

Cross-Correlation Study of the Temporal Interactions Between Areas V1 and V2 of the Macaque Monkey

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Nowak, L. G., M.H.J. Munk, A. C. James, P. Girard, and J. Bullier. Cross-correlation study of the temporal interactions between areas V1 and V2 of the macaque monkey. *J. Neurophysiol.* 81: 1057–1074, 1999. Cross-correlation studies performed in cat visual cortex have shown that neurons in different cortical areas of the same hemisphere or in corresponding areas of opposite hemispheres tend to synchronize their activities. The presence of synchronization may be related to the parallel organization of the cat visual system, in which different cortical areas can be activated in parallel from the lateral geniculate nucleus. We wanted to determine whether interareal synchronization of firing can also be observed in the monkey, in which cortical areas are thought to be organized in a hierarchy spanning different levels. Cross-correlation histograms (CCHs) were calculated from pairs of single or pairs of multiunit activities simultaneously recorded in areas V1 and V2 of paralyzed and anesthetized macaque monkeys. Moving bars and flashed bars were used as stimuli. The shift predictor was calculated and subtracted from the raw CCH to reveal interactions of neuronal origin in isolation. Significant CCH peaks, indicating interactions of neuronal origin, were obtained in 11% of the dual single-unit recordings and 46% of the dual multiunit recordings with moving bars. The incidence of nonflat CCHs with flashed bars was 29 and 78%, respectively. For the pairs of recording sites where both flashed and moving stimuli were used, the incidences of significant CCHs were very similar. Three types of peaks were distinguished on the basis of their width at half-height: T (<16 ms), C (between 16 and 180 ms), and H peaks (>180 ms). T peaks were very rarely observed (<1% in single-unit recordings). H peaks were observed in 7–16% of the single-unit CCHs, and C peaks in 6–16%, depending on the stimulus used. C and H peaks were observed more often when the receptive fields were overlapping or distant by <2°. To test for the presence of synchronization between neurons in areas V1 and V2, we measured the position of the CCH peak with respect to the origin of the time axis of the CCH. Only in the case of a few T peaks did we find displaced peaks, indicating a possible drive of the V2 neuron by the simultaneously recorded V1 cell. All the other peaks were either centered on the origin or overlapped the origin of time with their upper halves. Thus similarly to what has been reported for the cat, neurons belonging to different cortical areas in the monkey tend to synchronize the time of emission of their action potentials with three different levels of temporal precision. For peaks calculated from flashed stimuli, we compared the peak position with the difference between latencies of V1 and V2 neurons. There was a clear correlation for single-unit pairs in the case of C peaks. Thus the position of a C peak on the time axis appears to reflect the order of visual activation of the correlated neurons. The coupling strength for H peaks was smaller during visual drive compared with spontaneous activity. On the contrary, C peaks were seen more often and were stronger during visual stimulation than during spontaneous activity. This suggests that C-type synchronization is associated with the processing of visual information. The origin of synchronized activity in a serially organized system is discussed.

INTRODUCTION

Synchronization of neuronal activities has been proposed to play a fundamental role in information processing by allowing distributed neuronal populations activated by a common stimulus to be bound together into a single percept (Abeles 1982a; Damasio 1990; Milner 1974; Singer and Gray 1995; von der Marlsburg 1981). Related to this proposal is the hypothesis that synchronization allows a selection of postsynaptic neurons by virtue of a coincidence detection mechanism (Abeles 1982a; König et al. 1996).

Synchronized activities have been demonstrated extensively for neurons belonging to the same cortical area (for review: Fetz et al. 1991; Singer and Gray 1995). However, if synchronization signals the participation of different cells to the same assembly, it also should be observed between different cortical areas. In support of this notion, synchronization has been found in cat visual cortex between different areas of the same cortical hemisphere (Eckhorn et al. 1988; Engel et al. 1991b; Kat-suyama et al. 1996; Nelson et al. 1992) and between corresponding areas of opposite cortical hemispheres (Engel et al. 1991a; Nowak et al. 1995b). In addition to synchronized gamma range oscillation (Eckhorn et al. 1988; Engel et al. 1991a,b; Nowak et al. 1995b), nonoscillatory forms of synchronization also have been found that have been classified into three groups according to the width of the peak of the cross-correlation histogram (Nelson et al. 1992; Nowak et al. 1995b): a narrow type of peak (T for “towers,” a few milliseconds width) was observed mainly between cells having overlapping receptive fields and similar orientation preferences. An intermediate type of peak (C for “castles”), with a temporal precision in the tens of milliseconds range, was found to occur for cells independently of their receptive field separation, provided it was not >8°. The third type of peak that was encountered in these studies is one with a width of one or several hundred milliseconds (H for “hills”). This kind of synchronization was independent of the orientation preference of the recorded cells, and was observed even for cells having large receptive field separations.

In the cat, however, there are numerous indications that, to a large extent, information can be processed in parallel in different cortical areas: the lateral geniculate nucleus projects to all the visual cortical areas (Bullier 1986) and lesion or inactivation of area 17 does not produce a loss of response in extrastriate cortical areas (reviewed in Bullier et al. 1994). Thus it might be argued that the presence of synchronization between neurons of different cortical areas basically reflects the parallel organization of cat visual system.

In contrast, several lines of evidence suggest that the primate

visual system is organized in a serial manner: extrastriate areas receive only a sparse input from the LGN (Bullier and Kennedy 1983; Hernández-González et al. 1994; Wong-Riley 1976); when area V1 of the macaque monkey is inactivated, area V2 and areas of the occipito-temporal stream are silenced (reviewed in Bullier et al. 1994); also, latencies of neurons in area V1 are shorter than those measured in extrastriate cortex (reviewed in Nowak and Bullier 1997). These observations are consistent with the idea that neurons in V1 provide the drive to several cortical areas of the extrastriate cortex. This, however, questions the possibility of synchronization between neurons of areas located at different levels of the cortical hierarchy.

We have addressed this issue in macaque monkey areas V1 and V2, which clearly belong to different levels of the hierarchy, as evidenced by the morphology of their connections (Felleman and Van Essen 1991), the latencies of the neuron responses to visual stimuli (Raiguel et al. 1989; Nowak et al. 1995a), and the effects of inactivation of V1 on V2 neurons (Girard and Bullier 1989; Schiller and Malpeli 1977). To test for the presence of action potential synchronization between areas V1 and V2, we recorded single- and multiunit activities and calculated cross-correlation histograms.

To test more precisely the relationship between the serial organization of areas V1 and V2 and the temporal coherence of their neuronal activities, we used flashes as stimuli in addition to moving bars. Using flashed stimuli enabled us to measure precisely the latencies of the responses. It was then possible to compare the latency difference between area V1 and area V2 neurons with the displacement of the cross-correlation histogram (CCH) peak to understand if the later reflects the order of their activation.

Finally, we wished to determine to what extent the different types of CCH peaks are related to the processing of visual information. For that purpose, we compared the peaks obtained during spontaneous activity with those obtained during the responses to visual stimuli. Some of these results have been presented in abstract or preliminary form (Bullier et al. 1992; Munk et al. 1993; Nowak et al. 1994).

METHODS

Animal preparation, visual stimulation, and recording

Acute recordings were obtained from eight cynomolgus monkeys. Details on the surgical procedures have been given in previous publications (Girard et al. 1992; Nowak et al. 1995a). During recording, anesthesia was maintained with nitrous oxide/oxygen (70/30%) supplemented by fentanyl ($5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), whereas paralysis was maintained by continuous injection of pancuronium bromide (Pavulon, $0.08 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) in lactated Ringer solution. In parallel, the animal received a constant perfusion of 5% glucose (6–12 ml/h). Heart rate, end tidal CO_2 , and reactions to cutaneous stimuli were monitored to ensure a proper degree of analgesia.

Extracellular recordings of single and multiunits were obtained simultaneously in areas V1 and V2 with two tungsten-in-glass microelectrodes (Merrill and Ainsworth 1972). For each electrode, recorded sites were spaced apart by 80 or 100 μm in a track. At each recorded site, single- and multiunit activities were separated by window discriminators. TTL Pulses from the window discriminators were acquired through a 1401 interface (CED) for on- and off-line analysis using the software package Spike2 (CED).

Visual stimulation was produced by an optic bench and consisted of bars or spots that were flashed or moved across the receptive field of

the recorded cells. When a moving bar was used as stimulus, the velocity was usually of $1^\circ/\text{s}$, the movement amplitude was between 3 and 6° , and a pause of 3 s separated the movement in one direction and its reverse. When the stimulus was flashed, its size was adjusted to cover at least partially the receptive field centers of both recorded cells; the shutter was kept open for 3 s and closed for 3 s. The color and orientation of the stimulus were adjusted to optimize the responses at both recording sites. When color preferences differed, the color of the stimulus was chosen as to give responses at each recording site. When orientation preferences differed, the stimulus orientation was set at an intermediate value between the two preferred orientations.

Computation and fitting of CCHs

CCHs were computed using the occurrences of spikes in the V1 neuron as trigger for the averaging. Thus *time 0* in a CCH represents the time of occurrence of an action potential in the cell recorded in V1, and a positively displaced peak could indicate that the V2 cell was driven by the one recorded in V1. For computation and fitting of CCHs, we used the procedures described in Nowak et al. (1995b); these procedures are summarized briefly here. To reveal the temporal interactions in their different ranges, the CCHs were calculated with different time resolutions (5-ms binwidth and window width of ± 2.5 s and ± 0.5 s; 1- or 2-ms binwidth and window width of ± 0.1 s). CCHs were normalized by the binwidth and by the number of reference spikes, to give an ordinate in V2 spikes per second per V1 spike (Abeles 1982b).

A shift predictor correction procedure (Perkel et al. 1967) was used to separate the features of the CCHs that are related to interactions of neuronal origin from those resulting from the coactivation of the recorded cell by the visual stimulus (cf. Figs. 1 and 2). The shift predictor corresponds to a CCH for which the occurrence times of the action potentials in the V2 cell have been shifted by one stimulus period with respect to those in V1. Given the long duration of the stimulus period, the shifted CCH cannot contain features related to neuronal interactions (neuronal interactions produce effects on a shorter time scale: synaptic transmission takes place in the millisecond time range; "secondary effects" that can contribute to the CCH shape (Moore et al. 1970), such as bursting activities, display a time range that rarely outlasts a few hundred milliseconds). The shift predictor was subtracted from the raw CCH to reveal interactions of neuronal origin in isolation in the "subtracted CCH." In the absence of interaction of neuronal origin, the subtracted CCH appears flat (Fig. 1E). Another CCH, called the "side peak," was obtained by subtracting two adjacent shift predictors (1 with a 1-stimulus period shift, the 2nd with a 2-stimulus periods shift). The side peak was used to determine the noisiness resulting from the subtraction procedure and from the variability of neuronal activity from one stimulation cycle to the next.

Quantitative analysis was done by fitting Gaussian curves to the peaks in the subtracted CCH. The significance of the fitted structure was determined by comparing its height with the height of the bins in the side peak, recalculated to have a binwidth identical to the half-width of the Gaussian fit (Nowak et al. 1995b). For the significant peaks (Z score >3) (see Melssen and Epping 1987), the following parameters were extracted from the fitted Gaussian: peak width, peak position, peak area, peak height, and percentage engaged spikes (PES). The peak width was measured at the half-height of the curve fitted to the peak. The peak position and height were defined by the center and height of the Gaussian. The PES is the ratio of the peak area (P) over the area of the shift predictor below the peak (S) plus that of the peak [$\text{PES} = 100 P/(P + S)$]. It expresses the proportion of correlated spikes with respect to the total number of spikes present in a time window corresponding to the width of the subtracted CCH peak. In case the presence of more than one peak was suspected in the CCH, the goodness of fit was compared for one versus two fitted

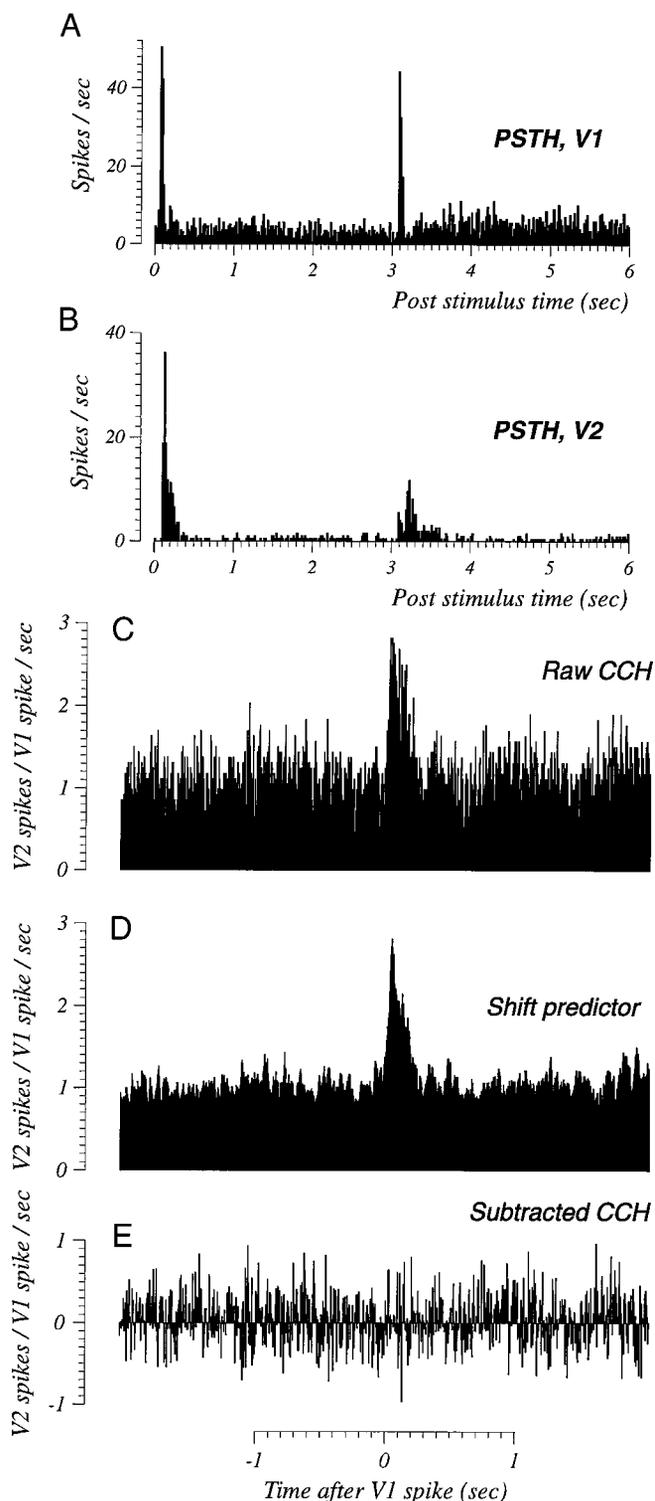


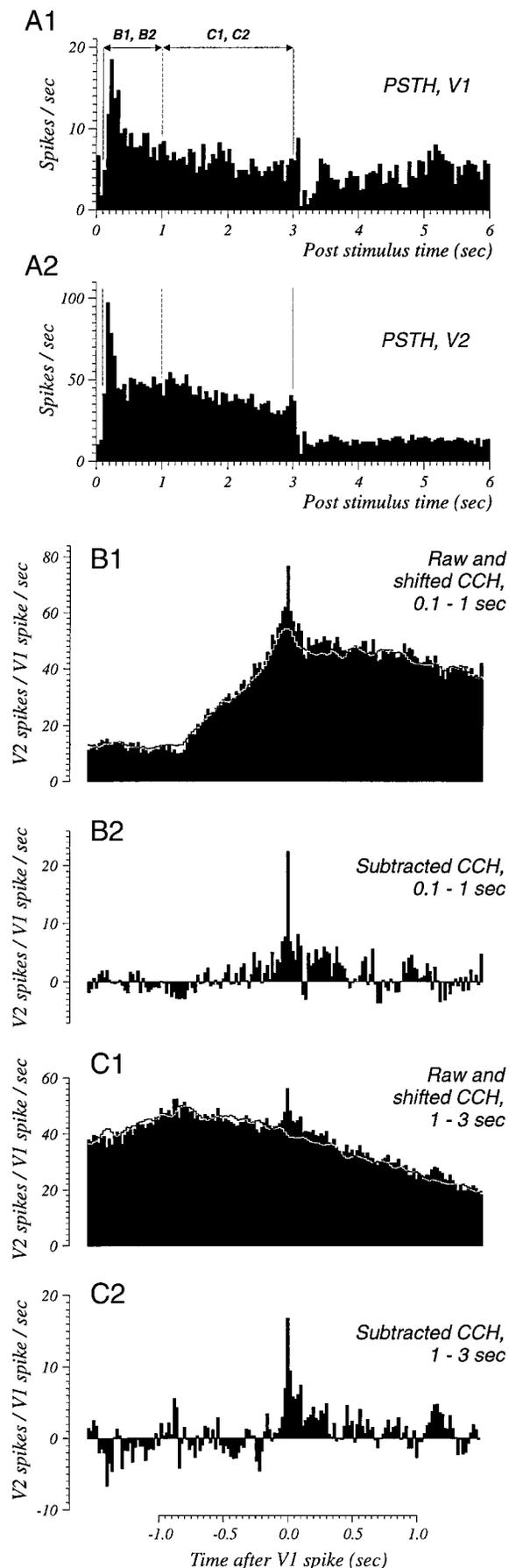
FIG. 1. Flat subtracted cross-correlation histograms (CCHs) can be obtained with flashes, despite the presence of a narrow stimulus-related synchronization. Example depicted corresponds to a pair of single units. Transient nature of the response to the flashing stimuli is evidenced by the PSTHs in *A* for the V1 cell and in *B* for the V2 cell. Raw CCH in *C* and shift predictor in *D* show the presence of a narrow peak due to the transient response. Shift predictor shows, in isolation, the influence of the visual stimulation on the CCH. Shift predictor but not the raw CCH has been smoothed. *E*: subtracted CCH, obtained by subtracting the shift predictor from the raw CCH, reveals the presence of interactions of neuronal origin in isolation. In this case, the subtracted CCH is flat, indicating there were no correlation of neuronal origin between the 2 cells. Binwidth is 5 ms.

Gaussians. The parameters listed above then were extracted from each of the Gaussian curves. The shape of the majority of broad peaks (H peaks) clearly departs from a Gaussian. Instead it displays an exponential shape (for example, Fig. 3C). For these cases, the fitted curve corresponds to a smoothed version of the broad peaks (3 bins running boxcar algorithm, usually 10 iterations). The significance level is given by the Z score calculated for the highest bin (binwidth, 5 ms) in the CCH. The peak height corresponded to the highest bin of the smoothed version of the peak, the peak width to the width at half-height.

For single-unit recordings, a minimal number of spikes is required to produce a significant CCH peak, i.e., a peak that stands above the noise level determined by the side peak. Below this minimum number of spikes, it becomes impossible to decide whether the CCH is flat or whether it *could* contain a peak. To evaluate this minimum number of spikes, we took single-unit CCHs presenting a significant peak, divided the corresponding recording period into smaller epochs (slices), and recalculated the CCH for each epoch. The slicing reduced the number of spikes available, therefore decreasing the signal-to-noise ratio of the peak versus the CCH baseline. The procedure was repeated until the peak could not be detected as significant by the fitting program. In these conditions, the CCHs of different slices may appear as flat, although a peak was present in the complete run. An additional factor that we took into account is the width of the shift predictor that gives an indication of the grouping of the spikes due to the visual stimulation. We calculated a “decision index,” which is the product of the spike counts in the two channels divided by the width of the shift predictor (in milliseconds). This procedure, applied to 11 CCHs, showed that significant peaks cannot be detected anymore when this index was <100 . This corresponds to 700 spikes from each unit for a 5-s-wide shift predictor peak or 300 spikes for a 1-s-wide shift predictor peak. Therefore whenever a single-unit CCH did not present a peak, we calculated the decision index. When this index was >100 , the CCH was considered as flat. When it was <100 , the CCH was considered as undecided and excluded from the sample.

The other problem we faced was that of instability in the firing rate of some neurons. Such instability violated the stationarity rule for random point processes (Cox and Lewis 1966) that is a prerequisite for averaging operations such as the calculation of CCHs. Indices of instability were a wavy baseline and/or asymmetric side peaks. We also checked for stability of recording by calculating rate histograms (mean firing rate per stimulus over stimulus number). This instability could be due to transient bursts of activity or, for multiunit recordings, to changes in the composition of the contributing units. By slicing the runs, it has been possible to recover stable portions of initially unstable recordings for 18 single-unit (su) pairs and 55 multiunit (mu) pairs. In other cases, despite slicing, the CCHs retained traces of instability. Due to instability, 131 mu CCHs have been excluded from further analysis. Due to the instability or to insufficient spike count, 198 su CCHs have been excluded from further analysis.

To separate the influence of the visual stimulation and that of the spontaneous activity on the features of the CCHs, we proceeded as follow: peristimulus time histograms (PSTHs) were calculated for both V1 and V2 cells from which we determined the time during which both neurons were activated by the stimulus. The action potentials from the V1 neurons that occurred during that period were isolated and used to calculate a CCH restricted to the visual response. The same procedure was used to calculate CCH obtained under spontaneous activity only: the action potentials in the V1 cell were isolated for a period during which neither cells were visually responsive as shown by the PSTHs. The baseline for the CCH calculated under spontaneous activity only is at 0 because the shift predictor also was subtracted in these cases. Because it is often difficult, with a flash response, to determine whether the activity after the transient response corresponds to a sustained response or to spontaneous activity, this analysis has been restricted to the moving bar stimuli.



RESULTS

Recordings from 295 pairs of sites using moving bars as stimuli and 134 pairs of sites using flashes were obtained in eight monkeys. Both moving bars and flashes have been used for 132 pairs of sites.

Both su and mu activities were recorded at each site. CCHs were calculated either for pairs of su or for pairs of mu. Some of the CCHs were discarded from further analysis due to instability of the recording or, for some su recordings, to an insufficient number of spikes (see METHODS section). The database on which the present paper is based is composed of 175 su and 205 mu CCHs computed with moving bars and 56 su CCHs and 93 mu CCHs computed with flashes as stimuli.

The peak resulting from the coactivation of the cells by the visual stimulus was isolated by calculating the shift predictor. The shift predictor, in turn, was subtracted from the raw CCH to yield the subtracted (or net) CCH in which interactions of neuronal origin can be seen in isolation.

The shift predictor technique commonly is used in the case of moving stimuli that produce rounded peaks in the CCH. However, flashed stimuli produced sharp peaks in the CCHs. It was not clear whether the shift predictor method could remove all the stimulus induced correlation in these conditions (cf. Melssen and Epping 1987). Figure 1 shows that flat CCHs can be obtained with flashes: despite the transience of the response (visible in the PSTHs, Fig. 1, A and B) and the resulting sharp peak in the raw CCH (Fig. 1C), the shift predictor technique removed all stimulus-induced peaks in the subtracted CCH (Fig. 1E), which therefore appears as flat (as the overwhelming majority of su cases with flashes).

A complementary control is presented in Fig. 2 for a pair of mu recordings. The flashing stimuli evoked responses that began with a transient (Fig. 2A, 1 and 2) while the CCH obtained for this pair presented a narrow peak. To determine whether the narrow peak was related to the transient response, we restricted the calculation of the CCH to two periods of the visual response. The first corresponds to the first second of the response, including the transient. The corresponding subtracted CCH contains a narrow peak above a broader pedestal (Fig. 2B2). However, the narrow peak also appears when the CCH (Fig. 2C2) is calculated for the sustained period of the visual response (1–3 s in Fig. 2A, 1 and 2) while the shift predictor appears flat for this time resolution (Fig. 2C1). These examples show that the presence of a peak in the CCHs is not necessarily associated with the presence of a transient in the flash response.

Three types of CCH peaks

Examples of subtracted CCHs computed between neurons in areas V1 and V2 appear in Fig. 3. All cases except Fig. 3F correspond to paired mu recordings. CCHs calculated from responses to a moving light bar are shown in Fig. 3, A and C.

FIG. 2. Sharp CCH peak during both the sustained or transient portions of the flash-evoked visual response. A1 and A2: peristimulus time histograms (PSTHs) of the 2 multiunit (mu) responses to a flashed bar. B1: raw CCH, calculated for the 1st second of the PSTHs in A1 and A2, which includes the transient part of the response. Shift predictor is shown superimposed as a line. B2: subtracted CCH for the 1st second of the visual response. C1: raw CCH for the sustained part of the visual response (1–3 s in PSTHs) with the shift predictor shown as a line. C2: subtracted CCH for the sustained visual response. Binwidth, 20 ms.

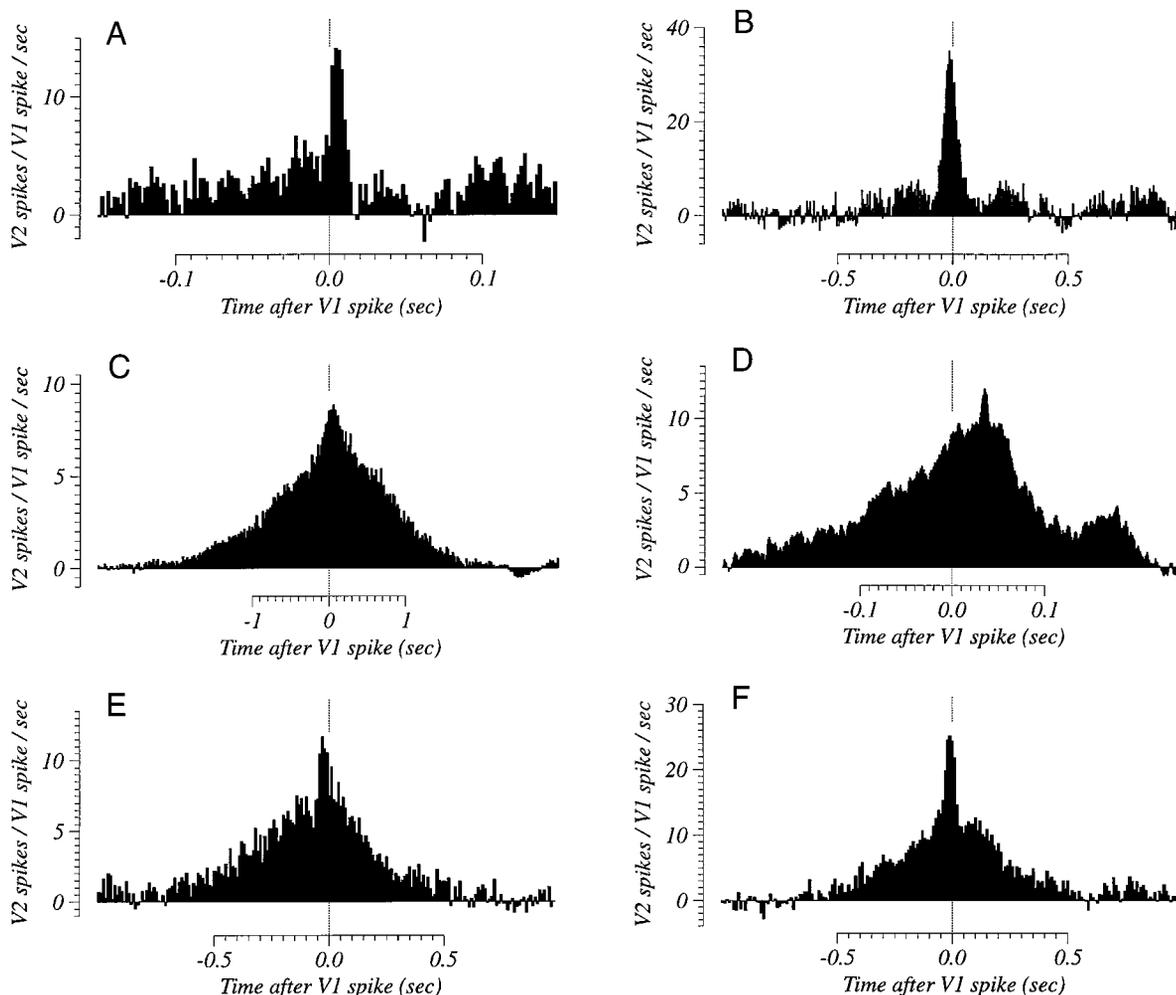


FIG. 3. Examples of subtracted CCHs. Peaks of different widths are shown in A–C (T, C, and H peaks, respectively). Note the different scales on the abscissa. Combinations of peaks with different widths are presented in D–F: D corresponds to the combination of a displaced T peak with a C peak. E and F illustrate the combination of C and H peaks.

Other cases correspond to CCHs obtained with flashed bars. Figure 3 illustrates the different widths of peaks observed (note the different time scales) and the fact that peaks of different width can combine (Fig. 3, D–F), even for pairs of su recordings (Fig. 3F).

In cat visual cortex, CCH peaks obtained from recordings performed in different cortical areas can be grouped in three different classes according to their width at half-height (Nelson et al. 1992; Nowak et al. 1995b). The distribution histogram of the log values of the peak width at half-height, shown on Fig. 4A, indicates that a tripartite distribution of peak width exists in the monkey as well. This histogram contains data from mu and su recordings with flashed or moving stimuli. Three modes and two gaps are visible. One gap corresponds to a value of 16 ms (integer value of $10^{1.2}$) and the other to a value of 178 ms (integer value of $10^{2.25}$). The peak width distributions are presented separately for moving bars and flashed stimuli in Fig. 4, B and C.

Because of similarity with data obtained in cat visual cortex, the three classes of peaks have been given the same names. T peaks correspond to the class of narrow peaks (<16 ms wide), C peaks to peaks of intermediate width (16–178 ms), and the widest peaks (>178 ms) are grouped in the H category (Table

1). Within each class, the peak width tends to be broader with moving bars than with flashes, but this does not reach significance in paired tests (Wilcoxon paired test, $P > 0.15$ in all the cases).

The relationship between peak width with moving bars and peak width with flashed stimuli for the pairs of units for which both types of stimuli were used is presented in Fig. 4D for C peaks and Fig. 4E for H peaks (the sample was too small in the case of T peaks). In the case of C peaks, there is a good correlation in most cases ($r = 0.85$ for peak width <120 ms with moving bars). No relationship between the widths measured for flashes and moving bars appears to hold for H peaks.

Incidence

The encounter rate of T, C, and H peaks for different stimuli is summarized in Fig. 5 and Table 1. Figure 5A, 1 and 2, presents the incidences of different peaks when the stimulus was a moving or a flashed bar. Most subtracted CCHs computed from su activities were flat. Under both stimulus conditions, the peaks that were most often encountered were of the H category. T peaks were only rarely observed. C peaks appeared with an intermediate probability. Note that the inci-

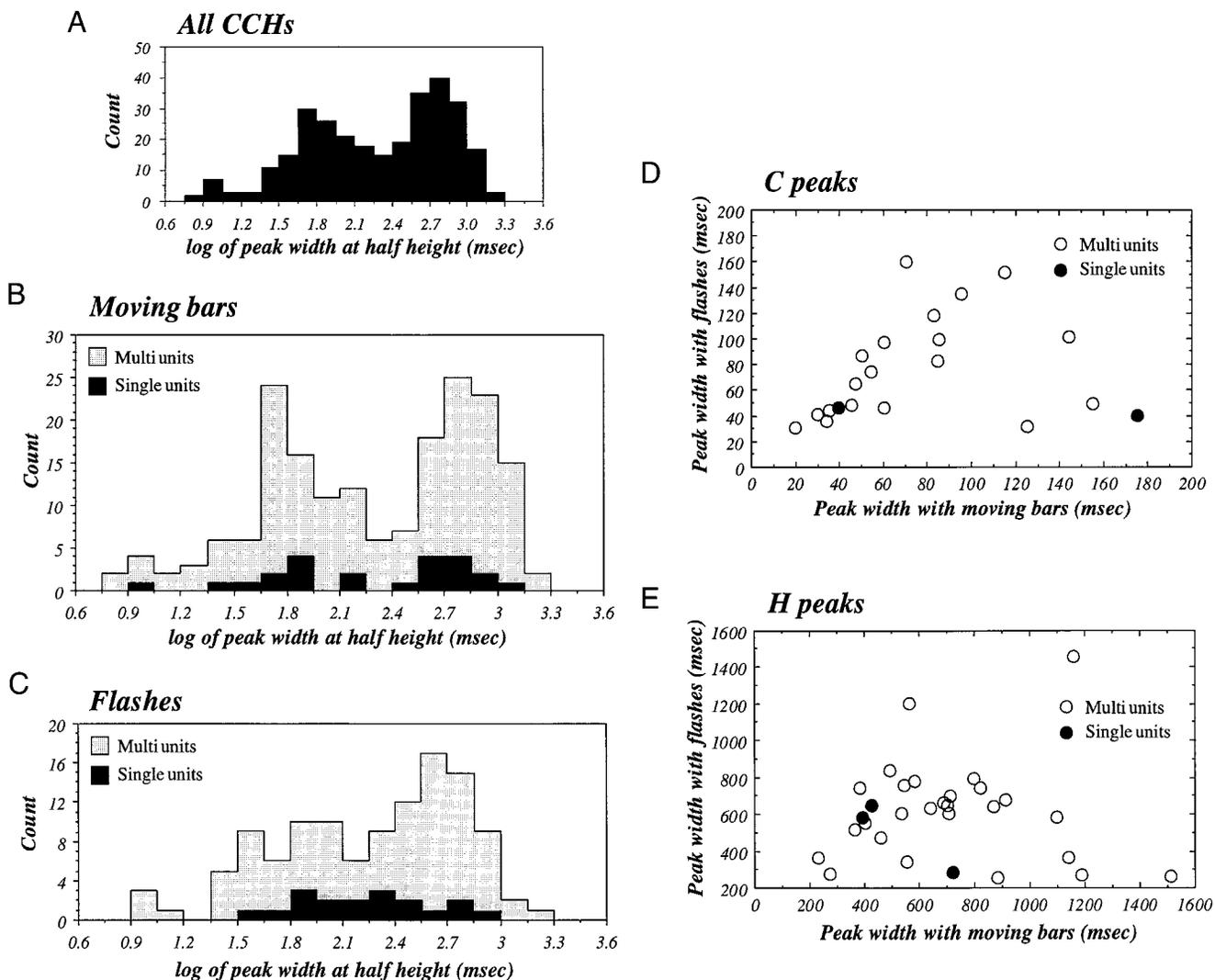


FIG. 4. Distribution of peak width. *A*: distribution histogram of the peak width for all the CCHs recorded with moving bars and flashes shown together to highlight the tripartite distribution of peak width. *B*: distribution histogram of peak width for CCHs obtained when neurons were activated with moving stimuli. *C*: distribution histogram of peak width for CCHs obtained from neurons activated by flashing stimuli. *D*: scattergram of peak width with moving bar vs. peak width for flashed stimuli for pairs of recording in which a C-type peak was observed in both conditions. *E*: scattergram of peak width for moving vs. flashing stimuli for pairs of recording in which peaks of the H-type were observed in both conditions.

dence rates of different peaks add up to $>100\%$. This is due to the combination of peaks of different widths that often occurred in a single CCH (Figs. 3, *D–F*, and *12B*).

Comparing the incidence rates of Fig. 5*A*, *1* and *2*, would suggest that flashed stimuli tend to produce more CCHs with peaks than moving bars. To determine whether this is the case, comparison must be restricted to the sample for which both moving bars and flashes were used. The corresponding incidences are shown in Fig. 5*B1* for su and in Fig. 5*B2* for mu recordings. The only statistically significant difference was observed for H peaks in mu recordings that are more frequent for flashed than for moving stimuli ($P = 0.001$; χ^2 test). Other peak types showed a similar trend, but the differences were not significant.

Peak position

We next wanted to test whether neural interactions revealed by the CCH peaks are such that spikes in V2 neurons tend to

follow spikes in V1, as suggested by a serial model of organization, or whether the CCH peaks are usually centered at zero, like in cat cortex, meaning that the two sites show correlated discharges with no phase lag or phase lead.

The distribution of the peak positions for H peaks is shown in Fig. 6 and Table 1. For moving bar stimulation (Fig. 6*A1*), the peak positions are distributed symmetrically around *time 0*, which corresponds to the mode of the distribution. The median of the position for H peaks is not different from 0 (1 sample sign test, $P = 0.8$ for both su and mu). With flashes (Fig. 6*A2*), although the distribution is not symmetrical around 0, the median peak position does not significantly differ from 0 ($P = 0.10$ for su and $P = 0.17$ for mu).

The distributions of peak positions are very broad in Fig. 6*A*, *1* and *2*. One could argue that the tails of the distributions correspond to peaks that signal serial connections between the groups of recorded cells. However, the distribution of peak width also appears very broad (Fig. 4). Therefore to detect

TABLE 1. Incidence, peak width, and peak position

	Incidence		Peak Width, ms		Peak Position, ms	
	Count	Percentage	Median	Interquartile	Median	Interquartile
T, su, flash	0	0.5	—	—	—	—
T, su, MB	1	0.6	10.2	—	2.0	—
T, mu, flash	4	4.3	8.6	2.7	19.0	43.0
T, mu, MB	7	3.4	8.6	4.4	2.0	4.25
C, su, flash	9	16.1	80.0	44.5	-13.0	39.37
C, su, MB	10	5.7	77.5	38.0	11.25	30.0
C, mu, flash	37	39.8	64.0	62.5	0	15.0
C, mu, MB	68	33.2	62.5	58.75	0	20.0
H, su, flash	9	16.1	300.0	378.75	37.5	117.25
H, su, MB	12	6.9	560.0	262.5	-45.0	193.75
H, mu, flash	56	60.2	475.0	332.5	15.0	73.0
H, mu, MB	84	41.0	645.0	430.0	2.5	110.25
Flat, su, flash	40	71.4	—	—	—	—
Flat, su, MB	156	89.1	—	—	—	—
Flat, mu, flash	20	21.5	—	—	—	—
Flat, mu, MB	90	43.9	—	—	—	—

MB, moving bar; mu, multiunit; su, single unit.

displaced peaks, it is necessary to normalize the position of the peaks with respect to their widths. For this, we calculated the displacement index (DI), which indicates whether the central part of the peak contains the origin of the time axis of the CCH: $DI = \text{peak position}/0.5 * (\text{peak width})$.

When this index takes a value between -1 and $+1$, it indicates that the upper half of the CCH peak overlaps with the origin of time (as illustrated in all examples of H peaks in Fig. 3). Such peaks are considered signs of synchronized activity. It is clear that practically all H peaks contain the origin of time

within their upper half (Fig. 6B, 1 and 2), indicating that H peaks correspond to synchronized activity within a time scale of hundred of milliseconds.

Figure 6C is a scatter plot of the peak positions for H peaks that were visible with both flashes and moving bars. The peak position tended to be maintained with both stimuli, but the correlation was not significant (mu: $r = 0.352$, $P = 0.06$).

Figure 7A, 1 and 2, shows the distributions of peak positions for C peaks. They are distributed symmetrically around the origin of time. For both stimulus conditions, the bulk of the

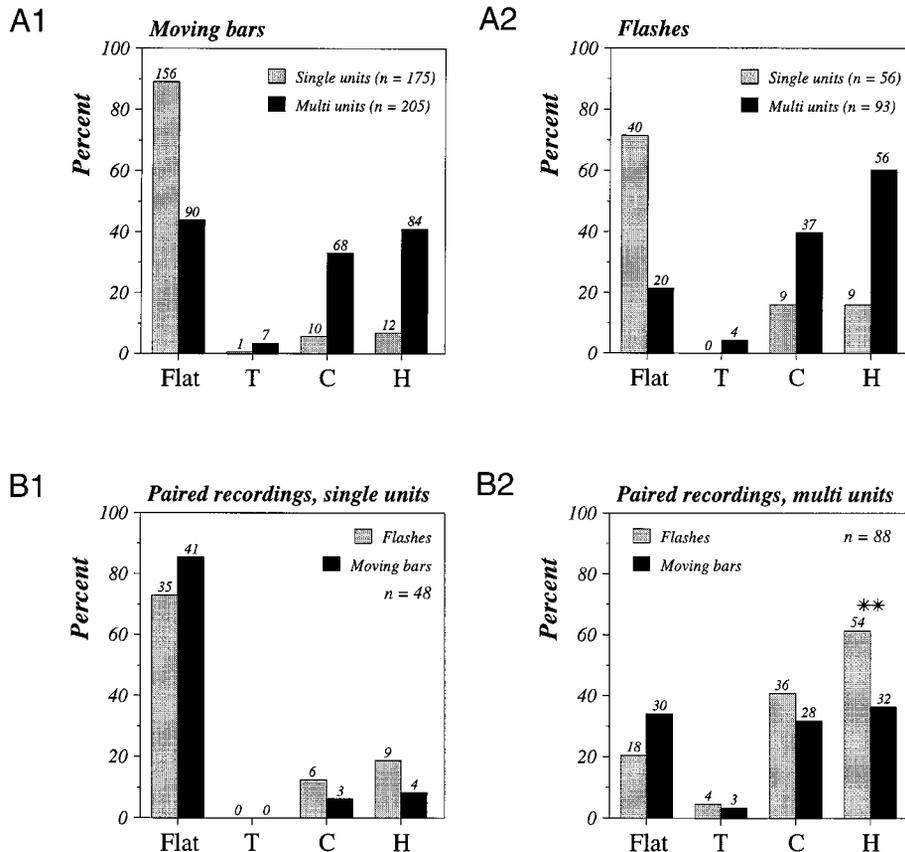


FIG. 5. Incidence of flat and significant CCH peaks. A1 and A2: incidence rates for peaks in CCHs calculated from responses to moving bars (A1) or flashed bars (A2) across the whole population. B1 and B2: comparison of incidence for recording sites stimulated with both moving and flashed bars.

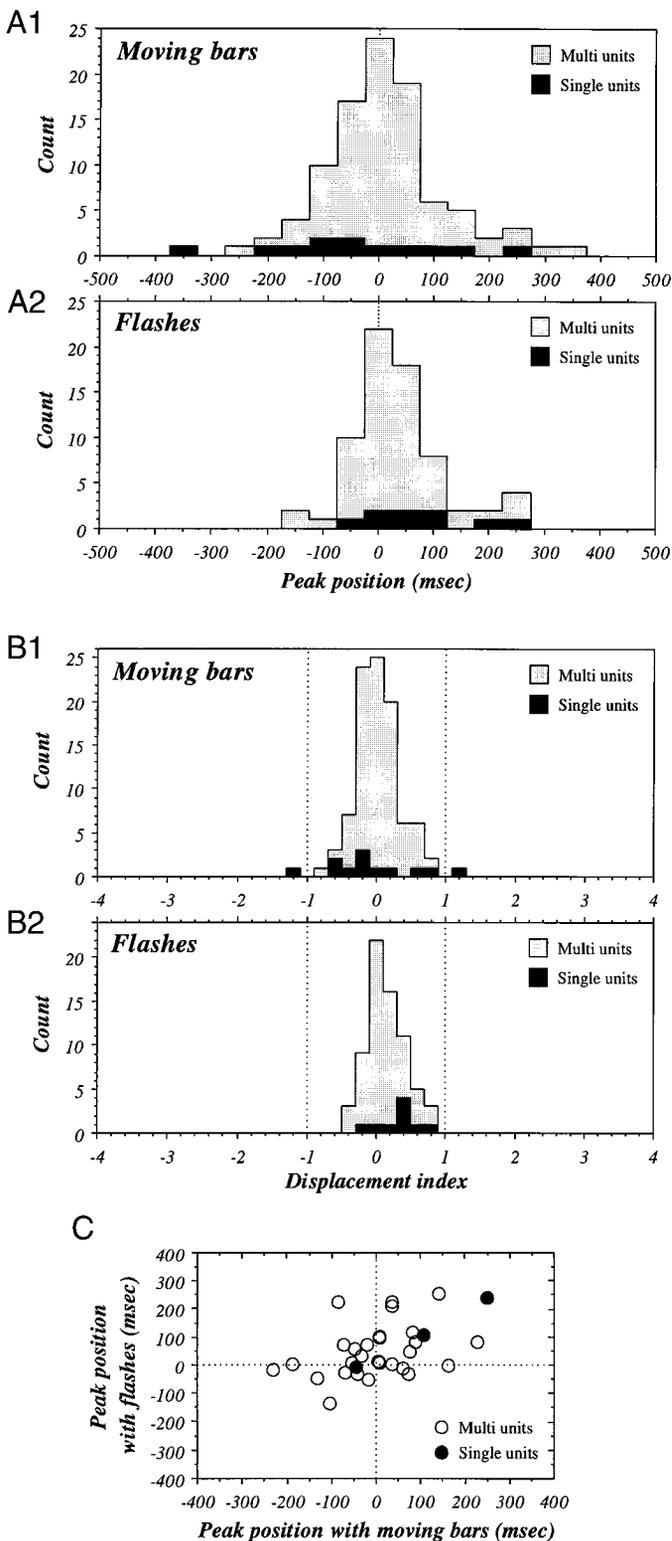


FIG. 6. Distribution of peak position for H peaks. *A1* and *A2*: peak position for H peaks observed in CCHs calculated from responses to moving (*A1*) or flashed bar (*A2*). *B1* and *B2*: distribution of displacement index for H peaks obtained with moving (*B1*) or flashing bars (*B2*). *C*: scattergram of peak position with moving stimuli vs. peak position for flashed stimuli for cases in which a H peak was obtained in both conditions.

peak positions is between ± 30 ms. The medians (Table 1) do not differ significantly from 0 (moving bar: $P = 0.34$ for su and 0.23 for mu; flash: $P = 0.51$ for su, $P > 0.9$ for mu).

In Fig. 7*B*, 1 and 2, are presented the distributions of displacement index for C peaks. Similarly to what has been obtained for H peaks, practically all C peaks overlap the origin of time with their upper half and therefore are considered to represent synchronization of activity within a time scale of tens of milliseconds.

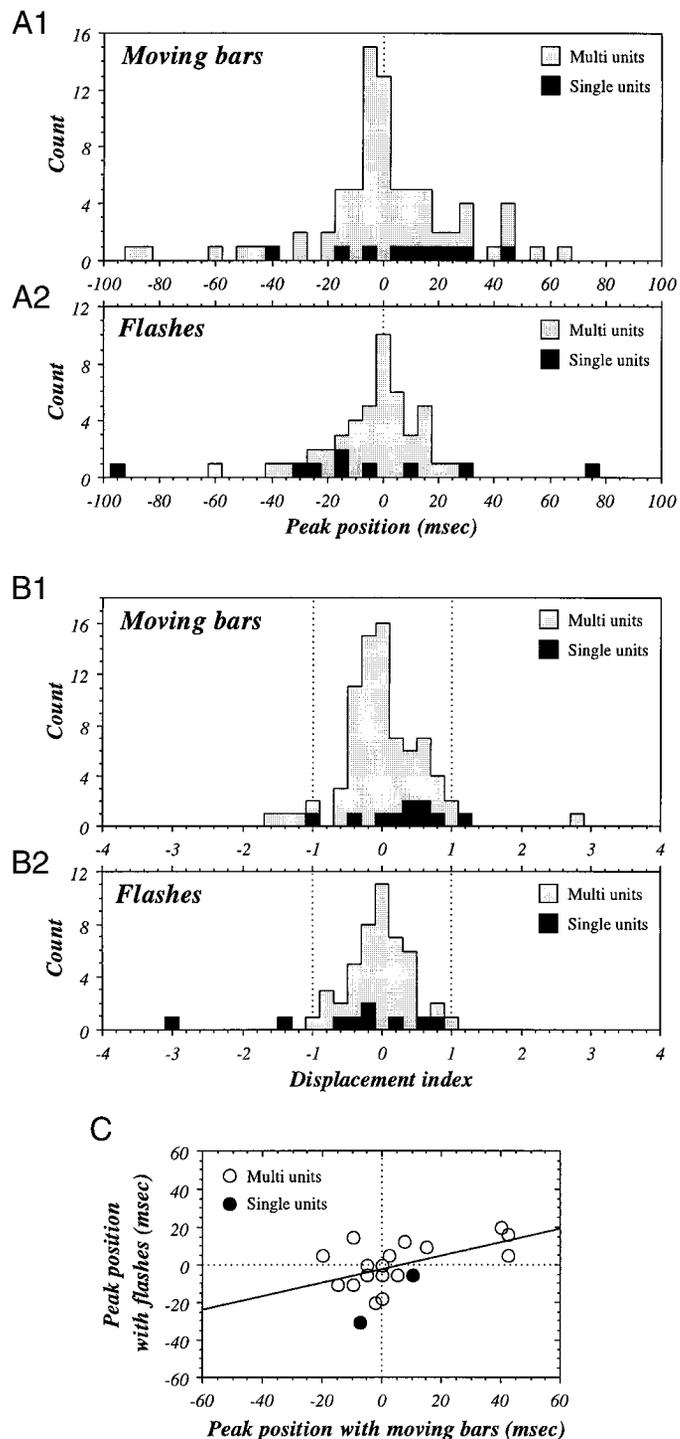


FIG. 7. Distribution of peak position for C peaks. *A1* and *A2*: peak position for C peaks observed in CCHs calculated from responses to moving (*A1*) or flashed bar (*A2*). *B1* and *B2*: distribution of displacement index for C peaks obtained with moving (*B1*) or flashing bars (*B2*). *C*: correlation of the peak position for C peaks that have been observed with both moving and flashed bar. Significant correlation is observed for mu C peaks. Regression line in *C*: peak position (flash) = $-2.286 + 0.386 * \text{peak position (moving bar)}$. $r^2 = 0.257$.

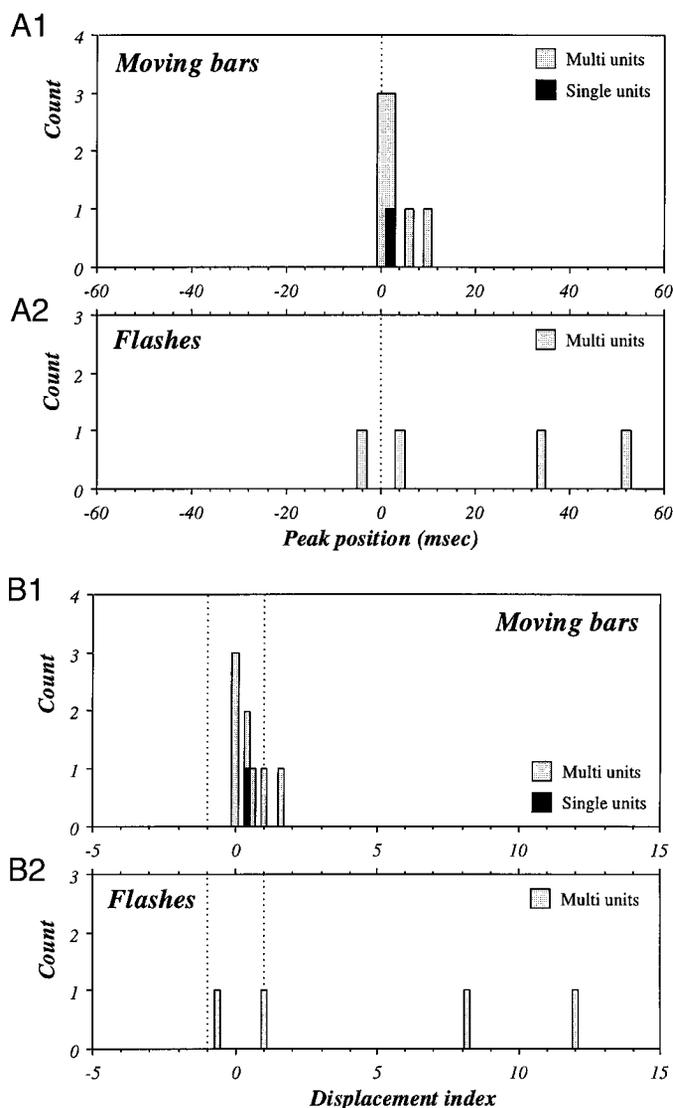


FIG. 8. Distribution of peak position for T peaks. A1 and A2: peak position for T peaks obtained in CCHs calculated from responses to moving (A1) or flashed bar (A2). B1 and B2: distribution of displacement index for T peaks obtained with moving (B1) or flashing bars (B2).

The scatter plot in Fig. 7C shows that when C peaks were obtained with both flashed and moving bars, they tended to maintain a similar position ($r = 0.527$, $P = 0.02$).

The distributions of positions for T peaks are shown in Fig. 8A, 1 and 2. Only four T peaks have been obtained with flashes; this is too small a sample for any conclusive statement. It is worth mentioning, however, that two of these peaks display considerably long latencies (1 is illustrated in Fig. 3D). With moving bars, it can be seen that the majority of T peaks display positive latencies. However, presumably as a result of the small sample, the median peak position is not significantly different from 0 ($P = 0.12$ for mu).

With flashes, two of four T peaks present a displacement index larger than one, in keeping with a drive of the V2 neurons by the one simultaneously recorded in V1 (Fig. 8B2). With moving bars, the origin of time is contained in the upper half of the T peaks in the majority of cases (6 of 8 cases, Fig. 8B1).

If we assume that the CCH peaks that overlap the origin of

time with their upper half reflect synchronization of activities, then synchronization characterizes the temporal interactions for the majority of neurons in areas V1 and V2, when their activities are correlated by mechanisms of neuronal origin.

Peak position and visual latency

Because flashes were used as stimuli in a number of cases, it has been possible to determine to what extent the functional connectivity, which presumably is revealed by the position of the CCH peak, is related to the difference in visual latency between V1 and V2 cells, which reveals their activation orders. In other words, if the visual latencies of the two recorded neurons differ by N ms, is the peak of the CCH displaced by the same amount?

Visual latencies were determined as described in Nowak et al. (1995a) for the ON and OFF responses to the flash. The latency of the V1 cell was subtracted from that of the V2 cell. When this latency difference takes a negative value, it indicates that the V2 cell was activated before the V1 cell recorded at the same time.

The relationship between latency difference and peak position in the case of T peaks is examined in Fig. 9A, 1 and 2. The sample size is not large enough for a statistical test, but it is interesting to notice the similar values obtained in several cases.

Figure 9B, 1 and 2, shows the relationship between latency difference and CCH peak position for the C peaks. For mu CCHs, a weak but significant correlation is observed for ON responses ($r = 0.404$, $P = 0.04$). However, in a mu recording, the cell that provides the earliest response determines the latency of the PSTH but does not necessarily contribute to the CCH peak. su cases should give a more precise measurement of the relationship between visual response latency and CCH peak position. Indeed, there appears to be a good correlation between these two variables when su only are tested (Fig. 9B1). The correlation coefficient was 0.78 in that case ($P = 0.02$).

Figure 9C, 1 and 2, illustrates the relationship between peak position and latency difference in the case of H peaks. There were no significant correlations for either su or mu recordings.

In summary, these data indicate that, at least for the C and presumably the T peaks, the position of the peak in a CCH is linked to the difference of response latencies of the recorded cells. Although peaks contained the origin of time in the majority of the cases and were considered by this criterion to represent synchronized activity, the peak position of the CCH takes a value that is related to the order of activation of the recorded cells. This apparent contradiction possibly results from the fact that the delay that takes place in a serial connection is likely to be smaller than the width of a CCH peak (see DISCUSSION).

Coupling strength

The strength of the CCH peaks was quantified by three measures: the peak height; the peak area, which is the number of spikes present in a peak per trigger spike; and the PES (percent engaged spikes), which expresses the number of correlated spikes over the total number of spikes (both correlated and uncorrelated) that appeared during a time window equal to the full width of the peak. Coupling strength data are summarized in Fig. 10 and Table 2.

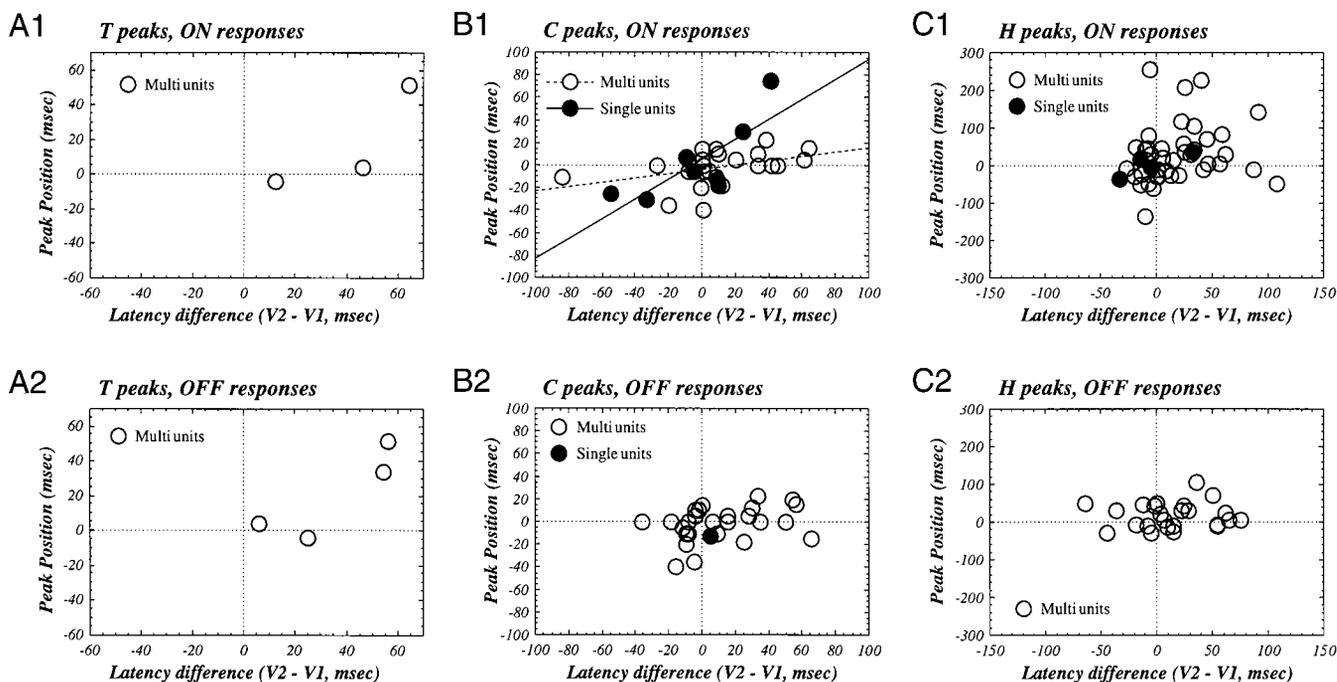


FIG. 9. Relationship between CCH peak position and the visual response latencies. Each scattergram compares the position of the CCH peak on the time axis with the difference between the response latencies to visual stimulation of the V2 and the V1 neurons. *A1* and *A2* present results for T peaks, *B1* and *B2* results for C peaks, *C1* and *C2* results for H peaks. Number of single-unit (su) pairs in which both units responded to the offset of the stimulus is lower than the number of pairs in which both units gave an ON response. As a consequence, the number of OFF responses latency differences for su pairs (black dots in *B2* and *C2*) is lower than for ON responses (*B1* and *C1*). Regression lines in *B1*: For mu C peaks: peak position = $-3.717 + 0.192 * \text{latency difference}$, $r^2 = 0.163$; for su C peaks: peak position = $4.852 + 0.885 * \text{latency difference}$, $r^2 = 0.608$.

Comparing su with mu CCH peaks shows that both peak height (Fig. 10A, 1 and 2) and area (Fig. 10B, 1 and 2) are higher for mu than for su recordings (Mann-Whitney U test, $P < 0.05$ in all the cases except for C with flash: $P = 0.1$; T peaks have not been tested due to small sample size). This is to be expected because, on average, more than one pair of units contribute to the peak obtained in a mu recording; by making the ratio of the median values of the peak areas, it appears that the number of pairs would range between 1.6 (H peaks, moving bar) and 3.6 (H peaks, flash). However, not all neurons contributing to a mu recording appear to be synchronized: this can be deduced by comparing the ratio presented above with the ratio of the number of mu spikes over su spikes accumulated during a recording, which gives the number of neurons contributing to a mu recording. This ratio is close to 8 (7.7 for V1, 8.25 for V2).

The proportion of spikes that are engaged in a correlation of neuronal origin represents only a small fraction of the total number of spikes. This is revealed by the percentage of engaged spikes (Fig. 10C, 1 and 2) that takes median values between 10 and 17% for su pairs, depending on the stimulus and peak types, and between 6 and 13% for mu pairs (Table 2). The PES is lower for mu than for su (Mann-Whitney U test, $P < 0.005$ for all types of peaks). This results from the fact that in a mu recording, not all the cells contribute to the peak but all contribute to the shift predictor.

Comparing coupling strength between different types of peaks does not show significant differences between the heights of C and H peaks. Peak areas of C and H peaks differ mainly because of the differences in peak widths. No signifi-

cant differences are observed between the PES of the three peak types.

Comparing coupling strength between flashed and moving stimuli indicates how it is influenced by the type of stimulus used. There was no effect on the peak area or peak height of H peaks. For C peaks, the peak area and peak height appeared different for flashed bars and moving bars ($P = 0.01$, Wilcoxon paired test), suggesting that the absolute coupling strength is larger with flashes than with moving stimulus. The relative coupling strength, measured by the PES, was larger for flashed compared with moving bars for both C peaks ($P = 0.005$) and H peaks ($P = 0.0002$). For H peaks, the difference in PES value must be due to the smaller response generated by flashed stimuli compared with moving bars because the stimulus type did not influence H peak areas.

Receptive field properties

No significant effects on encounter rates were observed with respect to the presence of orientation selectivity, to the differences in optimal orientation for pairs of sites with oriented receptive field, or to differences in color selectivity. This possibly is related to the small sample of T peaks, the incidence of which showed the strongest dependency on receptive field properties in earlier studies (Nelson et al. 1992; Nowak et al. 1995b).

We only found an effect of the respective positions of the receptive fields of the recorded cells. Altogether, the probability to obtain a significant correlation, whatever the peak type, was significantly higher when receptive fields overlapped (incidence of nonflat CCHs for mu recordings: 65.4%, vs. 45.9%

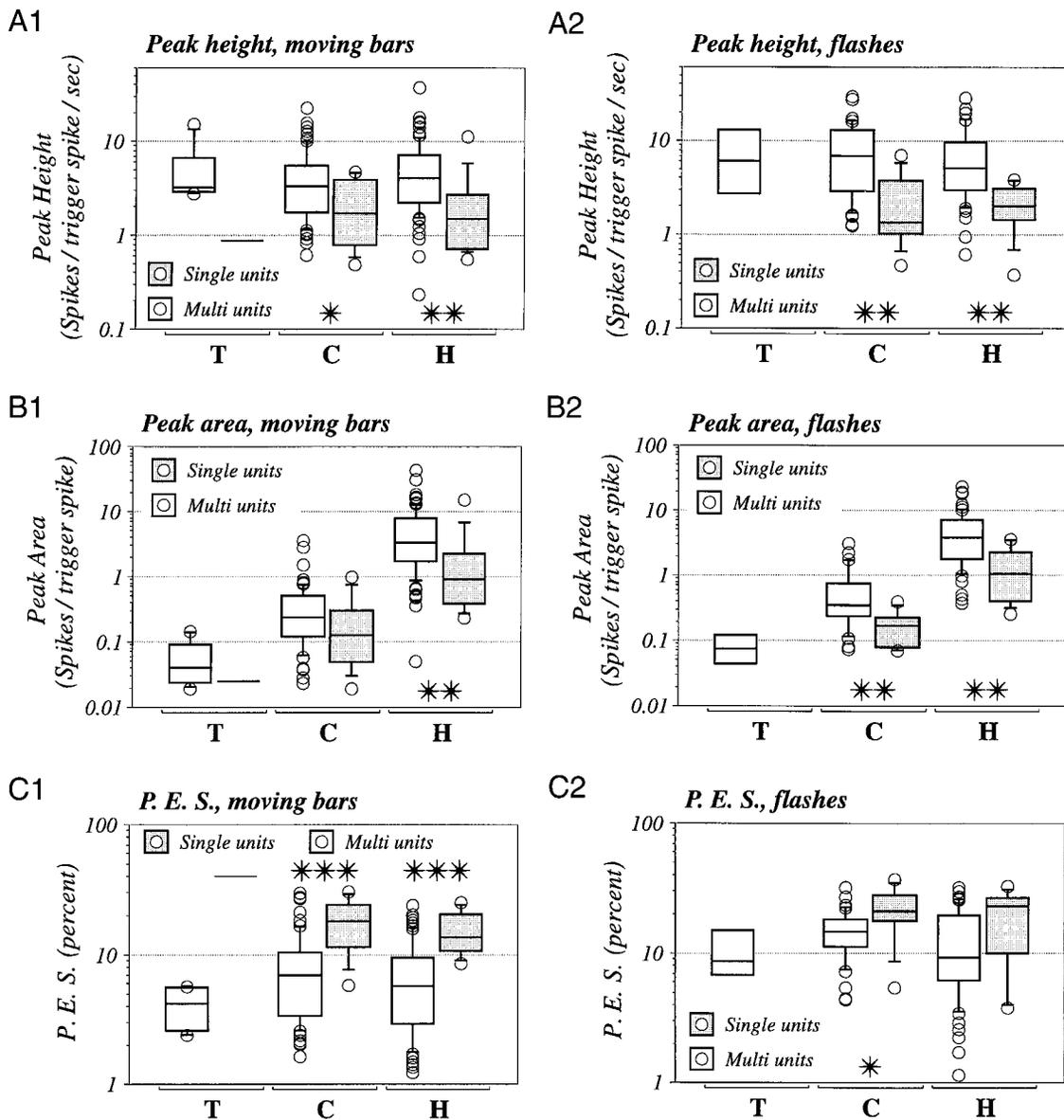


FIG. 10. Coupling strength for T, C, and H peaks. Results are presented in form of box plots for T, C, and H peaks. Central bar of the box represents the median of the population, the sides of the box, the 25th and 75th percentiles and the small horizontal bars the 10th and 90th percentiles. Individual cases below the 10th percentile or beyond the 90th percentile are represented as dots. *A1* and *A2*: peak height. *B1* and *B2*: peak area. *C1* and *C2*: percentage of engaged spikes (PES). Stars denote the level of statistical significance for difference in coupling strength between su and mu CCH peaks in Mann-Whitney *U* test (* $0.01 < P < 0.05$; ** $0.001 < P < 0.01$; *** $P < 0.001$.) T peaks have not been tested due to small sample size.

for nonoverlapping receptive fields, $P = 0.008$ in a χ^2 test) or when they were separated by $< 2^\circ$ (incidence of nonflat CCHs for mu recordings: 63.9%, vs. 31.1% for receptive fields separations between 2 and 5 degrees, $P = 0.0001$). The effects of receptive fields separation and overlap are presented separately for C and H peaks in Fig. 11. There was a higher encounter rate of C peaks when the receptive fields overlapped, totally or partially ($P = 0.02$; Fig. 11B). A similar effect was observed in the case of H peaks: although not significant ($P = 0.1$), there was a tendency for sites with overlapping receptive fields to be coupled more often by H peaks (Fig. 11B). Also, sites with receptive field center separations $< 2^\circ$ had a higher encounter rate of H peaks than sites with separations above this value ($P = 0.001$, Fig. 11A).

CCH peaks and visual drive

The effects of the visual stimulation on the probability to observe a peak and on its strength were examined by comparing CCHs calculated for a period restricted to the visual response of the cell with CCHs calculated for a period restricted to the spontaneous activity. Figure 12 illustrates this with an example representative of the general tendency observed: the responses of the neurons to the moving bar are represented by the PSTHs in Fig. 12A, *a* and *b*. The periods of recorded activity of the neurons are divided into a visual drive period (VD) and a spontaneous activity period (SA) and the CCHs displayed for each of the two periods in Fig. 12, *B* and *C*. Figure 12B shows that during the visual response, the sites are synchronized by a H and a C peak. During spontaneous activity

TABLE 2. *Coupling strength*

	Peak Height, spikes · trigger spike ⁻¹ · s ⁻¹		Peak Area, spikes/trigger spike		Percentage Engaged Spikes, %	
	Median	Interquartile	Median	Interquartile	Median	Interquartile
Moving bars						
C peaks						
Multiunits	3.29	3.78	0.23	0.39	6.90	7.01
Single units	1.72	3.16	0.13	0.25	18.33	13.01
H peaks						
Multiunits	4.03	5	3.39	6.18	5.73	6.63
Single units	1.51	1.98	0.907	1.904	13.60	10.01
T peaks						
Multiunits	3.25	3.70	0.04	0.066	4.18	2.97
Single units	0.86	—	0.024	—	39.72	—
Flashes						
C peaks						
Multiunits	6.82	9.86	0.34	0.52	14.72	7.01
Single units	1.36	2.78	0.17	0.15	20.90	10.33
H peaks						
Multiunits	5.04	6.6	3.78	5.28	9.26	13.10
Single units	1.98	1.65	1.05	1.83	22.98	17.06
T peaks						
Multiunits	6.05	10.12	0.075	0.075	8.63	8.35

(Fig. 12C), the C peak is absent and the size of the H peak is increased.

Three types of stimulus dependency were observed: some peaks were present only during the visual response and absent during the spontaneous activity, like the C peak of Fig. 12. A minority of peaks showed the opposite behavior. Finally some peaks were present during both the visual drive and the spontaneous activity, like the H peak of Fig. 12. The incidence of peaks displaying one of these three behaviors is summarized in Table 3 and in Fig. 13Aa for mu and Fig. 13Ab for su pairs.¹ Fifty-seven percent of the C peaks were present only during the visual response and absent during spontaneous activity, whereas 70% of the mu H peaks that were present with the visual stimulation remained during spontaneous activity. With respect to their stimulus dependency, H and C peaks differed significantly ($P = 0.002$ in a χ^2 test on pooled su and mu).

In 28 cases, the original CCH consisted of combination of a C and a H peak (as in Fig. 3, E and F). We examined these cases to determine whether peaks switch type depending on the presence of a visual stimulation. We found such switching in only two cases. The most often encountered pattern (12/28) consisted in a H peak being present during both visual drive and spontaneous activity and a C peak present during visual stimulation only (as in Fig. 12).

C and H peaks also differed with respect to the effect of the visual stimulation on their coupling strengths. To assess the changes in coupling strength, we computed a coupling strength ratio (CSR), which is the ratio of the peak height measured during visual drive over the sum of the peak height during spontaneous activity and visual drive [$CSR = PH_{vd}/(PH_{vd} + PH_{sa})$]. The index is 0 for peaks present only during spontaneous activity; it is 1 for peaks present only during visual drive; and a value of 0.5 corresponds to a peak height unchanged in both conditions. The data are summarized in Fig. 13Ba for C peaks and 13Bb for H peaks. Considering only the C peaks that were present with both spontaneous activity and visual drive

($0 < CSR < 1$, 40.7% of the mu cases), a tendency can be observed for the CSR to be >0.5 (mean CSR = 0.59, Fig. 13Ba). Hence, the height of the C peaks obtained with the visual response was larger on average than that for the spontaneous activity period (Wilcoxon paired test, $P = 0.03$ for mu).

H peaks that were present during both the visual response and the spontaneous activity period showed an opposite behavior (mean CSR = 0.42, Fig. 13Ba), and the height of the H peaks obtained during the period of visual response was smaller than the one obtained during the spontaneous activity ($P = 0.007$ for mu). Importantly, there was no correlation between the CSR and either the strength of the visual response or the level of spontaneous activity.

In summary, C peaks appear to be strongly associated to the presence of a visual stimulus, both in terms of incidence and coupling strength, whereas H peaks, although they tend to remain during both spontaneous activity and visual response, nevertheless appear stronger during spontaneous activity.

DISCUSSION

Three types of temporal correlation between areas V1 and V2 of the macaque

The cross-correlation method reveals the temporal coherence in the firing of neurons. Two different types of temporal coherence must be distinguished (Aertsen and Arndt 1993; Dickson and Gerstein 1974; Perkel et al. 1967). The first one, called “stimulus-locked temporal coherence,” results from the coactivation of the two recorded cells by the stimulation and is not directly related to neuronal interactions. It appears in isolation in the shift predictor (Figs. 1 and 2).

The second type of temporal coherence is the “neurally related temporal coherence,” which we referred also to as “correlation of neuronal origin.” This type of temporal coherence does not need a stimulus to be generated, as it can be observed with spontaneous activity (Fig. 12C). When visual

¹ The sample size was too small for T peaks for statistical tests.

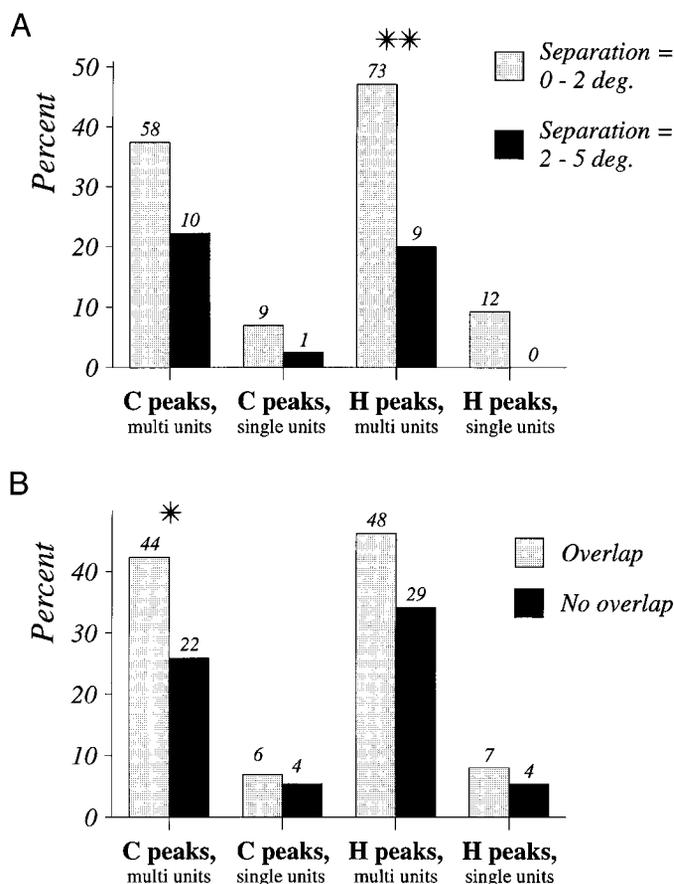


FIG. 11. Incidence of C and H peaks is influenced by the receptive field separation. *A*: incidence rates for C and H peaks for sites with receptive field centers separated by more or $< 2^\circ$. *B*: incidence rates for sites with overlapping or nonoverlapping receptive fields. Numbers above bars refer to the number of peak observed. Sample size is smaller in Fig. 11*B* because the neurons pairs with abutting receptive fields have been excluded from this analysis. Stars denote significance level in a χ^2 test (* $0.01 < P < 0.05$; ** $0.001 < P < 0.01$).

stimulation is used, the neurally related temporal coherence needs to be distinguished from the stimulus-locked temporal coherence. The shift predictor allows such a distinction and its subtraction from the raw CCH shows in the subtracted CCH the temporal coherence of neuronal origin in isolation (Figs. 1 and 2). Although, in terms of coupling strength, it represents usually $< 20\%$ of the stimulus-locked coherence (Fig. 10), the neurally related temporal coherence has received much of the interest of the studies on neuronal interaction and synchronization; our study deals with it as well.

The results of the present study show that the activities of neurons simultaneously recorded in areas V1 and V2 of the macaque monkey are correlated by mechanisms of neuronal origin in $\sim 10\%$ of the cases (su pairs). These correlations are revealed in the CCHs by peaks the widths of which are distributed in a trimodal fashion (T, C, and H peaks, Fig. 4). Three modes of neuronal correlation have been reported previously in the cat for the interactions between areas 17 and 18 of the same hemisphere (Nelson et al. 1992) and between areas 17 of both hemispheres (Nowak et al. 1995b). A bipartite or tripartite distribution of peak width also has been reported in several cross-correlation studies concerning neurons recorded within the same cortical area (Aertsen et al. 1991; Eggermont 1992;

Gochin et al. 1991; Hata et al. 1991; Krüger and Mayer 1990; Murphy et al. 1985; Swadlow et al. 1998).

The reason why CCH peaks have different widths might be related to different types and amount of burstiness. This is supported by the fact that the autocorrelation histograms (ACHs) calculated for the recorded units always showed features that were apparent in the CCH. In general, when an H peak was observed in the CCH, there was also an H-like structure in the ACH of at least one of the two recorded units. A similar observation holds for C peaks (see also Gochin et al. 1991; Nowak et al. 1995b). Bursts lasting 10 ms to several hundred milliseconds, presumably resulting from network properties, have been identified in cat cortex (Bowman et al. 1995; DeBusk et al. 1997; Legendy and Salcman 1985; Noda and Adey 1970). It has been shown that compensating for the presence of these bursts results in a narrowing of the CCH peaks (Eggermont and Smith 1996; Eggermont et al. 1993).

The encounter rate for T peaks in monkey ($< 1\%$ in su runs; Fig. 5) is much lower than in cat (11% for CCHs computed between areas 17 and 18, 17% between areas 17 of opposite cortical hemispheres). T peaks in the cat show the strongest dependency on the receptive field separation and properties (Nelson et al. 1992; Nowak et al. 1995b) and appear to be generated by the direct reciprocal connections between the two recorded sites (Munk et al. 1995). It is possible that the low encounter rate of T peaks in the monkey areas V1 and V2 is related to the highly modular nature of their connections, which makes recording from directly interconnected neurons a more difficult task than in the cat cortex. It also should be noted that narrow CCH peaks seem to be less common for interareal than for intraareal interactions (Cardoso de Oliveira et al. 1997; Roe and Ts'o 1997).

A number of studies have described a fourth type of synchronization, the synchronization of gamma range (30–80 Hz) oscillations. In cat visual cortex, such oscillatory synchronization has been shown in the local field potential and in mu recordings within cat area 17 (Eckhorn et al. 1988; Gray et al. 1989) as well as between different cortical areas (Eckhorn et al. 1988; Engel et al. 1991a,b; Nowak et al. 1995b). In the monkey cortex, oscillatory activity and synchronization has been demonstrated within visual and sensorimotor areas in su and mu activities as well as in the local field potential (Eckhorn et al. 1993; Frien et al. 1994; Kreiter and Singer 1992; Livingstone 1996; Murthy and Fetz 1992; Rougeul et al. 1979; Sanes and Donoghue 1993).

We did not observe oscillatory synchronization, except in a single case (of > 500 CCHs). We also checked whether oscillatory firing was present in su recordings by computing ACHs for > 200 su and found only a single case of gamma range oscillation. This very rare occurrence could be related to the fact that we computed ACHs and CCHs over a large number of repetitions of the stimulus to get a large enough signal-to-noise ratio. Such averaging might lead to the waning of the oscillatory activity, as reported by Kreiter and Singer (1992) and Livingstone (1996) in their studies from monkey visual cortex. However, calculating CCHs on the basis of one or a few stimulus repeats was unpractical in our case because it resulted in a signal-to-noise ratio that was too low to allow the detection of significant interactions (see METHODS).

Beside differences in anesthesia and visual stimuli, species difference might constitute a possible explanation of our failure

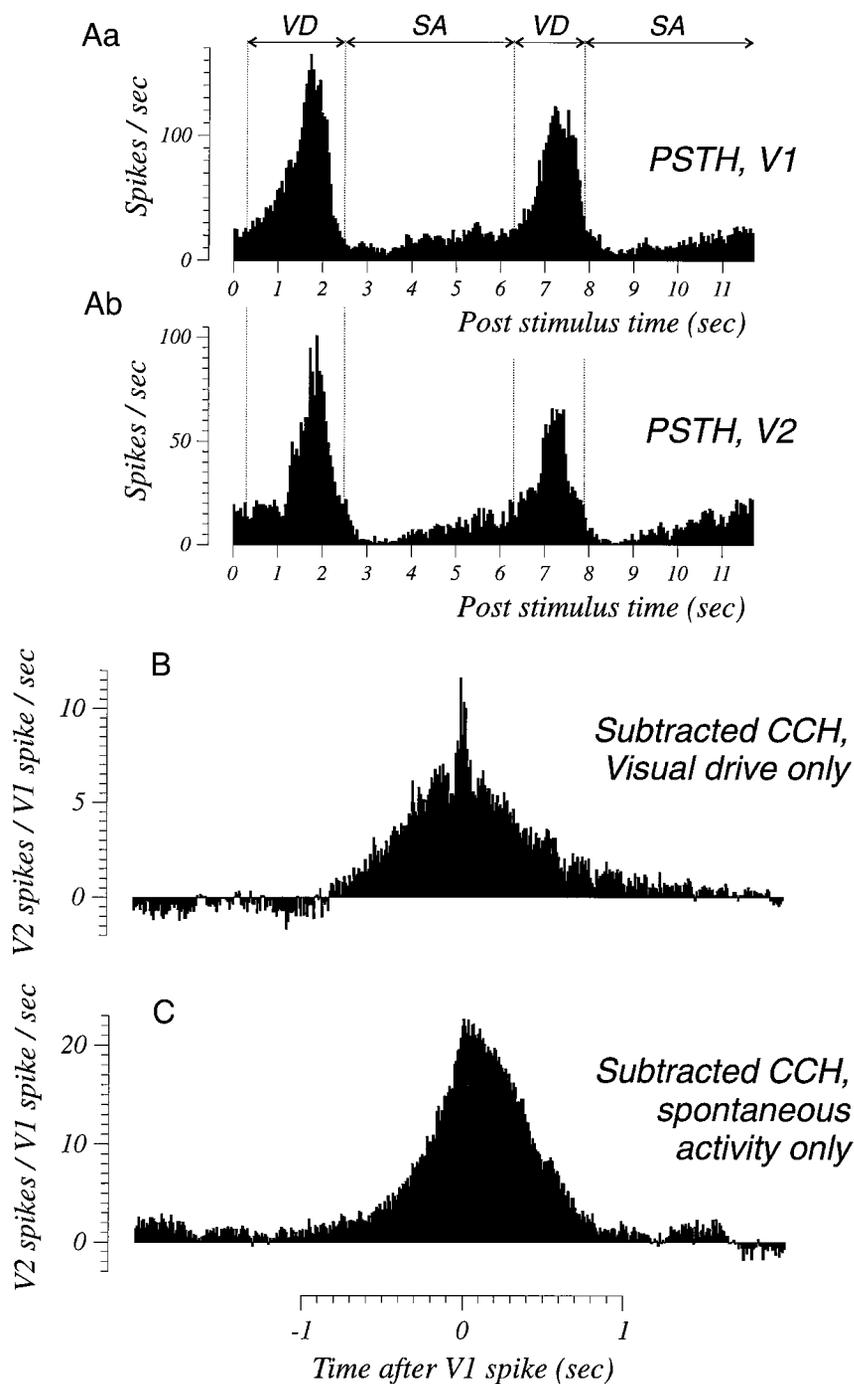


FIG. 12. Example of the stimulus dependency of synchronization. Recordings of 2 mu sites stimulated with a moving bar. *Aa* and *Ab*: PSTHs of the visual responses. *B*: subtracted CCH computed from spikes recorded during the visual drive period. *C*: subtracted CCH computed from spikes recorded during the spontaneous activity period.

to record synchronized oscillation between macaque areas V1 and V2. Most of the reports on synchronized gamma range activity were obtained in the cat (e.g., Eckhorn et al. 1988; Gray et al. 1989), whereas its presence in monkey proved to be more controversial (cf. Tovee and Rolls 1992; Young et al. 1992). It is noteworthy that in our preceding study on cortico-cortical interactions in the cat (Nowak et al. 1995b), 20% of the significant CCH peaks corresponded to synchronized gamma range oscillations. Although for the present study we used the same protocols for animal preparation, recording, visual stimulation, data analysis, and, in four cases (not reported in this study), the same anesthetics, we found almost no synchronized oscillations.

Synchronization in a serially organized system

The monkey visual system classically is thought as being organized in a serial manner. Anatomic studies showed that in the primate, contrary to other orders, the LGN input is focused onto area V1, and functional studies based on inactivation indeed showed that activity in area V2 is entirely dependent on the activity coming from V1 (reviewed in Bullier et al. 1994). One therefore would expect that neurally correlated activity in V1 and V2 displays signs of this organization.

T peaks that do not contain the origin of time in their upper half (displacement index > 1 , Fig. 8B) could be considered as representing serial connections (either mono- or polysynaptic).

TABLE 3. Influence of visual drive on incidence of different types of CCH peaks

Single/ Multiunits	Peak Type	Visual Drive Only	Spontaneous Activity Only	Visual Drive and Spontaneous Activity
Multiunits	T	3 (75)	1 (25)	0 (0)
	C	31 (57.4)	1 (1.9)	22 (40.7)
	H	16 (24.2)	4 (6.1)	46 (69.7)
Single unit	T	0	0	0
	C	4 (57.1)	1 (14.3)	2 (28.6)
	H	5 (55.6)	1 (11.1)	3 (33.3)

Numbers in parentheses represent percentage. The sample size is smaller than in other analyses because, in some cases, the number of spikes during spontaneous activity was too small for proper computation of the cross-correlation histogram (CCH) or because some neurons were not properly activated by the visual stimulus or they responded without sufficient temporal overlap (different direction selectivity or nonoverlapping receptive fields).

In this study, such peaks have been observed in only four cases in a total of >500 CCHs. They were displaced in the positive direction, indicating a possible connection from V1 to V2. Two T peaks showed exceptionally high values of the peak position (Fig. 8A2). These two peaks remained when the run was sliced into smaller periods and are therefore unlikely to represent artifacts. They may represent instances of synfire chains (Ables et al. 1993; Vaadia et al. 1991).

At the population level, the median peak position for C and H peaks in the present study is not significantly different from 0. In addition, the upper half of the CCH peaks overlaps the

origin of time in 94% of the cases (all peaks together). Similarly to what has been reported previously in the cat (Nelson et al. 1992; Nowak et al. 1995b), this indicates that the majority of neurons in macaque areas V1 and V2 synchronize their activities, when these are correlated by mechanisms of neuronal origin.

For C peaks, however, a correlation was observed between the position of the peak on the time axis and the difference in visual latencies to flashed stimuli (Fig. 9). This suggests that the position of a C peak is somehow related to the respective order of activation of the V1 and V2 neurons that are correlated.

There is some ambiguity in stating that C peaks represent instances of synchronized activity on the one hand and that they reflect the order of activation of the cells on the other. Measurements of visual response latencies show that, on average, V2 neurons are activated 10 ms later than neurons in area V1 (Raiguel et al. 1989; Nowak et al. 1995a) while the median of the axonal delay between these two areas is ~2 ms (F.-M. Huppé, P. Girard, and J. Bullier, unpublished data). This suggests that the latency of the serial links between areas V1 and V2 is at least one order of magnitude smaller than the median width for C peaks. It is therefore possible that burstiness, which may account for their width, masks the presence of a serial link (see also Creutzfeldt et al. 1980). Nevertheless, if the C peaks that are not exactly centered on the origin of time do correspond to hidden serial connections, it has to be noted

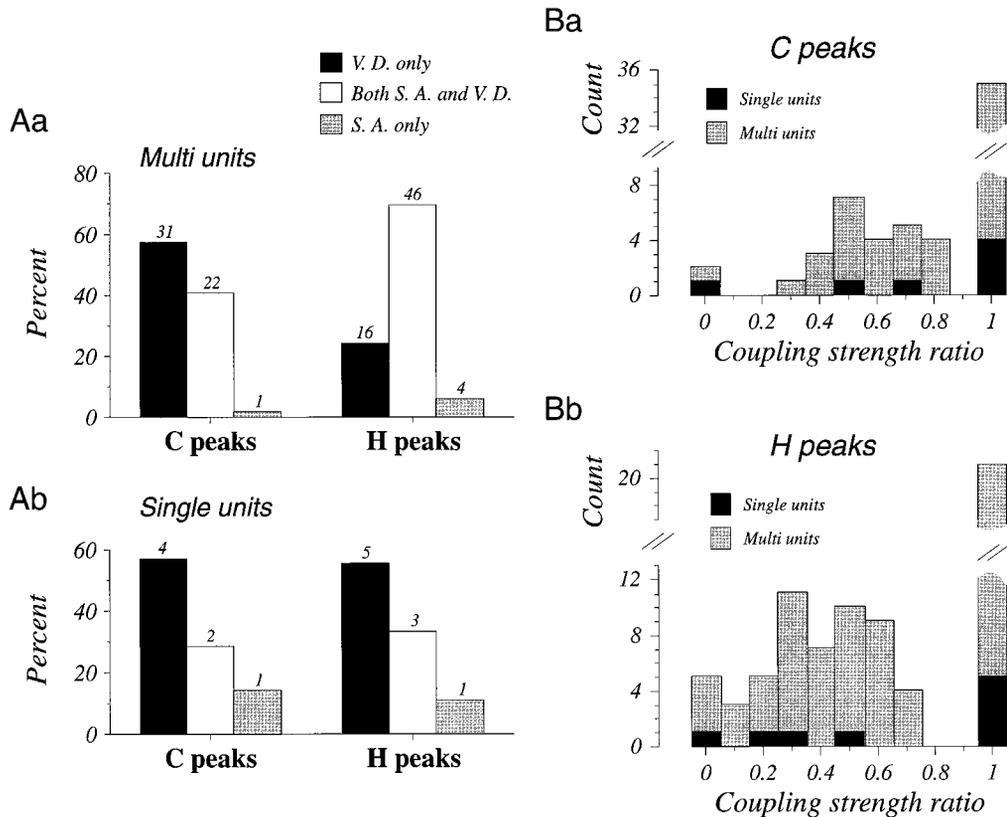


FIG. 13. Summary of the effect of visual stimulation on the incidence and strength of interareal correlation. Aa and Ab: incidence rates of C and H peaks that were observed only during visual drive (VD), only during spontaneous activity (SA), or during both spontaneous activity and visual drive. For mu pairs, C peaks are seen more often during visual drive only, whereas H peaks that are present during spontaneous activity tend to remain during visual drive. Ba and Bb: distribution of coupling strength ratio for C and H peaks.

that similar numbers of these are displaced to the right or to the left. In that respect, the position of a C peak on the time axis does not conform with a serial organization for areas V1 and V2.

Origin of synchronization and the effects of visual stimulation

Neuronal synchronization commonly is observed in cortex, and areas V1 and V2 are no exceptions to this rule. The occurrence of synchronization between areas V1 and V2 is not incompatible with their functional and anatomic relationship if one considers the temporal aspects of the visual responses: first, although visual response latencies in V1 are shorter than in V2, the overlap of latencies is so large that >40% of V2 cells already have started responding when 50% of V1 cells have not responded (Nowak et al. 1995a). Second, when a neuron is activated by a visual stimulus, its response does not stop after its first spike. Instead it continues to fire for a prolonged length of time in such a way that there is a large overlap between the periods of responses of neurons in V1 and V2 (see Figs. 1, 2, and 12). Altogether, there is a large temporal window during which neurons in both areas are simultaneously active. Then if mechanisms that can sustain it are at work, these activities might become synchronized.

Two mechanisms can explain the neurally related synchronization of neuronal activities. The first one is the common input hypothesis (Perkel et al. 1967), which postulates that neurons are synchronized by the common inputs they receive from neurons with bifurcating axons terminating in both structures. It is important to realize that, with the exception of the lateral geniculate nucleus, almost all the structures that project to area V1 also project to V2 and that some connections are made by bifurcating axons (Kennedy and Bullier 1985; Rockland and Drash 1996; Rockland et al. 1994). This concerns several subcortical structures, like the pulvinar and the claustrum, and also a number of areas that project in a feedback manner like areas MT and V4.

The second mechanism that can explain the presence of synchronized activity is of a more subtle nature and has been described in modeling studies (Arnoldi and Brauer 1996; Bush and Douglas 1991; Bush and Sejnowski 1996; Hansel and Sompolinski 1996; Koch and Schuster 1992; König and Schillen 1991). These studies have shown that two groups of neurons (with or without pacemaker properties) connected by axons having a finite conduction delay nevertheless can synchronize their activities. This is the consequence of the divergent nature of the connectivity, together with a prominent role played by inhibitory interneurons. This constitutes an emergent property of the cortical network.

Whether one or both of these mechanisms can explain the synchronization between areas V1 and V2 in the monkey cannot be determined at present. However, our previous study on interhemispheric synchronization in the cat (Munk et al. 1995) provides some indications. This study was based on the effect of cortical lesions and the transection of the callosal connections on the different types of neuronal correlation. We concluded that T peaks result mainly from the direct reciprocal connections between the two cortical areas. C peaks appeared to be reduced strongly in occurrence and strength after lesion of areas providing monosynaptic feedback inputs, which led us

to conclude that this type of correlation at least is facilitated by common inputs from higher cortical areas. The fact that C peaks are observed even between neurons with nonoverlapping receptive fields (Nelson et al. 1992; Nowak et al. 1995b; this study) is consistent with the loose retinotopic organization of feedback connections (Salin and Bullier 1995). The H type correlation appeared to involve both monosynaptic and polysynaptic corticocortical connections.

The influence of visual stimulation might help to determine further the origin of cortical synchronization. In the present study, we observed that 70% of the H peaks that are present during the visual response still are present during spontaneous activity. On average, these peaks were stronger during the spontaneous activity than during the visual response (Figs. 12 and 13). In unanesthetized cat, broad peaks appear during sleep in both the CCH and the ACH of cortical neurons (Noda and Adey 1970) but disappear during waking. H peaks also present similarities with the broad CCH peaks observed by Amzica and Steriade (1995) that appear during the slow cortical oscillations associated with sleep (Steriade et al. 1993). Together with a lack of obvious dependency on receptive field properties (Nelson et al. 1992; Nowak et al. 1995b; this study), this suggests that at least some of the H peaks are related to the sleep/wake cycle of the animal. The width of H peaks may reflect the temporal dispersion of activity in the polysynaptic network involving both the cortex and the thalamus (Amzica and Steriade 1995).

However, there was a number of cases for which H peaks were clearly stronger during the visual response and, in ~30% of the cases, they were absent during spontaneous activity (Fig. 13). Broad peaks, similar to H peaks, also have been observed in awake behaving animals performing tasks requiring a high level of attention (Aertsen et al. 1991; Gochin et al. 1991) and cannot, therefore, be associated with sleep or anesthesia. This suggests that there might be two different types of H peaks, one associated with sleep or anesthesia, the other associated with sensory processing. Their similarities in terms of width led us to group them together, but they might differ with respect to other aspects that remain to be determined.

Contrary to the general tendency observed with H peaks, the majority of C peaks appeared to be stronger during visual stimulation with >50% of them being present only during this period. This indicates that these peaks are associated with the processing of visual information. In this respect, C peaks appear to be similar to the synchronized gamma range oscillation that also appear preferentially during the visual stimulation (Engel et al. 1991a,b; Gray et al. 1989; Livingstone 1996; Nowak et al. 1995b). Therefore C peaks may represent, at least for some of them, the signature of common inputs provided by feed back connections, which would be gated by the presence of visual stimulation.

Conclusion

It has been proposed that synchronization of neuronal activity could solve the so-called binding problem (Abeles 1982a; Damasio 1990; Milner 1974; Singer and Gray 1995; von der Marlsburg 1981). The plausibility of this proposal is supported by our results demonstrating the presence of synchronization between two areas that otherwise, on the basis of other evidences, have been proposed to be organized serially. On the

other hand, synchronization also could be considered as the side effect of the functioning of the cortical network and might not convey any specific information by itself (Bush and Sejnowski 1996; Gawne and Richmond 1993; Shadlen and Newsome 1994). In any case, the presence of synchronization between areas V1 and V2, together with previous findings indicating a quasisimultaneity in their activations (Bullier and Nowak 1995), suggests that they are not only two successive relay stations for visual information processing. Instead, this indicates that neurons in areas V1 and V2 share common neuronal influences in such a way that the processing that takes place in area V1 is not independent from the one taking place in area V2.

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