodes were in precentral cortex (pre → pre). The average probability for 23 pairs in which 1 electrode was in precentral cortex and 1 in postcentral cortex (pre → post) is shown at right.

units also became synchronized during these movements, we recorded simultaneous LFPs and units bilaterally. Recordings were made at homologous sites in the arm and hand area of the motor cortex primarily during bimanual movements that involved coactivation of units at both sites. During unimanual movements, the cells contralateral to the inactive limb provided too few action potentials to calculate meaningful correlograms.

Forty-two pairs of bilateral single- and multiunit recordings were made in *monkey 1*. CTH parameters were similar in the two hemispheres. Of these 42 pairs, 22 (52%) had significant features in the OS-CCHs. A set of CCHs constructed for single units recorded bilaterally is shown in Fig. 15. As with the ipsilateral pairs, features were evident only when CCHs were constructed with spikes selected during oscillations (OS-CCHs).

PEAK LATENCY. The principal peak in the bilateral OS-CCH was usually located close to the origin (as for the ipsilateral pairs). Latencies were measured from OS-CCHs with the left hemisphere spikes as reference. The distribution of peak latencies (Fig. 16A) had a mean of 0.18 ± 8.03 ms ($n = 22$), indicating that neurons in the two hemispheres could become synchronized with near-zero delay. The mean la-

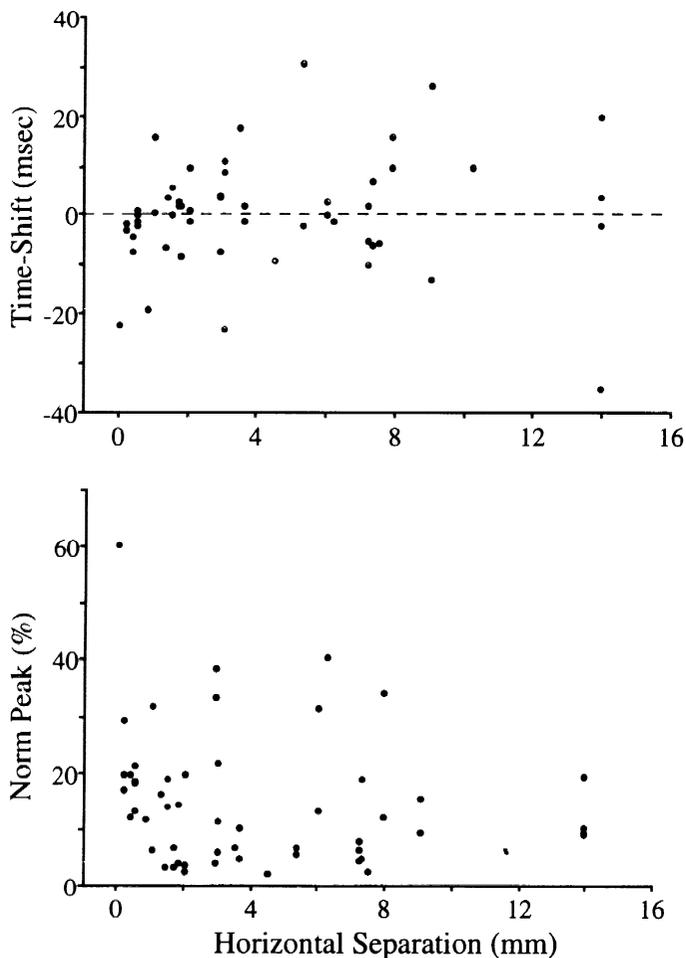


FIG. 14. Latency of OS-CCH peak from the origin and the normalized peak amplitude as a function of horizontal separation of electrodes for ipsilateral recordings.

tency was not significantly different from zero ($P > 0.1$) or from the value for ipsilateral recordings. The mean of the absolute values of peak latency was 5.9 ± 5.3 ms ($n = 22$), which also did not differ significantly from the corresponding value for ipsilateral pairs ($P > 0.1$).

CORRELOGRAM MAGNITUDE. The distributions of statistically significant normalized peak magnitudes and MPI for bilateral OS-CCHs are shown in Fig. 16, *B* and *C*. The mean value of normalized peak amplitude was $9.9 \pm 7.6\%$ ($n = 22$) and the MPI was $6.4 \pm 5.1\%$ ($n = 22$). Neither of these was significantly different from values for unilateral recordings ($P > 0.08$).

ARE OS-CCH FEATURES PREDICTABLE FROM CTHS? We determined whether the presence of modulation in the CTHs could predict the presence of a significant feature in the bilateral OS-CCH. Unlike ipsilateral pairs, units at bilateral sites were more likely ($P < 0.05$, χ^2 test, contingency table) to become synchronized during oscillations if both units were modulated in the CTH (21 of 35 or 60%) than if units at only one site were modulated (1 of 8 or 13%).

Task modulation and synchronization

Oscillations have been suggested to play a role in binding or associating neurons involved in global perceptual gestalts

(Engel et al. 1992; Singer 1994). We tested the possible motor correlate of such association by determining whether parameters of CCH between pairs of neurons had any relation to the degree of their task modulation. Because recordings were made predominantly during unconstrained free movements, the task relation of units was determined qualitatively on the basis of the modulation of firing rates during reaching movements. Responses to somatosensory stimulation were also determined for some neurons. Neurons that were classified as task related exhibited modulations in firing rate when the monkey reached for raisins in the Klüver board and/or when contralateral digits or hand were passively manipulated.

The associational hypothesis would predict that a pair of units that are both activated during coordinated reaching would be more likely to become synchronized. If only one or neither member of the unit pair was task modulated, their synchronization should be weaker or negligible.

Precentral pairs in which both units were task modulated were slightly more likely to have a feature in their OS-CCH than pairs with only one task-modulated unit (59 vs. 51%, Table 1). However, a χ^2 test indicated that the two proportions were not statistically different ($P > 0.2$). The probability of synchronization for two non-task-related precentral pairs was slightly smaller (44%, $P > 0.1$) than the probability for pairs in which one or both sites were task related. There were fewer pairs with one precentral and one postcentral unit. For these, the synchronization probability for pairs with both sites task related appeared to be smaller than that for pairs with one site task related (33 vs. 60%), but the χ^2 test indicated that the significance level was low ($P > 0.2$), presumably because of the low number of samples. Peak latencies and normalized peak amplitudes in the CCHs were not significantly different for pairs with both sites task related versus pairs with one or neither site task related ($P > 0.15$) (Table 1).

Units were also characterized by the nearest joint (digits, wrist, elbow, and shoulder) whose manipulation evoked responses. For instance, a neuron with a receptive field in the palm and a response to wrist flexion was classified as a "wrist unit." The probability of synchronization for pairs of units mapped to the same or adjacent joint (digit-digit, digit-wrist, wrist-wrist, wrist-elbow, etc.) was no different from that for pairs mapped to different joints (digit-elbow, digit-shoulder, wrist-shoulder). This result is consistent with the finding that correlation parameters did not change significantly with separation of electrodes and the known topographic organization of motor cortex.

In bilateral recordings, task-related units were preferentially selected, which precluded analysis similar to that for unilateral pairs. Nevertheless, the percentage of bilateral unit pairs that were synchronized during oscillations (52%, Table 1) was similar to the value for the unilateral pairs. Peak latency and normalized peak were not different from corresponding values for unilateral pairs ($P > 0.1$).

DISCUSSION

Relation between LFP oscillations and unit activity

LFP oscillations in sensorimotor cortex of awake primates have been shown to occur in relation to exploratory

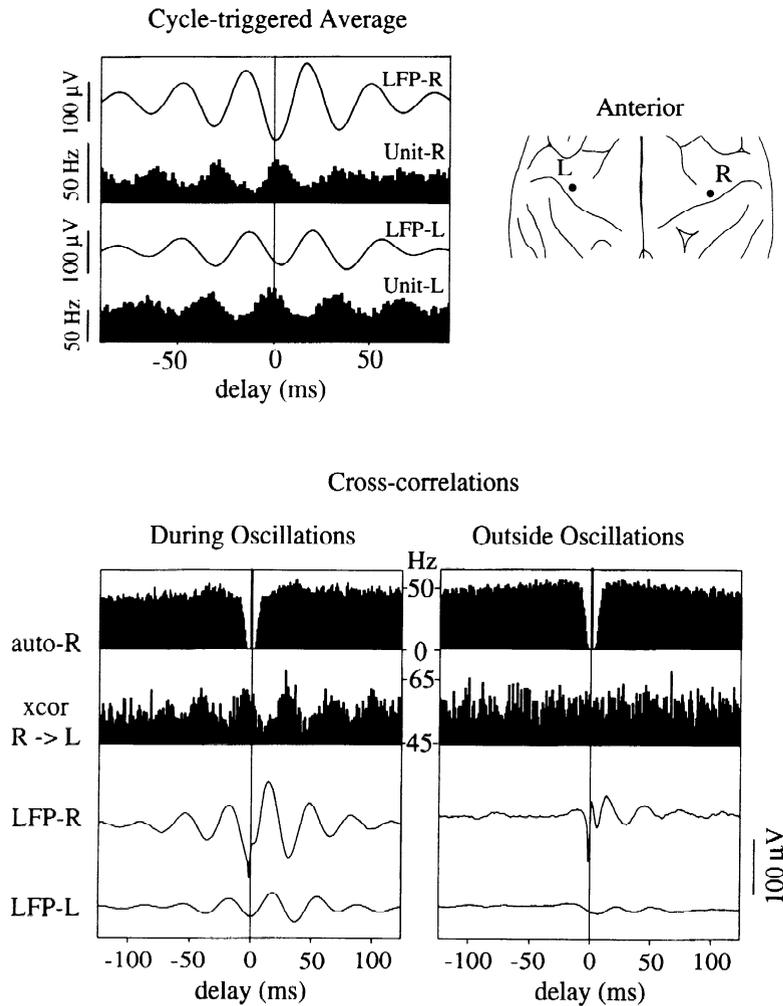


FIG. 15. CTHs and cross-correlation of units recorded simultaneously from the hand area of the motor cortex in both hemispheres. The monkey used both hands to search for raisins in a box outside its visual field. CTHs revealed strong synchronization of units with LFP oscillations (*top left*). Cross-correlation of the unit activity in the left hemisphere referenced to that in the right revealed synchronization of units during periods of LFP oscillations (*bottom left*). If unit triggers for cross-correlation were from periods outside LFP oscillations, no significant correlation was detected (*bottom right*).

and trained motor behavior (Gaàl et al. 1992; Murthy and Fetz 1992; Sanes and Donoghue 1993). Activity of many neurons becomes synchronized with LFP oscillations (Gaàl et al. 1992; Murthy and Fetz 1992). In the present study, we found that 66% of the units in the vicinity of the recording site became entrained with LFP oscillations. Furthermore, there was significant variability in the extent to which units could become oscillatory and in their phase relation to LFP oscillations. Cross-correlation analysis indicated that units could become synchronized with each other more frequently and more strongly during periods of LFP oscillations.

A significant finding was the lack of strong periodicity in the ACHs of units when all spikes (including oscillatory and nonoscillatory periods) were taken into account. Lack of periodicity in single-unit ACHs has been used to argue against the prevalence of oscillations in the visual cortex (Tovee and Rolls 1992; Young et al. 1992). We found that units that were strongly synchronized with LFP oscillations could nevertheless exhibit no apparent periodicity in their global ACHs. However, ACHs of spikes selected during oscillatory episodes often did show clear periodicity. There are two possible reasons for the absence of periodic side peaks in global ACHs. First, nonoscillatory periods, which were usually an order of magnitude longer

than oscillatory periods and contributed more spikes, tended to "wash out" the side peaks in ACHs. Second, the frequency of oscillations could vary from one episode to the next, so the superposition of different frequencies further tended to flatten secondary ACH peaks.

CTHs indicated that units tended to spike ~ 3 ms before the negative peak of LFPs. In some network simulations of oscillatory mechanisms, inhibitory neurons tend to fire $\sim 90^\circ$ out of phase with respect to excitatory neurons (Freeman 1968). Such a population of inhibitory neurons should fire at times distributed around 11 ms (assuming the principal peak at -3 ms to represent excitatory cells). The distribution of time shifts in the present study was largely unimodal, with a peak near -3 ms (Fig. 5). Assuming this model is applicable, the absence of a distinct earlier peak could reflect the recording bias against inhibitory neurons, owing to their smaller size and closed dendritic morphology. Moreover, the recurrent inhibition necessary to sustain oscillations could be provided by relatively few inhibitory neurons with sufficiently divergent connections. It is also possible that oscillations could be generated with negligible phase shifts between inhibitory and excitatory neurons, as suggested by other simulations (Bush and Sejnowski 1996; Jefferys et al. 1996).

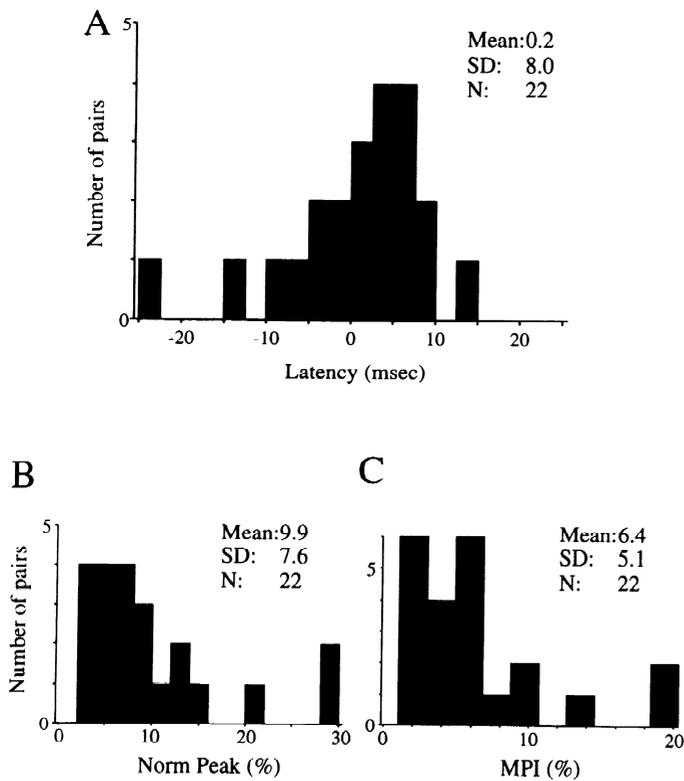


FIG. 16. Distribution of peak latency (A), normalized peak (B), and MPI (C) for units recorded bilaterally. Single and multiple units were pooled owing to small sample size and absence of obvious differences.

The extent to which spikes were modulated with LFP oscillations was characterized by the RMA. RMA values for neurons with phase shifts close to zero were higher than those for neurons with greater phase shifts. There were also more neurons with phase shifts closer to zero. These two observations are consistent with a model of interconnected neurons, whose cooperative effect would tend to cause strong synchronization of the neurons. In such a network, a large number of neurons would have phase shifts close to

zero with respect to their population average (equivalent to the LFP).

Mechanisms generating zero-delay synchronization across large cortical distances

Cross-correlations between pairs of units indicated that synchronization could occur with negligible delay even when units were separated by up to 20 mm ipsilaterally. Moreover, units recorded bilaterally in the motor cortex hand areas became synchronized with negligible delays. Nonperiodic synchronization between proximate neurons (<2 mm) in the motor cortex of monkeys has been studied previously (Kwan et al. 1987; Smith 1989). Common inputs from the major subcortical source, the ventrolateral thalamic nucleus, may explain central CCH peaks. Single thalamic afferents to the sensorimotor cortex have multiple arborization foci covering tangential distances of ≤ 6 mm (Deschênes and Hammond 1980; Shinoda and Kakei 1989). In addition to thalamic inputs, cortical neurons get up to 70% of their inputs from other cortical neurons (reviewed by White 1989). Therefore it seems reasonable to expect that cortico-cortical connections play a significant role in widespread synchronization. Cortical inputs to the motor cortex have been traced to the somatosensory areas, premotor area, supplementary motor area, and parietal areas (Jones and Wise 1977; Tokuno and Tanji 1993). Intrinsic connections within the motor cortex, both within-column and long-range horizontal axon collaterals of pyramidal neurons, also provide many of the inputs to motor cortical neurons (Ghosh and Porter 1988; Huntley and Jones 1991; Keller 1993; Matsu-mura et al. 1996). Although such monosynaptic connections between neurons provide a mechanism for synchronization, they are inadequate to explain the widespread periodic synchronization that occurs preferentially during oscillations. Clearly, if large groups of neurons become synchronized during oscillations, any pair of neurons need not be synchronized by inputs from common presynaptic neurons.

Oscillatory activity could synchronize cells with minimal delays even over large cortical distances. Theoretical studies have suggested that zero-delay synchronization is possible

TABLE 1. *Task relation and synchronization*

	Percent Synchronized	<i>n</i>	Peak Latency, ms	Normalized Peak, %
Precentral-precentral pairs				
Task-related units at:				
Neither site	44	7/16	1.1 ± 9.5	11.6 ± 10.8
One site	51	20/39	1.6 ± 13.4	13.9 ± 9.0
Both sites	59	33/56	-2.0 ± 14.7	14.4 ± 12.6
Precentral-postcentral pairs				
Task-related units at:				
Neither site	33	1/3	4.0	33.7
One site	60	3/5	-5.7 ± 9.2	10.3 ± 4.9
Both sites	33	5/15	0.2 ± 6.7	16.8 ± 12.3
Bilateral pairs				
Task-related units at:				
Both sites	52	22/42	0.2 ± 8.0	9.9 ± 7.6

Values for peak latency and normalized peak are means ± SD; *n* is number of pairs with synchronization in oscillation-selected cross-correlation histogram/total pairs tested.

even with significant and variable conduction delays, if neuronal firing is oscillatory (König and Schillen 1991). This is because the interspike interval is relatively constant for oscillatory firing patterns. The entrained spikes would be followed by an afterhyperpolarization during which synaptic inputs would be relatively ineffective in triggering spikes; instead, spikes would be more likely to occur at the end of this relatively silent period. Such burst-pause behavior might be enhanced by some cortical neurons that are intrinsically capable of generating bursts (Connors and Gutnick 1990; Llinás et al. 1991; Nuñez et al. 1992). In support of this hypothesis, it has been shown that long-range synchronization is usually accompanied by oscillatory activity in the visual cortex (König et al. 1995). Our results are compatible with this hypothesis, because correlation features were present only for spikes selected during oscillatory episodes.

Synchronization was also observed between bilaterally recorded units. The companion paper shows that LFP oscillations could become synchronized when the monkey made bimanual manipulations as well as unimanual ones (Murthy and Fetz 1996). Units in the motor cortex are commonly activated during movements of contralateral limbs, although some units also discharge with ipsilateral movements (Tanji et al. 1988). In the present data, the unimanual movements were not accompanied by sufficient numbers of spikes in ipsilateral cortex to calculate bilateral CCHs. Nevertheless, ipsilateral neurons sustained sufficient subthreshold membrane potential fluctuations to generate the LFP oscillations. When units in the two hemispheres were coactivated during bimanual manipulations, they could become synchronized with near-zero delays during oscillatory episodes, suggesting that synchronization of spikes could be used to organize specific patterns of activity required for coordinated control of both limbs. The most likely anatomic substrate mediating bilateral synchrony is the callosal projection (Jenny 1979; Jones 1986; Roullier et al. 1994). In the visual cortex, sectioning of the corpus callosum abolished synchronization of oscillations between areas 17 of the two hemispheres (Engel et al. 1991a; Munk et al. 1995). It seems likely that synchronization between the motor cortex of the two hemispheres is also mediated by callosal projections, although strong synchronization between thalamic afferents to the two hemispheres could also synchronize neurons in the two motor cortices. As seen with the ipsilateral pairs, bilateral unit synchronization was restricted to periods of LFP oscillations, further supporting the idea that oscillations could represent an efficient mechanism for generating synchrony over long distances.

Synchrony is probably not essential for sensorimotor association

A principal hypothesis regarding cortical oscillations has been that synchronization represents a temporal code used by populations of neurons involved in a common global function. Such temporal synchronization in the visual cortex is postulated to solve the binding problem, and there is good evidence to support this view (Eckhorn et al. 1988; Engel et al. 1991a,b, 1992; Gray et al. 1989; König et al. 1995; Singer 1994). One could consider the analogous issue of

coordinating sensorimotor cortex cells that generate complex movements involving multiple muscles and joints. The mechanisms by which neurons in different representation zones interact to produce coordinated movements remain largely unclear. Synchronous oscillations might provide a means of associating neurons that are coactivated during movement and define a functional neuronal ensemble. This hypothesis would predict that neurons whose activity must be coordinated during a sensorimotor task would have a greater tendency to be synchronized. We tested this by defining task relation broadly as any modulation of firing rate during free manipulatory limb movements. Using this criterion, we found that synchronization occurred slightly less often for precentral pairs with only one or neither unit task related than for pairs with both units task related. However, this difference was not statistically significant, indicating that the relation between synchronization and task modulation, if any, is more subtle. In particular, many neurons that were not task related nevertheless became synchronized during oscillatory episodes.

Possible consequences of coherent oscillations

An important aspect of the binding hypothesis is that temporal synchrony could provide a mechanism for coding gestalt or global relationships independently of rate coding of response features by individual neurons. It was therefore of interest to determine whether the occurrence of oscillations alters the average firing rates of neurons, in addition to imposing a temporal pattern on their spikes. If oscillatory activity mediated temporal binding independently of rate coding, the occurrence of oscillations should not disrupt the average firing rates. In fact, we found that during oscillations firing rates were clamped to a relatively narrow range. When the discharge rate before the oscillatory episode was higher than a certain value, the mean rate during the episode was reduced, and vice versa. This behavior can be understood in terms of the cell's response to two types of synaptic inputs: a continuously modulated drive that determines the modulated firing rate and a quasisinusoidal drive during oscillatory episodes that entrains spikes near the cycle peaks (cf. Baldissera et al. 1984 for motoneurons). Even if the oscillatory input provides no net synaptic depolarization, it can tend to clamp the mean rate. When the background rate is low, the oscillatory drive can raise the mean rate because of the enhanced efficacy of transient synchronous depolarization (Murthy and Fetz 1994; Reyes and Fetz 1993). When the background rate is high, the synchronous depolarizations raise the peak rates into a saturation range in which firing is limited by refractory mechanisms, thus reducing the overall net rate (Bernander et al. 1994; Murthy and Fetz 1994). In addition, any inhibitory component of the oscillatory synaptic input has an enhanced effect when superimposed on the excitatory drive generating high rates, and has relatively less effect during periods of lower firing rates. The fact that oscillatory input clamps the mean rate to a value that is typical of that unit outside the oscillations indicates that the excitatory and inhibitory effects tend to balance. Thus, on average, the oscillatory input would be neutral with respect to the modulated drive that controls firing rate.

Whatever their possible functional role, the oscillations do have significant consequences for neuronal interactions in cortex. During the oscillatory episodes, large populations of neurons in sensorimotor cortex receive synchronous excitatory and inhibitory synaptic inputs at a period of ~ 35 ms. This enhances synaptic interactions between all the connected cells whose intercellular conduction times correspond to a cycle period, because their action potentials arrive when the postsynaptic cells are closer to threshold. Conversely, the efficacy of interactions between neurons separated by conduction times of half a period is reduced. Thus synchronous oscillations would impose preferential interactions between neural populations separated by appropriate conduction times.

Finally, we might speculate on the possible behavioral function of the oscillations in the sensorimotor cortex. The plausible null hypothesis is that oscillations are merely an epiphenomenon of cortical excitability, appearing when a critical level of instability is exceeded. One problem with this notion is explaining why widespread periodic synchrony across cortical areas does not disrupt the normal function of the entrained populations. Alternatively, the nervous system might use coherent oscillations to some purpose. The idea that oscillations are required to bind together neural populations involved in sensorimotor behavior seems discrepant with the fact that oscillations occur in no regular relation to coordinated limb movements (at the time scale of ~ 100 ms) and that they synchronize both task-related and -unrelated neurons. Instead, our observations suggest that synchronous oscillations in sensorimotor cortex may be more involved in some aspects of arousal or attention (cf. MacKay and Mendonca 1995; Munk et al. 1996; Rougeul et al. 1979; Steriade et al. 1991). For example, the enhanced behavioral responsiveness could be associated with increased neural responsiveness produced by intermittent oscillations in membrane potentials. In addition, the synchronization of pre- and postsynaptic activity during oscillations could lead to potentiation of synaptic connections (e.g., Chen and Fetz 1993; Huerta and Lisman 1993; Markram and Sakman 1995; Pavlides et al. 1988). Preliminary evidence indicates that excitatory postsynaptic potentials evoked during the depolarizing phases of spontaneous oscillations are transiently enhanced (Chen and Fetz 1993; Huerta and Lisman 1993). Stimulation of the hippocampus during the theta rhythm can lead to long-term potentiation (Huerta and Lisman 1993; Pavlides et al. 1988). Such changes in synaptic efficacy would occur preferentially, as the cortical oscillations do, during periods of increased attention, and thus could play a role in motor learning. Another possible function of widespread coherent oscillations would be to serve as a reference carrier wave for a temporal phase code (cf. Hopfield 1995; O'Keefe and Recce 1993). Each of these possibilities suggests further experiments to determine which functions the oscillatory episodes might perform during attention or arousal.

We thank L. Shupe for programming, J. Garlid for technical assistance, and K. Elias for editorial help.

This work was supported by National Institutes of Health Grants RR-00166 and NS-12542 and by a grant from the Human Frontiers Science Program.

Present address of V. N. Murthy: CNL, The Salk Institute, 10010 N. Torrey Pines Rd., La Jolla, CA 92037.

Address for reprint requests: E. E. Fetz, Regional Primate Research Center, Box 357330, University of Washington, Seattle, WA 98195-7330.

Received 10 October 1995; accepted in final form 9 July 1996.

REFERENCES

- ABELES, M. Role of the cortical neuron: integrator or coincidence detector? *Isr. J. Med. Sci.* 18: 83–92, 1982.
- AERTSEN, A. M., GERSTEIN, G. L., HABIB, M. K., AND PALM, G. Dynamics of neuronal firing correlation: modulation of "effective connectivity." *J. Neurophysiol.* 61: 900–917, 1989.
- ALLUM, J. H. J., HEPP-REYMOND, M.-C., AND GYSIN, R. Cross-correlation analysis of interneuronal connectivity in the motor cortex of the monkey. *Brain Res.* 231: 325–334, 1982.
- BALDISSERA, F., CAMPADELLI, P., AND PICCINELLI, L. The dynamic response of cat α -motoneurons investigated by intracellular injection of sinusoidal currents. *Exp. Brain Res.* 54: 275–282, 1984.
- BERNANDER, Ö., KOCH, C., AND USHER, M. The effect of synchronized inputs at the single neuron level. *Neural Comput.* 6: 622–641, 1994.
- BUSH, P. C. AND SEJNOWSKI, T. J. Inhibition synchronizes sparsely connected cortical neurons within and between columns in realistic network models. *J. Comput. Neurosci.* 3: 91–110, 1996.
- CHEN, D.-F. AND FETZ, E. E. Effect of synchronous neural activity on synaptic transmission in primate cortex. *Soc. Neurosci. Abstr.* 19: 781, 1993.
- CONNORS, B. W. AND GUTNICK, M. J. Intrinsic firing patterns of diverse neocortical neurons. *Trends Neurosci.* 13: 99–104, 1990.
- COPE, T. C., FETZ, E. E., AND MATSUMURA, M. Cross-correlation assessment of synaptic strength of single Ia fiber connections with triceps surae motoneurons in cats. *J. Physiol. Lond.* 390: 161–188, 1987.
- DESCHÊNES, M. AND HAMMOND, C. Physiological and morphological identification of ventrolateral fibers relaying cerebellar information to the cat motor cortex. *Neuroscience* 5: 1137–1141, 1980.
- ECKHORN, R., BAUER, R., JORDAN, W., BROSCHE, M., KRUSE, W., MUNK, M., AND REITBOECK, H. J. Coherent oscillations: a mechanism for feature linking in the visual cortex? *Biol. Cybern.* 60: 121–130, 1988.
- ENGEL, A. K., KÖNIG, P., KREITER, A. K., SCHILLEN, T. B., AND SINGER, W. Temporal coding in the visual cortex: new vistas on integration in the nervous system. *Trends Neurosci.* 15: 218–226, 1992.
- ENGEL, A. K., KÖNIG, P., KREITER, A. K., AND SINGER, W. Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science Wash. DC* 252: 1177–1179, 1991a.
- ENGEL, A. K., KÖNIG, P., AND SINGER, W. Direct physiological evidence for scene segmentation by temporal coding. *Proc. Natl. Acad. Sci. USA* 88: 9136–9140, 1991b.
- FETZ, E. E., TOYAMA, K., AND SMITH, W. Synaptic interactions between cortical neurons. In: *Cerebral Cortex*, edited by A. Peters and E. G. Jones. New York: Plenum, 1991, p. 1–47.
- FREEMAN, W. J. Relations between unit activity and evoked potentials in prepyriform cortex of cats. *J. Neurophysiol.* 31: 337–348, 1968.
- GAÀL, G., SANES, J. N., AND DONOGHUE, J. P. Motor cortex oscillatory neural activity during voluntary movement in *Macaca fascicularis*. *Soc. Neurosci. Abstr.* 18: 355, 1992.
- GHOSH, S. AND PORTER, R. Morphology of pyramidal neurones in monkey motor cortex and the synaptic actions of their intracortical axon collaterals. *J. Physiol. Lond.* 400: 593–615, 1988.
- GRAY, C. M. Synchronous oscillations in neuronal systems: mechanisms and functions. *J. Comput. Neurosci.* 1: 11–38, 1994.
- GRAY, C. M., KÖNIG, P., ENGEL, A. K., AND SINGER, W. Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature Lond.* 338: 334–337, 1989.
- GRAY, C. M. AND SINGER, W. Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *Proc. Natl. Acad. Sci. USA* 86: 1698–1702, 1989.
- HOPFIELD, J. J. Stimulus representation and pattern recognition using action potential timing. *Nature Lond.* 376: 33–36, 1995.
- HUERTA, P. T. AND LISMAN, J. E. Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. *Nature Lond.* 364: 723–725, 1993.
- HUNTLEY, G. W. AND JONES, E. G. Relationship of intrinsic connections to

- forelimb movement representations in monkey motor cortex: a correlative anatomic and physiological study. *J. Neurophysiol.* 66: 390–413, 1991.
- JEFFERYS, J. G. R., TRAUB, R. D., AND WHITTINGTON, M. A. Neuronal networks for induced “40 Hz” rhythms. *Trends Neurosci.* 19: 202–208, 1996.
- JENNY, A. B. Commissural projections of the cortical hand motor area in monkeys. *J. Comp. Neurol.* 188: 137–146, 1979.
- JONES, E. G. Connectivity of the primate sensory-motor cortex. In: *Cerebral Cortex*, edited by E. G. Jones and A. Peters. New York: Plenum, 1986, vol. 5, p. 113–183.
- JONES, E. G. AND WISE, S. P. Size, laminar and columnar distribution of efferent cells in the sensory-motor cortex of monkeys. *J. Comp. Neurol.* 175: 391–438, 1977.
- KELLER, A. Intrinsic synaptic organization of the motor cortex. *Cereb. Cortex* 3: 430–441, 1993.
- KIRKWOOD, P. A. AND SEARS, T. A. The effects of single afferent impulses on the probability of firing of external intercostal motoneurons in the cat. *J. Physiol. Lond.* 322: 315–336, 1982.
- KÖNIG, P., ENGEL, A. K., AND SINGER, W. The relation between oscillatory activity and long-range synchronization in cat visual cortex. *Proc. Natl. Acad. Sci. USA* 92: 290–294, 1995.
- KÖNIG, P. AND SCHILLEN, T. B. Stimulus-dependent assembly formation of oscillatory responses. I. Synchronization. *Neural Comput.* 3: 155–166, 1991.
- KRUGER, J. AND AIPLE, F. Multimicroelectrode investigation of monkey striate cortex: spike train correlations in the infragranular layers. *J. Neurophysiol.* 60: 798–828, 1988.
- KWAN, H. C., MURPHY, J. T., AND WONG, Y. C. Interaction between neurons in the precentral cortical zones controlling different joints. *Brain Res.* 400: 259–269, 1987.
- LLINÁS, R. R., GRACE, A. A., AND YAROM, Y. In vitro neurons in mammalian cortical layer 4 exhibit intrinsic oscillatory activity in the 10–50-Hz frequency range. *Proc. Natl. Acad. Sci. USA* 88: 879–901, 1991.
- MACKAY, W. A. AND MENDONÇA, A. J. Field potential oscillatory bursts in parietal cortex before and during reach. *Brain Res.* 704: 167–174, 1995.
- MARKRAM, H. AND SAKMAN, B. Action potentials propagating back into dendrites triggers changes in efficacy of single-axon synapses between layer V pyramidal neurons. *Soc. Neurosci. Abstr.* 21: 2007, 1995.
- MASTRONARDE, D. N. Correlated firing of cat retinal ganglion cells. I. Spontaneously active inputs to X- and Y-cells. *J. Neurophysiol.* 49: 303–323, 1983.
- MATSUMURA, M., CHEN, D.-F., SAWAGUCHI, T., KUBOTA, K., AND FETZ, E. E. Synaptic interactions between primate precentral cortex neurons revealed by spike-triggered averaging of intracellular membrane potentials in vivo. *J. Neurosci.* In press.
- MUNK, M. H. J., NOWAK, L. G., NELSON, J. I., AND BULLIER, J. Structural basis of cortical synchronization. II. Effects of cortical lesions. *J. Neurophysiol.* 74: 2401–2414, 1995.
- MUNK, M. H., ROELFSEMA, P. R., KONIG, P., ENGEL, A., AND SINGER, W. Role of reticular activation in the modulation of intracortical synchronization. *Science Wash. DC* 272: 271–274, 1996.
- MURPHY, J. T., KWAN, H. C., AND WONG, Y. C. Cross correlation studies in primate motor cortex: synaptic interaction and shared input. *Can. J. Neurol. Sci.* 12: 11–23, 1985.
- MURTHY, V. N. AND FETZ, E. E. Coherent 25–35 Hz oscillations in the sensorimotor cortex of awake behaving monkeys. *Proc. Natl. Acad. Sci. USA* 89: 5670–5674, 1992.
- MURTHY, V. N. AND FETZ, E. E. Effects of input synchrony on the firing rate of a three-conductance cortical neuron model. *Neural Comput.* 6: 1111–1126, 1994.
- MURTHY, V. N. AND FETZ, E. E. Oscillatory activity in sensorimotor cortex of awake monkeys: synchronization of local field potentials and relation to behavior. *J. Neurophysiol.* 76: 3949–3967, 1996.
- NELSON, J. I., SALIN, P. A., MUNK, M. H.-J., ARZI, M., AND BULLIER, J. Spatial and temporal coherence in cortico-cortical connections: a cross-correlation study in areas 17 and 18 in the cat. *Visual Neurosci.* 9: 21–37, 1992.
- NOWAK, L. G., MUNK, M. H. J., NELSON, J. I., JAMES, A. C., AND BULLIER, J. Structural basis of cortical synchronization. I. Three types of interhemispheric coupling. *J. Neurophysiol.* 74: 2379–2400, 1995.
- NUÑEZ, A., AMZIKA, F., AND STERIADE, M. Voltage-dependent fast (20–40 Hz) oscillations in long-axonated neocortical neurons. *Neuroscience* 51: 7–10, 1992.
- O’KEEFE, J. AND RECCE, M. L. Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3: 317–330, 1993.
- PAVLIDES, C., GREENSTEIN, Y. G., GRUDMAN, M., AND WINSON, J. Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of the theta rhythm. *Brain Res.* 439: 383–387, 1988.
- PERKEL, D. H., GERSTEIN, G. L., AND MOORE, G. P. Neuronal spike trains and stochastic point processes. II. Simultaneous spike trains. *Biophys. J.* 7: 419–440, 1967.
- PRESS, W. H., FLANNERY, B. P., TEUKOLSKY, S. A., AND VETTERLING, W. T. *Numerical Recipes in C. The Art of Scientific Computing*. Cambridge, UK: Cambridge Univ. Press, 1990.
- REYES, A. D. AND FETZ, E. E. Effects of transient depolarizing potentials on the firing rate of cat neocortical neurons. *J. Neurophysiol.* 69: 1673–1683, 1993.
- ROUGEUL, A., BOUYER, J. J., DEDET, L., AND DEBRAY, O. Fast somatoparietal rhythms during combined focal attention and immobility in baboon and squirrel monkey. *Electroencephalogr. Clin. Neurophysiol.* 46: 310–319, 1979.
- ROULLIER, E. M., BABALIAN, A., KAZENNIKOV, O., MORET, V., YU, X.-H., AND WIESENDANGER, M. Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. *Exp. Brain Res.* 102: 227–243, 1994.
- SANES, J. N. AND DONOGHUE, J. P. Oscillations in local field potentials of the primate motor cortex during voluntary movement. *Proc. Natl. Acad. Sci. USA* 90: 4470–4474, 1993.
- SHINODA, Y. AND KAKEI, S. Distribution of terminals of thalamocortical fibers originating from the ventrolateral nucleus of the cat thalamus. *Neurosci. Lett.* 96: 163–167, 1989.
- SILLITO, A. M., JONES, H. E., GERSTEIN, G. L., AND WEST, D. C. Feature-linked synchronization of thalamic relay cell firing induced by feedback from the visual cortex. *Nature Lond.* 369: 479–482, 1995.
- SINGER, W. Putative functions of temporal correlations in neocortical processing. In: *Large-Scale Neuronal Theories of the Brain*, edited by C. Koch and J. Davis. Cambridge, MA: MIT Press, 1994, p. 201–238.
- SMITH, W. S. *Synaptic Interactions Between Identified Motor Cortex Neurons in the Monkey* (PhD thesis). Seattle, WA: Univ. of Washington, 1989.
- SMITH, W. S. AND FETZ, E. E. Effects of synchrony between primate cortico-moto-neuronal cells on post-spike facilitation of muscles and motor units. *Neurosci. Lett.* 96: 76–81, 1989.
- STERIADE, M., CURRÓ DOSSI, R., PARE, D., AND OAKSON, G. Fast oscillations (20–40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. *Proc. Natl. Acad. Sci. USA* 88: 4396–4400, 1991.
- TANJI, J., OKANO, K., AND SATO, K. C. Neuronal activity in cortical motor areas related to ipsilateral, contralateral and bilateral digit movements of the monkey. *J. Neurophysiol.* 60: 325–343, 1988.
- TOKUNO, H. AND TANJI, J. Input organization of distal and proximal forelimb areas in the monkey primary motor cortex: a retrograde double labeling study. *J. Comp. Neurol.* 333: 199–209, 1993.
- TOVEE, M. J. AND ROLLS, E. T. Oscillatory activity is not evident in the primate temporal visual cortex with static stimuli. *Neuroreport* 3: 369–372, 1992.
- TOYAMA, K., KIMURA, M., AND TANAKA, K. Cross-correlation analysis of interneuronal connectivity in cat visual cortex. *J. Neurophysiol.* 46: 191–201, 1981.
- TS’O, D. Y., GILBERT, C. D., AND WIESEL, T. N. Relationships between horizontal interactions and functional architecture in cat striate cortex as revealed by cross-correlation analysis. *J. Neurosci.* 6: 1160–1170, 1986.
- VAADIA, E., HAALMAN, I., ABELES, M., BERGMAN, H., PRUT, Y., SLOVIN, H., AND AERTSEN, A. Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. *Nature Lond.* 373: 515–518, 1995.
- WHITE, E. L. *Cortical Circuits: Synaptic Organization of the Cerebral Cortex—Structure, Function and Theory*. Boston: Birkhäuser, 1989.
- YOUNG, M. P., TANAKA, K., AND SHIGERU, Y. On oscillating neuronal responses in the visual cortex of the monkey. *J. Neurophysiol.* 67: 1464–1474, 1992.