Response Modulations by Static Texture Surround in Area V1 of the Macaque Monkey Do Not Depend on Feedback Connections From V2

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Hupé, Jean-Michel, Andrew C. James, Pascal Girard, and Jean Bullier. Response modulations by static texture surround in area V1 of the macaque monkey do not depend on feedback connections from V2. *J Neurophysiol* 85: 146–163, 2001. We analyzed the extracellular responses of 70 V1 neurons (recorded in 3 anesthetized macaque monkeys) to a single oriented line segment (or bar) placed within the cell classical receptive field (RF), or center of the RF. These responses could be modulated when rings of bars were placed entirely outside, but around the RF (the "near" surround region), as described in previous studies. Suppression was the main effect. The response was enhanced for 12 neurons when orthogonal bars in the surround were presented instead of bars having the same orientation as the center bar. This orientation contrast property is possibly involved in the mediation of perceptual pop-out. The enhancement was delayed compared with the onset of the response by about 40 ms. We also observed a suppression originating specifically from the flanks of the surround. This "side-inhibition," significant for nine neurons, was delayed by about 20 ms. We tested whether these center/surround interactions in V1 depend on feedback connections from area V2. V2 was inactivated by GABA injections. We used devices made of six micropipettes to inactivate the convergent zone from V2 to V1. We could reliably inactivate a 2- to 4-mm-wide region of V2. Inactivation of V2 had no effect on the center/surround interactions of V1 neurons, even those that were delayed. Therefore the center/surround interactions of V1 neurons that might be involved in pop-out do not appear to depend on feedback connections from V2, at least in the anesthetized monkey. We conclude that these properties are probably shaped by long-range connections within V1 or depend on other feedback connections. The main effect of V2 inactivation was a decrease of the response to the single bar for about 10% of V1 neurons. The decrease was delayed by $<$20 ms after the response onset. Even the earliest neurons to respond could be affected by the feedback from V2. Together with the results on feedback connections from MT (previous paper), these findings show that feedback connections potentiate the responses to stimulation of the RF center and are recruited very early for the treatment of visual information.

INTRODUCTION

As in many other structures of the visual system, the responses of neurons in area V1 can be modulated by stimuli presented outside the "classical" receptive field (RF). These modulations provide a comparison between stimuli inside and outside the RF, a mechanism allowing the integration of local and global information. For example, a proportion of V1 neurons gives a stronger response to a single bar flashed in their RF and embedded in a field of bars of orthogonal orientation flashed outside their RF, than to a bar surrounded by bars having the same orientation (Knierim and van Essen 1992). Perceptually, these stimuli are quite distinct. The bar surrounded by bars of orthogonal orientation is more salient, it "pops out" (Treisman and Gelade 1980). The center/surround properties of V1 neurons can therefore be part of the neural basis of preattentive parallel processes. The automatic character of such preattentive processes is in keeping with the fact that the orientation-selective modulations by the surround can be recorded in the neurons of anesthetized animals (Li and Li 1994; Nothdurft et al. 1999; Sengpiel et al. 1997; Sillito et al. 1995).

The orientation-selective surround modulations are presumed to be generated at the cortical level, as orientation selectivity first appears in V1 (Hubel and Wiesel 1962). One possible structural basis for such orientation-specific modulations is the set of horizontal connections that link together neighboring neurons in V1. Lateral long-range connections within V1 connect neurons with nonoverlapping RF (Salin and Bullier 1995), but they preferentially connect neurons with similar orientation preferences (Gilbert 1992; Tamura et al. 1996). As V1 RF are small, there is a need for numerous and extensive connections to cover the whole extent of the surround of the RF, which can cover up to 10 times the size of the RF (Levitt and Lund 1997).

Feedback connections from higher order areas are ideal candidates for these modulations, as neurons of these areas have larger RF than V1 neurons and their projections display a high degree of convergence. Contrary to feed-forward connections, feedback connections have been described as nonvisuotopically organized, meaning that a given target cell in V1 receives input from cells in higher areas having RFs extending beyond that of the target cell (Salin and Bullier 1995; Salin et al. 1992, 1995). Feedback connections from V2 in the monkey (Barone et al. 1995; Rockland and Virga 1989) are numerous: about 10 million or more V2 axons project to area V1, and the mean degree of convergence of area V2 afferents is high, perhaps more than 100 afferent axons per V1 cell (Budd 1998). These connections convey information concerning a region of visual field approximately five to six times the size of the average V1 RF (Angelucci et al. 2000).

The orientation-specific modulation of responses to center/

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surround stimuli is observed 15–20 ms after the response onset (Knierim and van Essen 1992; Nothdurft et al. 1999). Delayed modulations for textured surround of different orientations have also been demonstrated in awake monkeys (Lamme 1995; Zipser et al. 1996). In these studies, the delay was even larger (50–100 ms). As the responses of V2 neurons lag the V1 responses by about 10 ms (Nowak et al. 1995), such a delayed modulation provides another argument suggesting that orientation-dependent modulations depend on the feedback from V2.

Functional studies of cortico-cortical feedback connections are rare (Salin and Bullier 1995). The only available data concerning feedback influences on center/surround interactions in the macaque monkey suggest that feedback from MT play a role in figure/ground segregation (Hupé et al. 1998). When MT was inactivated, V3 neurons tested at low salience were no longer suppressed by a background stimulus (extending far away from the RF) moving coherently with a bar that swept across the RF. Even if center/surround interactions were not directly studied in that paper, the results suggested that feedback connections play a role in such interactions. Similar results have been found in areas V2 and V1 (Bullier et al. 2000).

We therefore decided to test whether center/surround interactions observed in V1 neurons depend on the feedback from V2. We used stimuli made of light bars flashed in and around the RF, to which the responses of V1 neurons are well documented, and are similar in awake and anesthetized monkeys (Knierim and van Essen 1992; Nothdurft et al. 1999). We tested surround suppression created by bars of similar orientation as the central bar, as well as modulations of the response that depended on the orientation properties of the surround.

In preliminary experiments, we had found that only a few V1 neurons were affected by V2 inactivation. The effects observed on this small sample were, however, unexpected. Two major effects could be observed: a decrease of the response to a single bar in the RF and strong increases to "surround-only" stimuli, i.e., stimuli made of bars placed only in the surround and that did not elicit any response in the control condition. In these cases, changes in the center/surround responses were observed, but they followed the increases of response of the surround-only stimuli and thus could be explained by linear summation mechanisms and not by a change in the center/surround interactions, which were never observed. These results have been described in an abstract form (Hupé et al. 1997), and one example has been published (Bullier et al. 1996; Payne et al. 1996). We proposed a model that could explain these surprising results. The basic idea of this model was that feedback connections from V2 gated the V1 intrinsic connectivity and had virtually the power of modulating, but not shaping the center/surround interactions (Hupé et al. 1997).

In these preliminary experiments, we had used three micropipettes filled with GABA 100 mM to inactivate V2. Anatomical data indicated that it was probably not sufficient to inactivate the whole extent of the convergence zone of V2 to a given V1 neuron. We tested in our model the effects of partial inactivation and found that it explained why we had observed effects in only a few V1 neurons, and why the surround-only responses were the predominant effect. We predicted that if we were able to inactivate the whole feedback input from V2 to V1 cells, we should not only observe effects quite systematically, but we should also see an equivalent proportion of effects (decreases) on the center response and on the surround response (increases). The role of feedback was therefore understood as a push-pull mechanism (Bullier et al. 1996; Payne et al. 1996).

Another possible explanation of the increases of the surround-only responses was provided by recent results that show that the size of the V1 RF depends on the state of the electroencephalogram (EEG) of anesthetized animals (Wörgötter et al. 1998). As our preliminary experiments had been done without any systematic control of the EEG during the control and inactivation phases, it was possible, even if unlikely, that, among the great number of tests that had been done, changes of the EEG had occurred precisely when GABA was injected. This could have lead to an increase of the RF size, and thus the previously unresponsive surround stimulus now had encroached on the RF, leading to the observed increases of response to the surround only stimulus.

We therefore decided to undertake a new series of experiments with more extensive inactivation of V2 and a careful control of the EEG state of the animals before and during the V2 inactivation. In the present paper we describe results obtained in three monkeys where we carried out extensive inactivation of V2 by GABA under control of the EEG state. We did not find any increase of the response to the surround stimuli when V2 was inactivated. We also did not find any effect of feedback connections on the center/surround interactions. We nevertheless observed decreases of response to the center stimulus, as already reported in the preliminary experiments. These effects were observed from the very beginning of the visual response.

METHODS

Physiology

Recordings were obtained from three anesthetized and paralyzed cynomolgus monkeys. Procedures were similar to those described in the companion paper (Hupé et al. 2001). In addition, we recorded the EEG and we calculated the fast Fourier transform on-line to check the depth of the anesthesia and also to monitor, on-line and off-line, the changes of the EEG states, especially within the 10- to 30-Hz range. We excluded some neurons from the analysis because of changes in the EEG state during the recording session (see DISCUSSION).

We used window discriminators (Neurolog) to isolate multi-unit activity from background in the V2 recordings. These recordings in V2 were done to monitor the efficiency of the inactivation by GABA (Fig. 2). For V1 recordings, we used a spike discriminator (MSD, from Alpha Omega) to extract single units and to monitor the identity of the neuron under study during periods of control, V2 inactivation, and recovery. We did not always record perfectly isolated neurons. In the case of multi-unit recordings, we first verified that the isolation index (II) (see Hupé et al. 2001) was similar in all the controls. When the II was below 0.8, we were especially cautious. If we observed some change during the V2 inactivation, we always tried to see whether it was possible to explain it by a change in spike isolation. Several attempts with different templates were even done if necessary, and the resulting peristimulus time histograms (PSTHs) were compared. We excluded some neurons from the analysis because of changes in isolation. Some sites for which the isolation was close to 0 were called "multi-unit" but were, however, kept for the analysis if the II did not change. In addition, if the response of these multi-unit clusters changed during the V2 inactivation, a special attention was

given to the stationarity of responses across controls and recovery, and if these recordings were sufficiently similar, the site was then kept.

Data sampling

After the first stage rejections due to changes in EEG or isolation, the responses of 70 V1 neurons (28 single units, 17 poorly isolated units, and 25 clusters of 2–4 units) to 7 stimuli were analyzed.

The minimum discharge field (RF in this paper) was plotted with a hand-held ophthalmoscope. The RFs were all located between 2 and 3° from fixation, in the lower right quadrant. A high contrast bar (120 cd/m^2, approximately 1 log unit above the background luminance) was optimized in size for each neuron. The length of the bar was between 0.1 and 0.8° (median value = 0.25, 75% of values between 0.15 and 0.3°). Its width was between 0.025 and 0.25° (median value = 0.05, 75% of values between 0.05 and 0.075°). Orientation was optimized to within 30° by measurement of an orientation-tuning curve. Three kind of stimuli were used: *1*) the bar alone flashed in the center of the RF; *2*) "surround-only" stimuli made of several bars identical to the center bar and flashed outside of the RF center, so they do not elicit any response; and *3*) center/surround stimuli.

The bars were regularly spaced. The space between the central bar and the surround bars was increased until the elimination of any response to the surround-only stimuli. In some cases, however, the surround triggered neuron responses even when the bars were far away from the plotted RF. The space was then chosen to be sure that no bars of the surround encroached on the RF. One to three (typically 2, for 80% of the neurons) rings of surround bars constituted the surround stimulus. The surround stimulus was therefore made of 6, 18, or 36 bars. Typical stimuli with one ring of surround bars are shown on Figs. 7–9. The surround covered 1.4–7.9° of visual field. Typically, the surround diameter was 5–8 times (70% of the cases between 6 and 10 times) larger than the length of the bar and was 3–4° across (70% of the cases between 2.3 and 5.6°). Extreme values of 3–19 times the length of the bar were obtained for the largest and smallest VI RF.

The stimuli were named following Knierim and van Essen (1992) and Nothdurft et al. (1999):

C, Center alone, bar flashed at the optimal orientation in the center of the RF of the neuron.

C/S, Center and iso-oriented surround (creating a uniform field of bars).

C/S′, center and cross-oriented surround (creating an orientation contrast between the center and the surround).

C/l, Center and iso-oriented bars only along the axis of preferred orientation of the neuron (creating a discontinuous line of bars).

The "surround-only" stimuli were called, respectively S, S′ and L.

The stimuli were presented for 500 ms with an inter-trial interval of 1 s, on a computer monitor driven by a Truevision Vista Board under the control of a Matlab program. Each recording run consisted of 20 repetitions of a set of the 7 stimuli interleaved in random order. At least three runs were carried out for each neuron.

V2 inactivation

We chose to use GABA injections for inactivation of V2 (Hupé et al. 1999). Inactivation by GABA has the advantage of confining the inactivation zone to a limited region, which was crucial given the proximity of areas V1 and V2. GABA inactivation also spares the axons, which is important as the fibers coming from the lateral geniculate nucleus (LGN) to V1 travel just along the deep layers of V2. Finally, even large-scale GABA inactivation, when properly done (Hupé et al. 1999), has effects that do not last too long, so it is possible to record V1 neurons after the V2 inactivation to see functional recoveries from the effects. GABA inactivation regions are always restricted (Hupé et al. 1999): it was therefore not possible to inactivate the whole area V2, as we had done in a previous study for MT using cryoloop cooling probes (Hupé et al. 1998). By using several micropipettes filled with GABA, it was, however, possible to inactivate a reasonably large portion of the region of V2 projecting back to a given point of V1. To know where this point of V1 was, we took advantage of the retinotopic laws of connections (McIlwain 1973; Salin and Bullier 1995): basically, neurons of different areas that look at the same point of the visual space are interconnected.

Preliminary mappings were therefore done in V1 and V2 to find neurons in retinotopic correspondence. A microelectrode was inserted in V1 perpendicularly to the pial surface a few millimeters posterior to the lunate sulcus. A V2 site was chosen when the microelectrode hit the deep layers of V2 after traveling a few hundred micrometers through the white matter, remained in V2 for at least 1 mm and no more than 1.5 mm, then crossed the lunate sulcus (short period of silence) and reached an area with large RFs (V3 or V4; see Fig. 1*A*). We plotted on Fig. 1*B* the progression in RFs (dotted rectangles) obtained during a typical mapping penetration through V1, V2, and V3. In addition, but for *monkey P* only, the mapping microelectrode was removed and replaced by a device made of three microelectrodes spaced by about 2 mm from each other. This device served as a test device to determine the whole extent of the RF covered by the inactivation device. The plots obtained by these three electrodes are numbered (1, 2, and 3) in Fig. 1*B*. Another microelectrode was then placed in V1, several millimeters caudal and medial to the three-microelectrodes device, and penetrations were repeated until V1 RFs were found that were in the middle of the V2 RFs (1, 2, and 3). The chosen V1 site RF is represented by the filled black square on Fig. 1*B*. The V1 region in retinotopic correspondence with V2 was always several millimeters behind the V2 device, at least in our experimental conditions (the angle of the penetration in V1-V2 was adjusted to make it possible), so these neurons did not lie on the way of the inactivation device to V2, and therefore could be recorded in intact cortex.

The V2 mapping microelectrode (or the 3-microelectrodes device for *monkey P*) was then removed, and the dura matter was dissected to allow the penetration of a compound device made of six micropipettes filled with GABA 100 mM (*monkeys N* and *P*) or 200 mM (*monkey Q*) and three or five (*monkey Q*) recording microelectrodes (Fig. 1*C*). The V2 RF plotted for the microelectrode placed in the middle of the device (*arrow 1* on Fig. 1*C*, E1 in Fig. 1*D*) is represented by the filled gray square on the Fig. 1*B*. The V1 and V2 RFs overlap. All the plotted V2 RFs belong to the region of V2 inactivated by GABA: this gives an idea of the aggregate of receptive fields (ARF) of the inactivated region. It is about 2.5° in diameter and very well centered on the V1 RF.

We used electrolytic lesions in V1 and V2 to aid reconstruction of electrode tracks on histological sections stained with cresyl violet. Figure 1*A* shows a photograph of a histological parasagittal section in V2 with a lesion (arrow) made at the end of the experiment by one of the microelectrodes of the device (7 μA for 7 s). We can see also the tracks of two elements of the device (probably 1 microelectrode and 1 micropipette) through the white matter and V2. Despite repeated GABA injections in V2, it is clear that the cortex remained in good condition until the animal was killed and perfused.

The device was built as previously described (Hupé et al. 1999). The micropipette tips were about 1 mm away from each other; the microelectrodes were 350–700 μm away from one micropipette, in the middle of and around the micropipettes (Fig. 1*D*). We designed the inactivation device so that the microelectrode recordings could both give a good estimate of the size and location of the V2 inactivated zone, and to check for the proper inactivation of V2 neurons during the experiment. All the tips of the micropipettes were always in one plane orthogonal to the long axis of the micropipettes. The tips of the three microelectrodes were staggered in depth, about 200 μm below, at the same level and about 700 μm above the plane of the micropipette tips. This geometric disposition along the main axis of the device can be seen on Fig. 1*C*, with the tip of one microelectrode

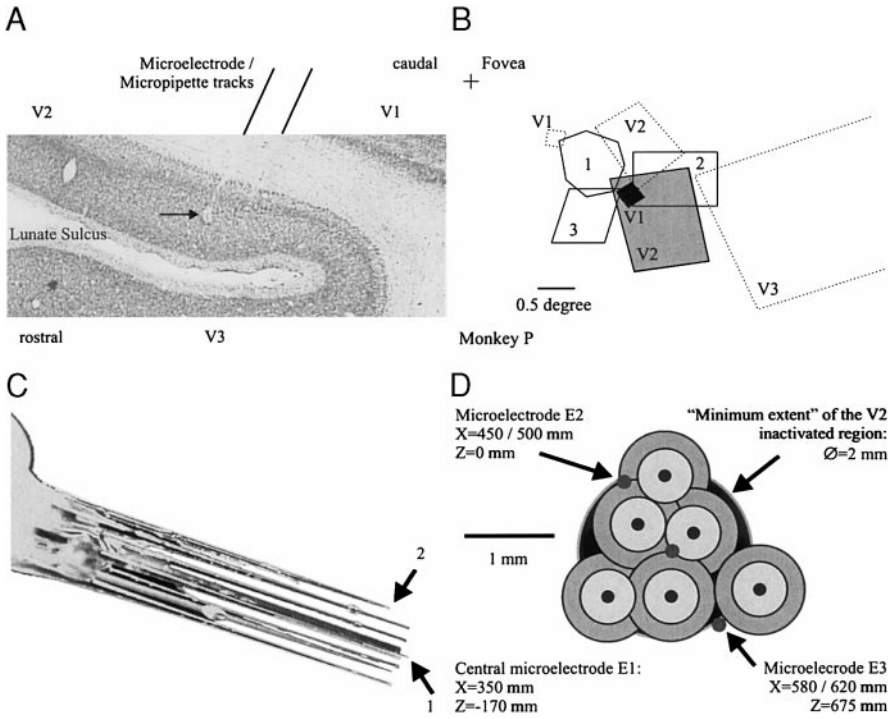

FIG. 1. *A*: photograph of a histological parasagittal section in V2 (see text for explanations). *B*: receptive fields (RFs) plotted for *monkey P*. The dotted RFs labeled V1, V2, and V3 were plotted along a single mapping penetration. The RFs labeled 1, 2, and 3 correspond to neurons recorded on 3 different electrodes positioned in V2 in another mapping penetration. The black/gray RFs labeled V1 and V2 were obtained during the inactivation experiment. See text. *C*: picture of the inactivation device that we used for the recordings in *monkey P*. The picture was taken after the experiment. A similar device was used with *monkey N*. A device with 5 microelectrodes was used with *monkey Q*. The spaces between the elements were then larger, as 200 mM GABA was used instead of 100 mM. *D*: plot of a frontal view of the inactivation device shown in *C*. The micropipettes tips (small black disks) are separated by distances inferior to 1 mm. All measures were done under a microscope equipped with a graticule before the experiment and checked after the experiment. Small gray disks represent the tips of the microelectrodes. The distances from each microelectrode to their closest micropipette(s) are indicated [called *X* coordinate, the lateral distance in Hupé et al. (1999)]. The *Z* distance is the distance from the tip of the microelectrodes to the plane of the tips of the micropipettes. Minus means below (i.e., in the superficial layers of V2 once the device is well positioned). Microelectrode tips E1 and E3 are indicated by the *arrows 1* and *2*, respectively, in *C*. The light gray disks around the micropipettes represent the calculated inactivation zones following an injection of 50 nl of 100 mM GABA (see Hupé et al. 1999, Fig. 9) at, respectively, the *Z* position of about 0 or 700 μm (i.e., for a lateral distance of about 500 μm from the tip of the micropipette), and the *Z* position of about −400 or 1,100 μm (i.e., for a lateral distance of about 350 μm). If the device was optimally positioned in V2, the small disks would therefore represent the regions of inactivation at the very top and bottom borders of V2, and the large disks the mean region of inactivation around the pipettes. The large black disk behind the inactivation disks represents a rather homogeneously inactivated region of 2-mm diam, which is the minimal extent of V2 region that we consider to have fully inactivated. Note also that 50 nl of GABA is not a priori sufficient to inactivate the neurons recorded by the microelectrode E3, which is 675 μm above the tip of the pipettes. As during the experiment we injected GABA until these neurons were inactivated (see Fig. 2), we are confident that our inactivations were always larger than those represented here.

protruding in the middle of the pipettes (*arrow 1*), and one microelectrode whose tip is behind the other tips (*arrow 2*). We had shown previously that, when injected in the cortex, GABA goes up along the pipettes while diffusing, resulting in ellipsoid inactivation zones centered well above the tip of the pipettes (Hupé et al. 1999). We therefore wanted to place the tips of the micropipettes in the upper third of V2 (i.e., in layer 3), so we could inactivate both the superficial and the deep layers of V2, which both send feedback connections to V1 (Barone et al. 1995; Kennedy and Bullier 1985). The location of the microelectrodes allowed us to check during the whole experiments that the micropipettes were still in about the same position. These microelectrodes allowed us also to check that GABA properly inactivated both superficial and deep layers. The minimal extent of V2 region that we consider to have fully inactivated is 2 mm wide (large black disk on Fig. 1*D*). According to calculations based on the published sizes of V2 RFs as a function of their eccentricity and on the V2 magnification factor (Gattass et al. 1981), the ARF of a 2-mm-wide V2 region at 2.5° eccentricity should be about 3.5°: this value fits quite well our own mappings made in situ and shown in Fig. 1*B*.

V2 inactivation was carried out by means of successive injection of 25 or 50 nl of GABA 100 or 200 mM simultaneously in the six pipettes (Hupé et al. 1999). Recording of V1 neurons started about 30 s after the first injection, to ensure that V2 was well inactivated when we started to test the effect of feedback inactivation. These injections produced a complete inactivation of a V2 region 2–4 mm diam during the whole period of test (3.5 min) as predicted by our preliminary experiments (Hupé et al. 1999) and as verified by the microelectrodes placed at the periphery of the inactivated region (Fig. 2).

GABA (100 or 200 mM) was dissolved in a solution of artificial cerebrospinal fluid (ACSF; in mM: 150 NaCl, 10 Glc, 1.2 NaH_2PO_4, 3 Kcl, 1.25 $CaCl_2$, and 1 $MgSO_4$, pH 7.2). The GABA solution was pumped by a Harvard PHD 2000 programmable pump that acted on six gas-tight 7110 Hamilton syringes (10 μl), connected to the glass capillaries of the device (A-M systems, 0.4 mm ID) with FEP tubing (CMA/Microdialysis) and corresponding tubing adaptors. The whole system was filled with the GABA solution and was free of bubbles. The device was positioned in V2 by gently lowering it through V1 and

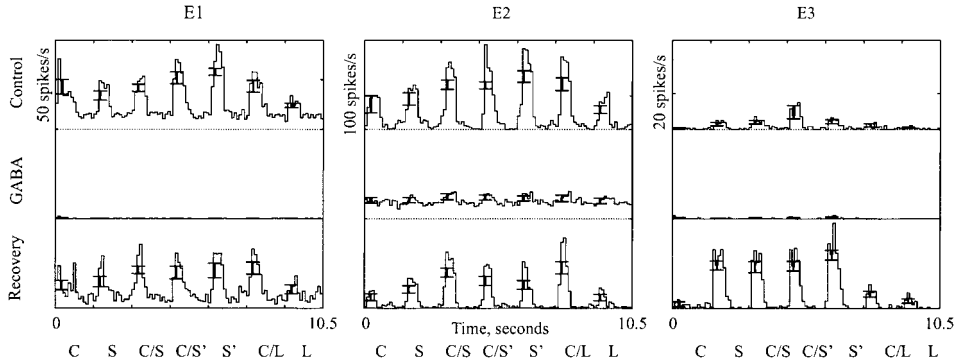

FIG. 2. Example of inactivation of V2. Multi-unit activity recordings of the V2 neurons were obtained with the 3 microelectrodes E1, E2, and E3 of the inactivation device plotted on Fig. 1*D*, while the V1 neuron PBL11 was tested (see Fig. 3, *bottom peristimulus time histograms (PSTHs);* see Fig. 1*B* for the plots of the RF of V1 and V2 neurons). The device was already for 30 h in V2 when this recording was carried out. Four successive injections of 25 nl, 100 mM GABA in each micropipette were achieved, so the total volume of 100 mM GABA injected in V2 was 600 nl. The recording started after the second injection. Note the complete disappearance of neural activity on E3, which is the furthest away from the micropipettes. Some residual activity can be observed on E2; but the evoked activity is negligible compared with what was recorded during the control, and what looks like spontaneous activity was in fact just electronic noise due to the communication between the computer and the Harvard pump connected to the micropipettes, as could be checked off-line. Such electrical artifacts could never affect the recordings of V1 neurons, as they were always rejected by the spike sorting device (MSD). The GABA recording was done 9 min after the control recording and the recovery recording 40 min after the GABA recording. Twenty repetitions of the sequence were carried out in each condition (recording time = 3 min, 30 s). Bin width = 100 ms. One SE is plotted below and above the mean response obtained during the 500 ms of stimulus presentation for each stimulus.

the white matter, avoiding surface blood vessels and continuously recording spike activity and ejecting GABA solution through the micropipettes to prevent intrusion of cortical material in the micropipettes and possible clogging. Volumes of GABA solution were injected according to computer-controlled protocols (Symphony software) with a precision of 2 nl.

Analysis of effects of V2 inactivation on the ON response strength

Spikes were counted between 5 ms before and 495 ms after response onset. The method of latency measurement is described in the accompanying paper (Hupé et al. 2001). The same latency was used for all the stimuli and was the minimum one measured for the stimuli C, C/S, C/S′, and C/l. Note that the minimum latency was usually that of the response to the optimal stimulus, which was the stimulus C in most of the cases. The mean spontaneous activity recorded during each run was then subtracted.

We first compared for each stimulus the response strengths between two control runs of 20 stimulus repetitions each (Hupé et al. 1998); if the test was significant, the response of the neuron to this stimulus was discarded, and the response was considered as not stationary. Sixty-six neurons were kept after this first stage of analysis. Two of these neurons were not stationary for the stimulus C, but were stationary for the stimuli C/S and C/S′; two other neurons were not stationary only for the stimuli C/S or C/S′; 64 neurons were therefore included for the analysis of the effects of V2 inactivation onto the response to the stimulus C, and also 64 neurons were included for the analysis of the orientation-dependent surround modulations, but only 62 neurons were used in both studies. Tests were then done between the control runs and the GABA run.

We used the bootstrap Student *t*-test (Efron and Tibshirani 1993) with 10,000 bootstrap replications. As four responses to different stimuli were studied simultaneously, there was an increase of the type I error. The actual error was controlled with a procedure adapted from Manly (1997): instead of applying the same set of randomizations to the data, we applied the same set of bootstrap replications. The significance level was here therefore a controlled 5% type I error (see Hupé et al. 2001).

We also tested the activity of the neurons when surround-only stimuli were presented. The comparisons of such "responses" could be statistically tricky, as most often there were only a few spikes, and the "response" was irregular. The response histograms therefore not only differed usually from the Normal distribution, but were also asymmetric with a lot of zero values. We thus used the Randomization test (Manly 1997) instead of the bootstrap *t*-test if proportions of 0 values was larger than 2/3. The logic was then not to compare the means any more, but to ask the following question: is the number of times (that there are spikes when the stimulus is present) different in control and when V2 is inactivated? The three surround-only stimuli were compared simultaneously with the usual procedure for multiple comparisons (Manly 1997).

Response categories

Cells were classified after the criteria of Nothdurft et al. (1999), which were adapted from Knierim and van Essen (1992). We were interested in two properties of the surround: the orientation and the spatial distribution of the bars. We computed two nonorthogonal sets of criteria. The labels for these two sets (1st orientation, then spatial configuration) are indicated after the name of the neuron within each box of Fig. 3.

SURROUND ORIENTATION COMPARISON SET (STIMULI C, C/S, AND C/S′).

NM: Not Modulated cells. The mean responses to the stimuli C, C/S, and C/S′ were not statistically different (1st 2 neurons of Fig. 3).

GS: General Suppression. C/S < C and C/S′ < C (3rd and 4th neurons of Fig. 3).

S: Suppression. C/S < C or C/S′ < C, but not GS.

OC: Orientation Contrast. C/S′ > C/S (5th neuron of Fig. 3).

UF: Uniform Field. C/S > C/S′ (last neuron of Fig. 3).

F: Facilitation (Enhancement). C/S > C or C/S′ > C (last neuron of Fig. 3).

All these categories are not mutually exclusive, and some neurons were therefore classified in two categories: for example the last neuron of Fig. 3 was a "UF" and a "F" neuron.

SURROUND SPATIAL CONFIGURATION COMPARISON SET (STIMULI C, C/S, AND C/L).

E-S: "End-Stopped." C/l < C. We used this term by analogy with the property of end-zone inhibition, even if we did not have the means

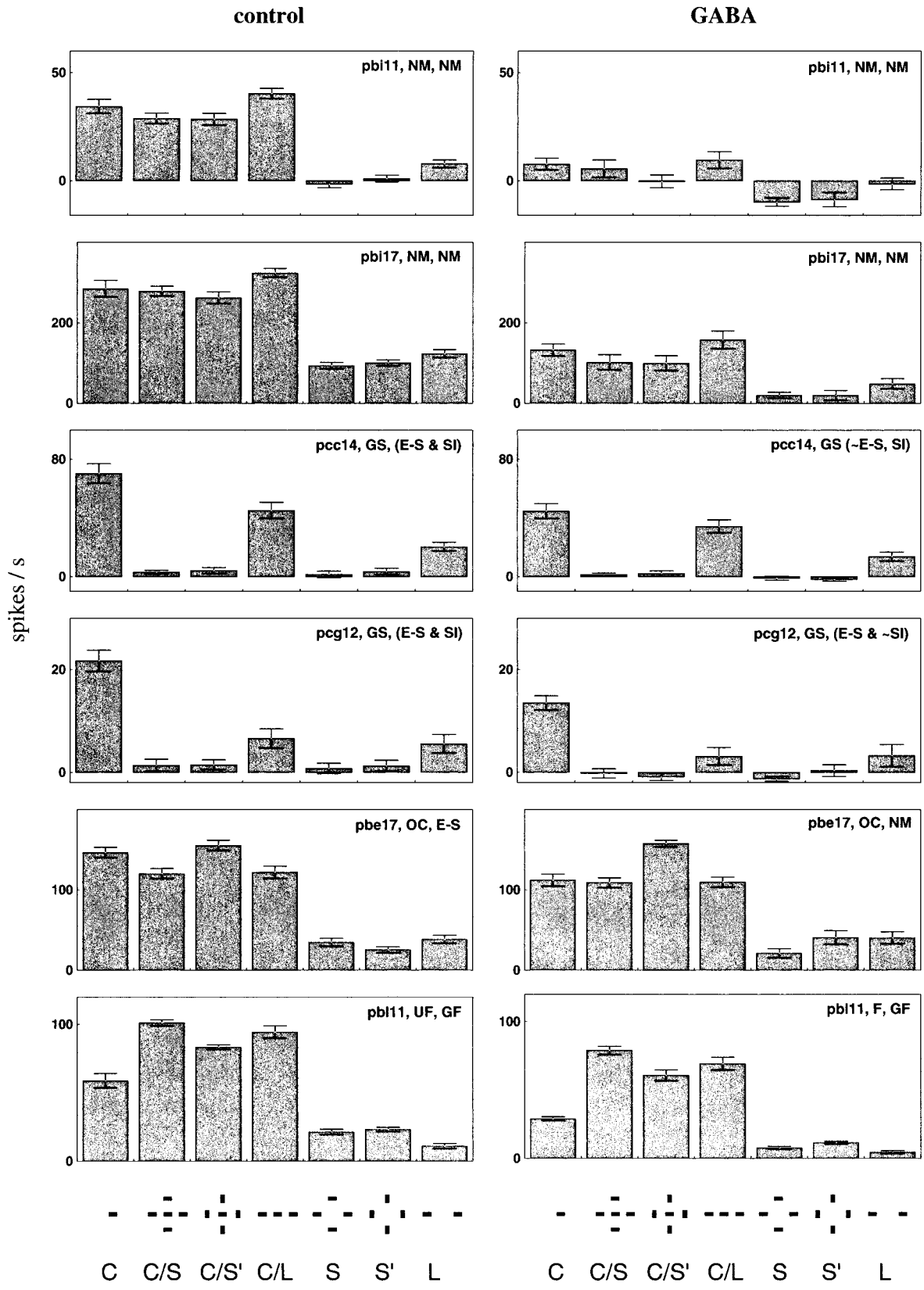

FIG. 3. Mean responses ±1 SE to the 7 stimuli depicted at the *bottom* of the figure for the 6 neurons for which the response to the single bar (stimulus C) significantly decreased during GABA. *Left*: responses during control. *Right*: responses during V2 inactivation (GABA). The responses to the center, the 3 center/surround, and then the 3 surround only stimuli are shown. The neurons were classified as a function of their differential response to the 4 1st stimuli (see METHODS). In each box, we printed the name of the neuron, then the class they belong to for the surround orientation comparison set (comparisons of the responses to the 3 1st stimuli), and then for the spatial configuration comparison set (response to the stimuli C, C/S, and C/l).

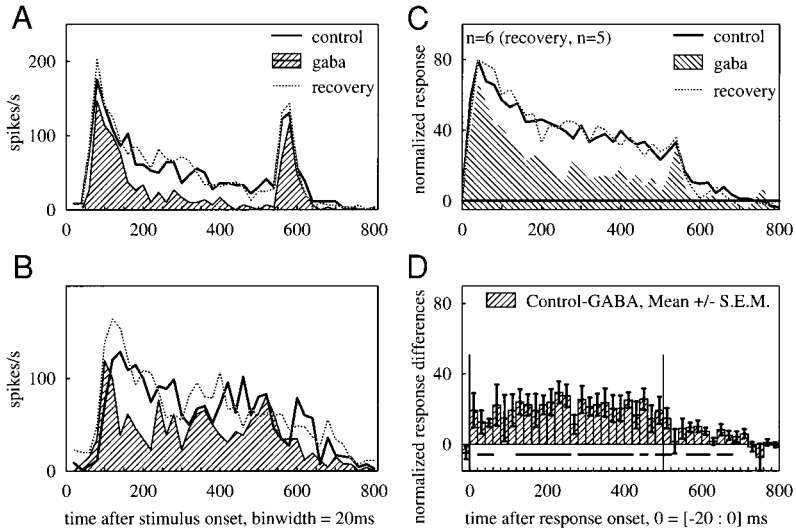

FIG. 4. Time course of the effects of V2 inactivation on V1 neurons. Bin width = 20 ms. *A*: example of a significant decrease of response (−51%, $P = 0.003$) observed on a neuron with an early response (latency = 46 ms). Case pbl11, single unit. *B*: example of a significantly decreased response (−37%, $P = 0.022$), observed on a neuron with a late response (latency = 82 ms). Case pcc14, multi-unit. *C*: the responses of the 6 neurons for which the ON response was significantly decreased by V2 inactivation were pooled. The recovery was recorded for only 5 neurons. Note that control and recovery traces are almost perfectly superimposed. There is no change of the mean peak OFF response. *D*: measure of the time course of the decrease of response due to V2 inactivation. The 1st significant bin is the 2nd one (20–40 ms after response onset), when tested with the classical (not MCP) Wilcoxon test; 4/6 neurons showed a decrease of response also in the 1st bin (0–20 ms) after response onset. Significant values ($P < 0.05$) could be obtained only when at least 5 neurons showed a decrease in a given bin. This histogram shows the excitatory contributions of feedback connections from V2 to the ON responses of V1 neurons.

to know whether these cells were really "end-stopped"[1] (3rd, 4th, and 5th neurons of Fig. 3).

SI: Side Inhibition. C/l > C/S. The response was significantly suppressed by the flanks (or sides) of the surround (Bishop et al. 1973), and not only by the end-zones (3rd neuron of Fig. 3).

NM: The neurons that were classified neither E-S nor SI.

Our statistical criteria were more conservative than those described in other published studies, which used a confidence interval of one SE. The SE corresponds to an error level of 5% only when the distribution of the population is Normal and the number of measures is large enough. For small samples [e.g., around 10, which was the maximum number of measures done by Knierim and van Essen (1992); Nothdurft et al. (1999) made 10–20 measures], Student tables have to be used. Moreover, we observed that the distributions of the responses were frequently far away from the Normal distribution; in these cases, a criterion of one SE does not mean anything. In addition, the SE does not compensate for the increase of the type I error when multiple comparisons are done, as is the case in those studies.

For each series of 20 repetitions (*control 1*, *control 2*, and GABA), we made a Kruskal-Wallis nonparametric ANOVA to test the differences of responses between the four stimuli. Then we made post hoc tests, which protect against the experimentwise type I error (Day and Quinn 1989; Ludbrook 1991). Steel's test with Fligner's modification (equivalent to the parametric Dunnett's test) was used to test each center/surround against the center alone condition. The joint-rank stepwise Ryan's test was used to test all the other possible comparisons of pairs. One exception was made for the OC cells, which were classified OC after one planned comparison done between the C/S and C/S′ responses, with the hypothesis that C/S < C/S′ (Conover post hoc test; a 1-way bootstrap Student *t*-test was also carried out; both tests gave always similar significance levels).

Our goal was to be sure that neurons that are grouped together belong to the same category, so it made sense to pool their responses. We therefore looked for a good protection against the type I error. Even if the post hoc tests that we have chosen are among the ones that best protected also against a too large increase of the type II error (compared with Sheffe's test for example), it was, however, true that we lost some power. The reason why we considered the comparison between the stimuli C/S and C/S′ as a planned comparison was that we expected that some neurons respond more to the C/S′. This "Orientation Contrast" property has been presumed to be functionally important and also to depend on feedback connections (Knierim and van Essen 1992; Nothdurft et al. 1999).

[1] We did not measure the response of the neuron to a single bar of increased length.

RESULTS

Effects of V2 inactivation on the ON responses of V1 neurons to a single bar flashed in the center of the RF

The responses of 6 of the 64 neurons decreased significantly during V2 inactivation. No increase was observed. We carefully checked the responses of these six neurons. We discarded the responses of three other neurons for which the change of response was also significant but very close to the 5% level, as we could not exclude definitively that the change might be due to poor stationarity.[2] Note that 3/64 = 4.67% corresponds closely to the proportion of effects one would expect with a 5% error level. We excluded these neurons from this analysis (without deciding whether the effect was real or not) and therefore had 6 neurons whose response was significantly decreased over a population of 61 neurons. The mean responses to the single bar for these neurons are shown on Fig. 3 (*left column* within each box) during control (*left column*) and GABA (*right column*).

The time course of the effects of V2 inactivation on V1 responses is illustrated in Fig. 4. Figure 4, *A* and *B*, shows two examples of significant decreases. The first example was one of the earliest responding neurons in our sample, and the decrease was already significant ($P = 0.011$) when the first 50 ms of response were compared in control and V2 inactivation conditions. The second example was the neuron having the significant decrease that had the longest latency; it showed no change for the first 50 ms of response ($P = 0.92$). This example was the least representative of the sample, as can be concluded from looking at the population histogram in Fig. 4*C*. This histogram was computed the same way as described in the previous paper (Hupé et al. 2001). The decrease of response is present from the beginning of the response. Figure 4*D* shows the histogram of differences of normalized responses, control minus GABA. Significant differences can be observed after the first 20 ms of responses (2nd bin of response). Given our small sample of affected neurons, it made no sense to make multiple

[2] The response changed already between the two controls, not significantly, but with the same trend as the observed change during V2 inactivation. Moreover, the responses did not recover, and it was not possible to decide whether it was due or not to a partial recovery of V2. These three neurons were, however, kept in the analysis of center/surround interactions.

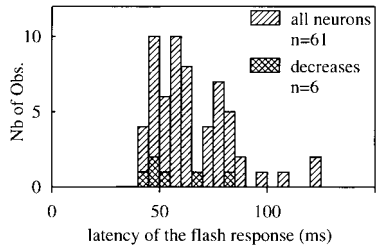

FIG. 5. Histogram of the latencies of the 61 V1 neurons responses to C that were recorded and tested during V2 inactivation. The latencies of the significantly affected neurons are shown. Note that several neurons affected by V2 inactivation have short latencies (both distributions are not statistically different, which can be explained by the small sample of affected neurons).

comparison procedure (MCP) tests (see Hupé et al. 2001). Significant results ($P < 0.05$, 1-way test) of the classical Wilcoxon (exact) tests are symbolized by the black line below the histogram.

Figure 5 presents the histogram of latencies of the V1 neurons. As in the case of the MT inactivation experiment (Hupé et al. 2001), even early responding neurons in V1 could be affected by V2 inactivation.

Effects of V2 inactivation on the responses to the surround-only stimuli

We never observed any significant increase of the response to the three "surround-only" stimuli when V2 was inactivated, contrary to what we had observed in the preliminary experiments (see INTRODUCTION).

Analysis of the effects of V2 inactivation on center/surround interactions

ANALYSIS OF SINGLE NEURONS. We first looked at the responses of the V1 neurons for which the response to the stimulus C decreased during V2 inactivation (Fig. 3). The responses of these neurons to the center/surround stimuli also decreased, so the differences of response for the different stimuli, when present during control, were generally also present during GABA. We wanted to know whether these neurons share any common feature, especially with regard to the surround modulations. This was not the case because the neurons were homogeneously distributed in the different classes (Fig. 3, *left boxes*). All of these neurons were classified similarly for the orientation modulations during control and GABA (Fig. 3, *right boxes*), with the exception of one neuron that was UF (and F) during control and only F during GABA (note, however, that the classification test is less powerful in the GABA condition as there are less spikes). The modulations dependent on the spatial configurations seemed to be less stable: two neurons were not E-S any more, and one was not SI any more. However, it was not obvious when looking at the responses that there were major changes in these modulations.

We then looked for significant effects of V2 inactivation on the response to center/surround stimuli (C/S, C/S′, and C/l). These effects were rare and rarely independent of the effect on the center-alone condition (not shown). The stimulus C condition was in fact the one for which we observed most often significant effects. However, this does not mean that there was no effect of V2 inactivation on the center/surround interactions, as the proper way of studying center/surround interactions is to compare simultaneously the changes of responses to the different stimuli: changes in the interactions could be present, whereas the response to each stimulus was not significantly affected. This happens when there is a modest increase of the response for one stimulus, and a modest decrease of the response for another stimulus. The interaction between the stimulus and the inactivation of V2 were thus studied for each neuron. Seventy neurons were studied with center/surround stimuli while V2 was inactivated with GABA injections. As we wanted to observe the possible effects of GABA on the interactions of response between all the stimuli, we did not reject at this stage of the analysis the responses that were significantly different between two controls for one of the stimuli. We looked at the interactions between the responses to the four center/surround stimuli and the effect of the treatment (control/GABA) with a (parametric) two-way ANOVA for each neuron. We also checked whether significant interactions were found when we did the test between the first and the second control. As long as only the global result of such an ANOVA matters, and not the post hoc comparisons, this test is robust even when the distributions are not Normal and the variances not always similar. For detailed comparisons, we had to use nonparametric tests (see METHODS).

Ten neurons had been tested with only one control, and had no interaction effect [$F(3,x)$, $P > 0.05$]. Sixty neurons were tested first with a two-way ANOVA between the four stimulus conditions and the three runs (2 controls and 1 GABA). If the interaction was significant, these neurons were also tested with two other two-way ANOVAs, between the two controls, and between the mean control and the GABA. Fifty-five neurons had no significant interaction [$F(6,x)$, $P > 0.05$]. Five neurons had an interaction effect [$F(6,x)$, $P < 0.05$]; two of them had a significant interaction effect between the two controls, two between the average control responses and the responses during V2 inactivation, and one was significant for both tests. In conclusion, if one just addresses the question of the effect of V2 inactivation onto the surround modulations in V1, $3/70 = 4.3\%$ neurons were significantly affected, given a type I error of 5%. This proportion of observed effects matches very well the expected 5% error level. About the same proportion of effects was observed when the test was done between the two controls: $3/60 = 5\%$ of the neurons showed a significant P value, whereas nothing had been changed between these two conditions (false-positive cases). One can conclude therefore that these effects of V2 inactivation might be due to chance.

However, this analysis could have missed some influences of V2 inactivation too small to reach the significance level in individual neurons, but that could appear at the level of the population. In addition, the analysis averaged the whole response during 500 ms and could therefore have missed effects in the temporal domain. We therefore carried out a population analysis to increase the signal/noise ratio.

POPULATION ANALYSIS. To pool together the responses of different neurons, we first had to identify subpopulations of neurons homogenous for the type of surround modulations (see METHODS). The breakdown of the population (64 neurons) in the different classes of the surround orientation comparison set is presented in the pie-chart of Fig. 6. Our proportions of GS (33%), OC (19%), and UF cells (6%) are smaller than those described by Nothdurft et al. (1999), as expected given the fact

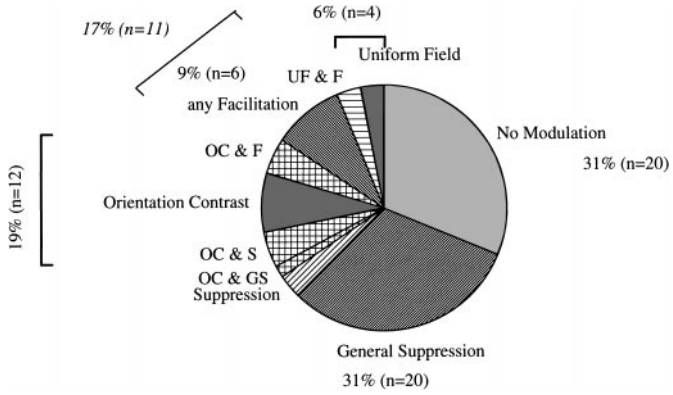

FIG. 6. Breakdown of the 64 neurons sample into 5 main classes and 5 mixed classes. See METHODS for the description of the classification criteria.

that our criteria are more conservative. The differences between their and our proportions were, however, not statistically significant.[3]

We were particularly interested in three kinds of modulations: surround suppression, orientation contrast enhancement, and side inhibition.

General suppression. Twenty-one neurons were classified GS on the basis of their response to the control stimuli. All of them were still classified "GS" on the basis of their responses to the stimuli presented while V2 was inactivated.

There was a possibility that GS cells were less suppressed by the surround during GABA. To detect such a trend, we pooled the responses of 22 GS or S cells. We selected the cells that were not OC when tested in the control condition (20/21 GS cells and 2/5 S cells). To give a similar weight to each neuron, irrespective of its response strength, the response was normalized to the response obtained during the presentation of the bar alone (stimulus C). The normalization was always done with reference to the stimulus C in control condition. It is obvious from Fig. 7*A* that there was no change in the strength of the suppression.

Finally, the response could change during a specific period of the spike train. A population PSTH was computed with the same neurons. Normalization was done to the peak response obtained during the flashing of the stimulus C in control condition. The time reference was the onset of the response to C during control (see Hupé et al. 2001). Once again, we could not find any difference between the control condition and the GABA (Fig. 7, *C* and *D*).

Orientation contrast. Twelve neurons were classified OC on the basis of their mean response in control condition. Among these 12 neurons, 8 were still classified OC during the GABA injections. However, the four neurons that were not OC during GABA were also not OC during one of the two controls. In addition, one neuron was OC during GABA but never during controls.

We pooled the responses of the 12 cells that were OC in the control condition and observed that there was no difference between the responses for the control and under GABA (Fig. 8*A*), even when looking at the time course of the modulation (Fig. 8, *C–F*).

The histograms of differences between the responses to the stimuli C/S and C/S′ (Fig. 8, *E* and *F*) show that the response diverged after 40 ms of response. A MCP Wilcoxon test was done on the 20-ms bins between 20 ms before and 200 ms after the response onset (Hupé et al. 2001). The first significant bin was the [40:60]-ms bin ($P < 10^{-3}$) in both the control and the GABA condition.

Side inhibition. Seventeen neurons were classified SI on the basis of their mean response in control condition, and only seven in the GABA condition. However, almost no effect could be observed on the mean population response nor on the time course of the response, even when we took only the 10 neurons that were not SI anymore during GABA (not shown). Our "side inhibition" criterion could, however, have missed interesting properties of V1 neurons, as it did not distinguish inhibition originating uniformly from the surround from inhibition com-

[3] It should be stressed that it is quite unrealistic to give a precise idea of the percentage of neurons belonging to the different categories. In addition to the fact that neurons can change of modulation type with changes in the parameter of stimulation (Li and Li 1994), it should be stressed that neurons showing the same surround modulations were usually clustered, as it is the case for most neurons properties. The final distribution of neurons between the different categories would at the end depend on the explored territories. The study of several neurons belonging to the same class can just hopefully help us to increase the signal-to-noise ratio, to make more precise conclusions concerning the behavior of single cells.

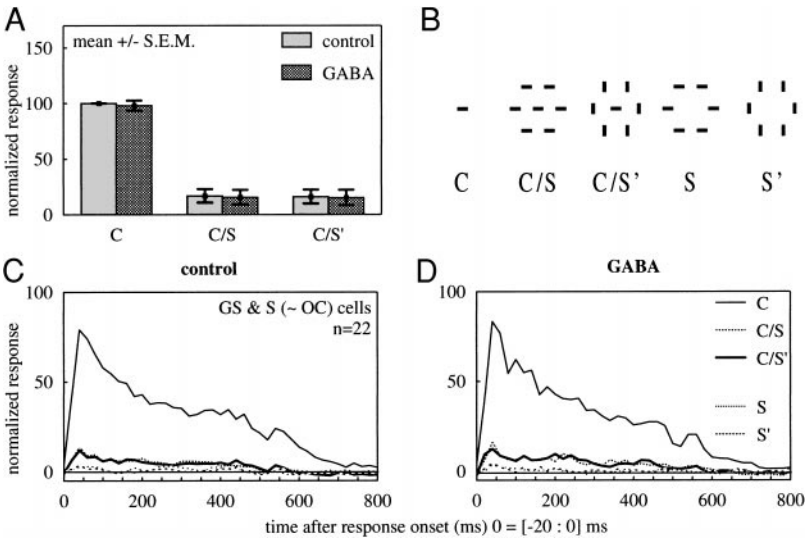

FIG. 7. No effect of V2 inactivation on the surround nonspecific suppression. *A*: normalized population responses. Responses were normalized to each neuron's response to the optimal center bar measured during the control period; these values were then averaged for 22 neurons (20 GS cells and 2 S cells, see text). *B*: stimuli. *C*: time course of the surround modulation. The responses of the 22 neurons were temporally aligned on the onset of response, with a 5-ms precision. Responses in successive bins were then added, to obtained 20-ms binwidth histograms. The amplitude was normalized to the peak response to the stimulus C measured during the control period. The traces are shown for the optimal stimulus, the center/surround stimuli, and the surround-only stimuli (*bottom traces*, here and in all the other plots). Note that the mean suppression is almost complete and present from the 1st bin of response. *D*: same as *B*, but during inactivation of V2 by GABA.

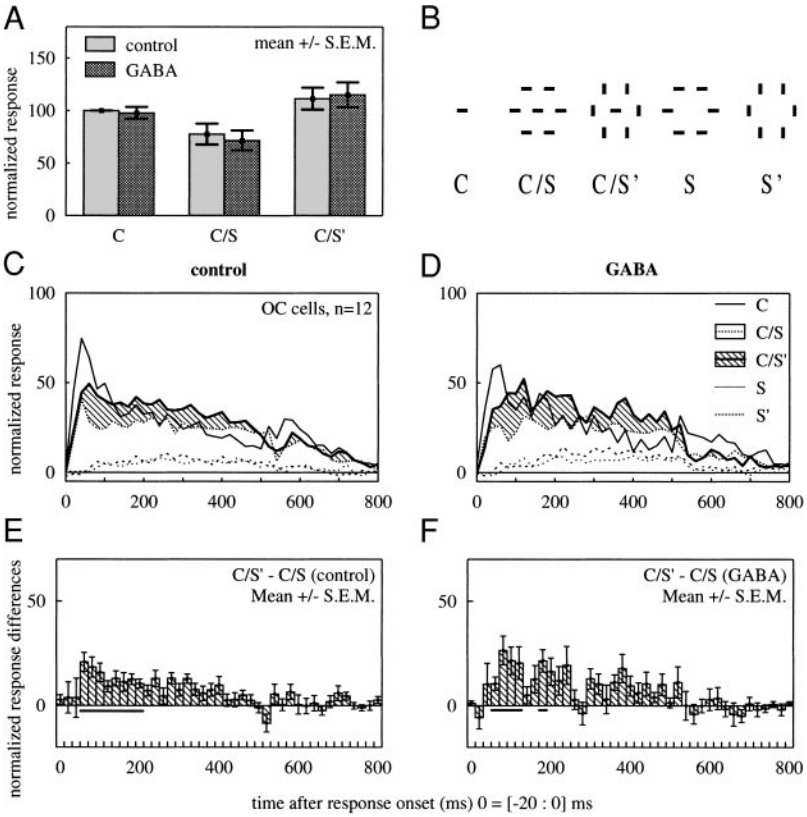

FIG. 8. No effect of V2 inactivation onto the orientation contrast enhancement. Same conventions as in Fig. 7. The responses of 12 OC cells were pooled together for all the stimuli except for the stimulus C, for which the responses of 2 neurons were statistically different during the 2 controls. These responses were rejected after the normalization had been done. The mean response to the stimulus C of only 10 cells is therefore plotted. *A*: normalized population responses. *B*: stimuli. *C* and *D*: time course histograms. *E* and *F*: histograms of differences between the responses to the stimuli C/S and C/S′. The difference of normalized response C/S′-C/S was computed for each neuron, and then computed in a population histogram, for control and then during V2 inactivation. One SE is plotted below and above the mean response, so one can directly read the level of significance of paired *t*-tests done between the responses to both stimuli (assuming a Normal distribution). The bin called "0" is in fact the last bin before response onset (−20 to 0 ms). The horizontal dark bar below the histogram indicates which bins were significant ($P < 0.05$) when a MCP Wilcoxon exact test was done. The first significant bin is the 4th one (40−60 ms after response onset, see text). Only bins up to 200 ms after response onset were tested.

ing specifically from the flanks. In the first case, one could expect that inhibition was additive, and that therefore the response to C/S should be less than the response to C/l. Subcortical mechanisms could explain such a result. On the other hand, if the flanks suppressed significantly the response more than the end-zones, it means that the surround was not spatially homogenous. As lateral geniculate nucleus (LGN) neurons have circular suppressive surrounds, the spatial selec-

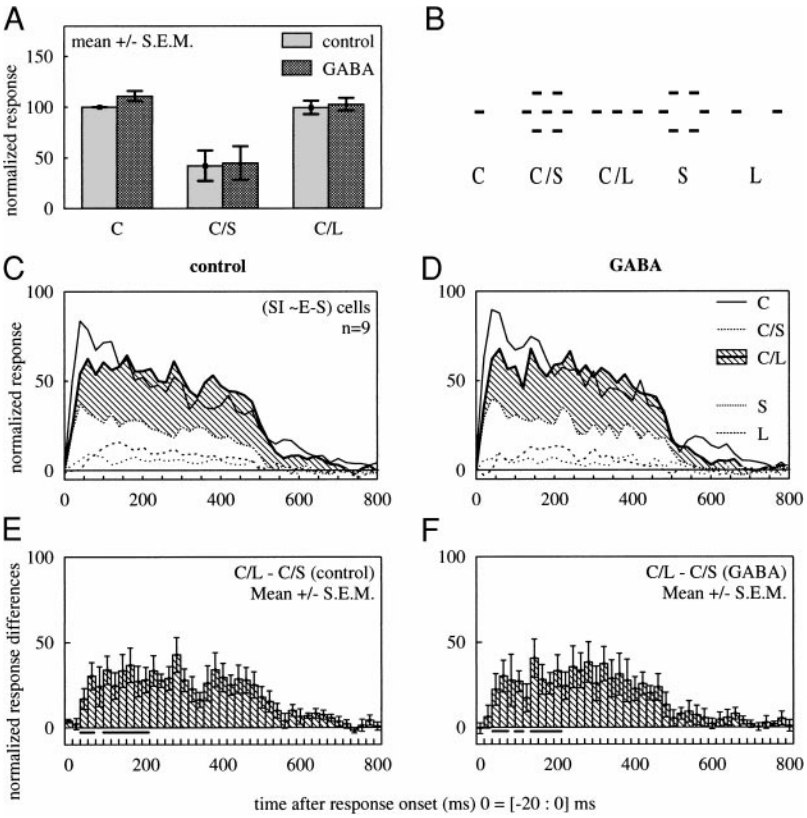

FIG. 9. No effect of V2 inactivation on the modulations that depend on the spatial configuration of the surround. Same conventions as in Fig. 7 and as in Fig. 8*E* for *E* and *F*. See text.

tivity of these V1 neurons might be of cortical origin, similarly to the Orientation Contrast property.

As we did not test neurons with flank-only surrounds, we selected the Side Inhibition neurons that were not E-S (Fig. 9), to target neurons for which inhibition came only from the flanks of the surround. Side inhibition can indeed be independent from end-stopping (Born and Tootell 1991). The flanks of the surround significantly suppressed the responses of nine neurons. None of these nine neurons became E-S, but four were not SI any more during V2 inactivation (2 were also not SI when the tests were done in individual controls).

The population histograms show, however, that there was no effect of V2 inactivation (Fig. 9, *A*, *C*, and *D*). Interestingly enough, the flanks suppression was delayed relative to the onset of the response to C (Fig. 9*C*). The histograms of differences between the responses to the stimuli C/S and C/l (Fig. 9*E*) show that the response diverged after 20 ms of response (MCP Wilcoxon test done on the 20-ms bins between 20 ms before and 200 ms after the response onset; the 1st significant bin was the [20:40]-ms bin, $P = 0.043$). The time course was similar during V2 inactivation (Fig. 9*F*).

Other modulations. No effect of V2 inactivation could be detected when population histograms were computed for each category (Facilitation, Uniform Field, End-Stopping). More detailed observations and figures can be found in the APPENDIX.

It was generally assumed that feedback connections have an influence on the late part of the response (Lamme et al. 1998). As we computed the whole response, for which the early part was the strongest, we could have missed modulations of the late part of the response. Interesting late modulation can appear small compared with the amplitude of the early response (Roelfsema et al. 1998). We therefore computed the late part of the responses, from 100 to 500 ms, and made the classification tests again. We specifically looked at the significant late enhancements of response. Then we selected the neurons for which the early response (0–100 ms) was not modulated by the surround (precisely the early response did not increase more than 5% if it ever increased for the given surround). Thirteen neurons matched these criteria. No effect of V2 inactivation was found on this late modulation (see APPENDIX, Fig. A2, *E* and *F*).

DISCUSSION

Inactivation

It is always difficult to assess the validity of negative results: the conviction that center/surround interactions of V1 neurons do not depend on feedback from V2 depends therefore on the efficiency of our inactivation method.

INACTIVATION OF NEURONS WITH GABA. GABA has been used in numerous studies to inactivate neurons, and we had also made extensive tests of this method (Hupé et al. 1999). The validity of V2 inactivation was also assessed by recording with microelectrodes in V2 that were attached to the injection micropipettes. However, some micropipettes were far away from any microelectrode, and we could not control physiologically the effects of GABA injections in these pipettes (see Fig. 1*D*). Clogging of some of the micropipettes during the experiment might therefore have happened, although the openings of the pipettes were large: 30–35 μm OD, 15–20 μm ID with an additional bevel of 30–40 μm (Hupé et al. 1999). In addition, the setup was designed in order that any clogging during the experiment would be detected rapidly: all junctions from the syringes to the micropipettes were tight, and the type of syringes as well as the way of filling-in the micropipettes with GABA allowed us to be sure that there were no air bubbles in the whole injection line. No compression was possible, and the only way out for GABA was the tip of the micropipettes. We had tested the setup with clogged micropipettes and observed that in this case the tubing adaptor slipped along the needle of the syringe until the tubing disconnected from the syringe. This happened after a few hundreds of nanoliters of GABA injection. This never happened during the three experiments described here; we also checked that there was no visible slipping of any of the tubing adaptors.

INACTIVATION OF THE CONVERGENCE ZONE FROM V2 TO V1. Anatomical studies could give us an idea of the spatial extent of the V2 neurons that project to a given point in V1 (the convergence zone of Salin et al. 1992). Typically, after 0.5- to 1-mm wide injections of Cholera Toxin B in V1, the maximal extent of retrograde label in layers 5/6 was 3–6 mm along the antero-posterior axis (i.e., across the V2 CO stripes), and 7–9 mm along the medio-lateral axis (i.e., along the CO stripes) (A. Angelucci, personal communication).

However, the distribution of cell density is more or less Gaussian, with the maximal number of neurons labeled in the center. For example, after a 1 by 2–3 mm wide injection of Fast blue in V1, the extent of the labeled region in V2 spans more than 4 mm along the dorso-ventral axis (Barone et al. 1995, Fig. 4). As the number of labeled neurons were counted in each histological section (P. Barone and H. Kennedy, personal communication), we could calculate that about 85% of the labeled neurons were included in a diameter of 2 mm, and about 97% in a diameter of 3 mm.

Our inactivation zones in V2 had a minimal diameter of 2 mm for the first two monkeys, and 3 mm for the third monkey, thus encompassing only the region of maximum density of feedback. It is known that GABA does not diffuse more than 500 μm beyond the tips of the pipettes, and that beyond 300 μm the extent of the inactivation zones is rapidly reduced (Hupé et al. 1999). We tried to position the GABA pipettes at a depth corresponding to a distance of about 400–500 μm from the surface of V2 in the lunate sulcus, to inactivate layers 2–3, which contain numerous neurons projecting to V1 (Barone et al. 1995, Fig. 4). One difficulty is that the thickness of V2 is not constant, and that the orientation of the micropipette device was only approximately orthogonal to the V2 layers. We therefore do not know precisely where all of the pipettes tips were positioned with respect to the surface of V2 in the lunate sulcus: the inactivation of the upper layers might therefore have been less homogenous than the inactivation of the deep layers. This is potentially less serious since the convergence zone in the upper layers is smaller than in the deep layers (Barone et al. 1995; Perkel et al. 1986).

Two further arguments are important: first of all, we were not concerned with the total feedback input to a 1-mm-wide region in V1, but only with the input to the V1 neurons that we were recording. We might therefore have overestimated the

size of the V2 region we had to inactivate. Second, we could not be sure that the respective placements of our electrodes in V1 and V2 corresponded to the anatomical labeling. We based these placements on the functional property of overlapping receptive fields of interconnected neurons. Theoretically, the V2 neurons that are at the center of the convergence zone should have RFs overlapping the V1 neuron RF, and we can see in Fig. 1*B* that we were quite successful in this operation. But given the fact that V2 RFs are much larger than V1 RFs, there is a considerable lack of precision: many V2 neurons have RFs overlapping a given V1 RF. We were more precise by additional mappings and by recordings through microelectrodes placed at the periphery of the inactivation device, in order that the V1 RF was in the middle of the V2 RFs (Fig. 1*B*). This way, we could be sure that our inactivation device was placed in the center of the convergence zone of the V2 neurons projecting to the recorded neuron in V1.

In a recent anatomical study of the V2 to V1 feedback connections, the ARF of the region in V2 labeled by an injection in V1 was calculated from measured and published data. It was found that the ARF of the labeled V2 region was about five to six times the size of the ARF of the V1 injection site. For example, for an ARF of a V1 injection site of 1.02°, the ARF of the V2 labeled cells was 5.4° (Angelucci et al. 2000; Lund et al. 1999). We can estimate the ARF of our V2 inactivation site plotted on Fig. 1*B* to be about 2.5° across, whereas the V1 RF was 0.25° across, with the RF being $<$0.25° away from the center of the V2 ARF. In the case of the *monkey Q* (GABA, 200 mM, more spacing between the micropipettes), we even reached an inactivation ARF of more than 3° across along the vertical meridian for a 0.5° across V1 RF. If we think in terms of size of the inactivated visual field, we can therefore conclude that we probably inactivated the whole V2 feedback input to a single V1 neuron.

TOTAL INACTIVATION OF AN INPUT IS NOT A PRIORI NECESSARY FOR OBSERVING FUNCTIONAL EFFECTS OF THE INACTIVATION. Other studies have shown the function of cortical connections by inactivating only a part of them (Alonso et al. 1993; Martinez-Conde et al. 1999; Merabet et al. 1998). This is particularly evident for the studies of intrinsic long-range connections, which have been studied by Crook and co-workers (Crook and Eysel 1992; Crook et al. 1996, 1998) with GABA inactivation, which were at least one order of magnitude smaller than ours. In addition, we had a functional proof of the efficiency of V2 inactivation, as significant decreases on the responses of V1 neurons to a single bar were observed.

V1 WAS NOT INACTIVATED BY GABA. As we observed effects on the V1 responses, this is an important point to address. We are confident on this point because the white matter between V1 and V2 acts as a barrier for GABA diffusion, as directly tested previously (Hupé et al. 1999). Also, we never saw a general decrease of the response in V1 when we reached the deep layers.

Effects of V2 inactivation on the responses of V1 neurons

The responses to the bar flashed in the center of the RF decreased when their feedback input from V2 was inactivated in 10% (6/61) of our sample. This was quite unexpected, as it is usually assumed that the RF properties of V1 neurons are shaped by both their LGN input and intrinsic connections within V1, the debate being rather of the relative weight of the feed-forward and intrinsic influences (Sompolinsky and Shapley 1997). This result is, however, in good agreement with the study of feedback connections from MT: we had found that the responses of V1, V2, and V3 neurons to a single moving bar were affected in 40% of the sample when MT was inactivated (Hupé et al. 1998).

All the effects observed in V1 with V2 inactivation were observed in only two penetrations, and four of them were observed in a single one. It could be argued that the inactivation method was efficient only for these two penetrations, where the proportions of affected neurons were 4/11 and 2/13, i.e., 36 and 18% of the neurons. The first value gives a proportion similar to what had been observed for the V1, V2, and V3 neurons when area MT was thoroughly inactivated (Hupé et al. 1998).

An alternative explanation could be that the role of V2 feedback connections depends crucially on some specific properties of V1 neurons. As neurons that share the same properties are often clustered (DeAngelis et al. 1999; Maffei and Fiorentini 1977; Payne et al. 1981), this would explain why we found effects in some penetrations and not in others. Because we did not analyze all the properties of V1 neurons, we could not really test this hypothesis. We did not find any specificity of the affected neurons concerning the size of the RF or the orientation selectivity. The affected neurons were also distributed in both superficial (3 neurons) and deep layers (3 neurons). This small sample precluded any conclusion concerning the general properties of the V1 neurons affected by V2 inactivation.

Interestingly enough, all the effects consisted in decreases of the responses, confirming the predominantly excitatory influence of feedback connections that we had found when MT was inactivated: 84% of the effects for the bar moving alone were decreases of response (Hupé et al. 1998). This excitatory influence is also in agreement with the results found in the rat (Gonchar and Burkhalter 1999; Johnson and Burkhalter 1996, 1997; Shao and Burkhalter 1996). These findings contradict the results of Sandell and Schiller (1982), who found increases as well as decreases of V1 responses when they inactivated area V2 of the squirrel monkey. This discrepancy can be either due to the species that they used, or to the lack of control of their inactivation method, as they did not check whether some V1 cells were not directly inactivated by cooling, as already noted by Salin and Bullier (1995), or even to different statistical techniques.

Even if we did not study whether the effects of V2 inactivation depended on the parameters of the center bar (we did not measure orientation curves during GABA injections, for example), it seems, however, that the excitatory influence from V2 is rather nonspecific, as when the response to the bar was decreased, similar decreases of response were observed for the center/surround stimuli, or even for the surround-only stimuli in the cases where it was present (see the 2nd and 6th examples of Fig. 3). The response gain of some V1 neurons could therefore be controlled by the feedback from V2.

In the preceding paper we showed that the effects of feedback connections onto V1–V3 are extremely rapid. However,

this may be related to the fact that MT neurons are activated early after visual stimulation, possibly by connections bypassing area V1 (see DISCUSSION of the preceding paper). It was therefore interesting to study another model of feedback for which there is no such limitations. Feedback connections from V2 to V1 are interesting because, even if there are some direct connections from the LGN to V2 (Bullier and Kennedy 1983), which therefore bypass V1, this pathway does not seem to be functionally autonomous, as inactivation of V1 leads to a complete silence of V2 neurons (Girard and Bullier 1989; Schiller and Malpeli 1977). Second, V2 neuron responses lag V1 responses by about 10 ms (Nowak et al. 1995), and most sharp cross-correlogram peaks are displaced from the origin in a direction compatible with a drive from V1 to V2 (Nowak et al. 1999; Roe and Ts'o 1999). We therefore expected that feedback influences from V2 to V1 would be delayed, as is usually assumed for feedback connections in general (Knierim and van Essen 1992; Lamme et al. 1998). Contrary to our hypothesis, but similarly to the result of the inactivation of feedback connections from MT, there was no visible delay of the effects of V2 inactivation on the responses of V1 neurons. The decrease of response when the feedback input was removed was visible in the first 20-ms bin of response and significant after 20 ms. Early effects were observed in neurons with short latencies as in the experiment with MT inactivation (Hupé et al. 2001). In another sample recorded in preliminary experiments described earlier (Bullier et al. 1996), we also found decreases of the response to stimulation of the RF center when V2 was inactivated. These decreases were also observed most often at the onset of the response (see Fig. 1 of Bullier et al. 1996).

Given the fact that the latencies of the responses of V2 neurons lag V1 latencies by about 10 ms, it was quite surprising that influences of feedback connections could be observed within the same order of temporal magnitude. Note, however, that the conduction times between V1 and V2 can be very short (about 1 ms: Girard et al. 2000), and that a delay of up to about 15 ms for one fast V1-V2-V1 loop could go undetected given our temporal resolution.

The rapid feedback effects on V1 neurons after V2 inactivation suggests that what we observed in the case of MT inactivation (Hupé et al. 2001) was not due to the specific temporal properties of this area but that it is a general property of feedback connections that usually act on the entire temporal extent of the response. This makes sense if we recall that the initial part of the response of a neuron carries 70% of the information (Heller et al. 1995; Tovee et al. 1993). Acting on the initial part of the response is therefore essential if feedback connections play a role in the processing of visual information by the cortex.

Absence of effects of V2 inactivation on the center/surround interactions in V1 neurons

Contrary to what we expected, we could not detect any modification of the center/surround interactions in V1 neurons when V2 was inactivated. Even if we were not sure of inactivating the whole convergence zone of V2 to V1, the proportion of the inactivated region was sufficiently large that we could expect to see at least some change in the responses to the center/surround stimuli. The effects on the center response were conclusive in that respect. The fact that these neurons kept their surround modulations whereas their general level of activity changed (Fig. 3) is a strong argument in favor of mechanisms responsible for the center/surround modulations that do not depend on the V2 feedback. Moreover, we tested numerous V1 neurons located in the tracks where effects had been observed on the center response, the V2 inactivation being done then exactly in the same conditions, and the overlap of the RF being also identical, and no effect was observed on the center/surround interactions.

Comparison with previous studies

In previous experiments made on four other monkeys, we had recorded more than 100 neurons. We used three micropipettes of GABA 100 mM, creating inactivation zones larger than those reported in other studies where a single micropipette was often used (Alonso et al. 1993; Crook et al. 1998; Martinez-Conde et al. 1999; Merabet et al. 1998). Even if we know that inactivation of such a size could not a priori inactivate all the V2 neurons of a convergent zone, it is likely that at least in some of these experiments we inactivated a great part of the V2 feedback input of the V1 tested neurons. In these experiments also, we never saw any specific change of the center/surround modulations. As mentioned above, we had observed in a few cases decreases of the response for the bar flashed in isolation in the center of the RF (Bullier et al. 1996), and we reproduced this result in the present experiments.

On the contrary, we were not able to replicate in the present experiments our earlier finding of increases to responses of surround-only stimuli (Bullier et al. 1996). This can be verified on the population histograms presented in RESULTS, where the responses to the surround only stimuli are always plotted. Even neurons that gave a little response to these surround-only stimuli showed no increase of response. A possible explanation for the discrepancy of the results of both studies could be that the surround-only effects would have been precisely due to a partial inactivation of V2 (leading to an asymmetry of the feedback influences). A more likely explanation is that the surround-only effects reported earlier could have been due to an increase of the size of the RF concomitant to a change of the EEG state.[4]

We have several arguments in favor of this explanation. First

[4] The fact that a perfect recovery of the initial response occurred in some instances, which we presented (Hupé et al. 1997) and published (Bullier et al. 1996; Payne et al. 1996), seemed to reach the limits of the probability: it appears unlikely that the change in EEG occurred precisely during the period of V2 inactivation and not during other periods. However, responses to stimuli activating only the surround were not observed to change during the control period because such cases were rejected from our sample because of poor stationarity or because we judged that the stimulus was too close to the RF center. Concerning the recovery period, we were not surprised by responses during recovery that differed from the control or the GABA period because we knew from earlier experiments that the total recoveries of all the neurons after GABA injections could take up to 1 h (Hupé et al. 1999), and rebounds of activity in V2 could a priori produce strange effects. Thus we did not test for the presence of changes in response to surround-only stimuli either between the controls or between the GABA and recovery runs and we analyzed *only* the changes that occurred during the V2 inactivation. Such changes could have occurred a lot more frequently, explaining that sometimes we could observe them during the V2 inactivation period.

of all, when looking back at some neurons whose response had been only recorded in control condition but not subjected to a test of V2 inactivation because of poor stationarity, we could observe indeed that a response to the surround-only stimulus was present in one of the two controls. Second, we measured the EEG activity of the three monkeys for which the results have been presented here, and we did observe large increases of surround-only responses in control runs, increases that were correlated to increases of synchronization of the EEG, in perfect agreement with the results of Wörgötter et al. (1998). Even if we cannot rule out that our previously observed effects of V2 inactivation could have some link with the role of feedback connection (different causes being able to produce similar effects), it is, however, more likely that they were due to changes in the general EEG state.

In our last three experiments, not only could we better assess the level of anesthesia by on-line checking of the EEG, but also all the recordings were checked off-line. When a change in the EEG power could be observed between controls and GABA, the neuron was rejected for further analysis. The 70 neurons kept for analysis and presented in this paper were all the neurons that successfully passed this initial step.

Neurophysiological basis of center/surround interactions

CENTER/SURROUND INTERACTIONS WITH STIMULI MADE OF BARS OF DIFFERENT ORIENTATION OR DISPOSITION. The effect of the surround most often observed in control condition was a strong suppression of the response irrespective of the orientation and spatial parameters, agreeing with what has been observed in other studies made on the macaque monkey (Knierim and van Essen 1992; Nothdurft et al. 1999). As noted by those authors, the nonspecific suppression arising homogeneously from stimulation of the surround is a general property of neurons found at all levels of the visual system, starting with retinal ganglion cells. General suppression might therefore be transmitted and amplified from low to higher levels through feed-forward projections. This hypothesis is supported by the observation that general suppression is always observed from the beginning of the response (Fig. 7) (see also Knierim and van Essen 1992; Li et al. 2000; Nothdurft et al. 1999), and that the near surround is the most powerful region to inhibit the responses to stimulation of the RF center (Born and Tootell 1991; Li et al. 2000; Nothdurft et al. 1999).

The modulations that depend on the orientation of the surround or on the spatial distributions of the bars are of particular interest as these properties must emerge at the level of V1, where orientation selectivity is first observed. Orientation selectivity and tuning are thought to depend, at least in part, on V1 long-range intrinsic connections (Crook and Eysel 1992; Crook et al. 1998). Accordingly, orientation-dependent surround modulations in the LGN of the cat seem to depend on the feedback from V1 (Sillito et al. 1993). The generation of end-inhibition in the cat primary visual cortex superficial layers might depend also on interlaminar connections from the deep layers (Bolz and Gilbert 1986; but see Grieve and Sillito 1991).

We studied two classes of neurons that showed surround properties elaborated at the cortical level: Orientation Contrast neurons (OC) and Side Inhibition (SI) neurons (more precisely SI neurons that were not E-S, see RESULTS). These specific modulations presented a significant delay respective to the response onset. Thus we observed that the C/S and C/S′ curves differentiated after some delay (Fig. 8*C*). The difference was statistically significant after 40 ms of response (Fig. 8*E*). A similar but shorter delay for the orientation-selective surround modulation had already been observed by Knierim and van Essen (1992) and Nothdurft et al. (1999), who found a difference 15–20 ms after the response onset. However, the resolution of those measurements was limited because the responses of the different neurons were simply added, irrespective to their latency of response, thus smearing the timing of the effect across the population. Their results poorly reflect what happens at the level of single cells: only one example was shown (the Fig. 7 of Nothdurft et al. 1999), and one can see that the traces of the C/S and C/S′ responses appear to differentiate after 30 ms of response (no statistical criterion was given), in very good agreement with our data.

A 20-ms delayed modulation was also demonstrated in our results for the SI property (Fig. 9*E*), which deals with the classically described side inhibition (Bishop et al. 1973; Born and Tootell 1991). To our knowledge, such a delayed modulation has not yet been reported.

Such delays are in keeping with the hypothesis that these effects are not shaped by feed-forward input. Delayed modulations have often been thought to depend on feedback connections, as it was logical that, for example, the transfer of the information from V1 to V2 and then from V2 to V1 needs some time. Accordingly, the responses in V2 lag by 10 ms the responses in V1 (Nowak et al. 1995). Since V2 is also the area that sends the strongest feedback input to V1, it was the most obvious candidate for shaping the delayed space and orientation-specific center/surround interactions. However, our data do not confirm this role.

The delay could rather correspond to the involvement of V1 long-range lateral connections (Bringuier et al. 1999; Grinvald et al. 1994), as conduction times of these connections seem to be rather slow, in comparison, for example, with the conduction times of feedback connections (Girard et al. 2000). Other data on the influences from outside the receptive field of V1 neurons can also be interpreted in the general framework of the V1 long-range connections (Dragoi and Sur 2000; Gilbert 1992, 1998).

Another possibility is that horizontal and feedback connections are both involved in center/surround interactions in V1: in effect, V1 cells that contribute to the surround modulations receive also feedback connections from V2. Whereas our inactivation zone was large enough to remove most of the V2 feedback (direct) input to the recorded V1 cell, it was not sufficient to inactivate all the feedback connections to the V1 neurons that project to the recorded neuron (indirect input). Center/surround interactions could therefore depend on lateral connections in V1, but these interactions could be modulated by the feedback from V2 on this entire network. However, if V2 feedback exerted a systematic modulation of V1 interactions, then we should have observed at least a slight change in the strength of center/surround interactions when V2 was inactivated, as the whole V1 network had some of its feedback from V2 removed, given the divergence of feedback connections to V1 neurons.

NEAR VERSUS FAR SURROUND INFLUENCES. Our stimuli contained a smaller number of bars (6–36, typically 18) than the stimuli used in previous studies and covered therefore a smaller region of the visual field (typically 3–4°, see METHODS) than in these studies where the entire screen was covered by the stimulus (Knierim and van Essen 1992; Nothdurft et al. 1999). The modulations of the center response are, however, maximal near (<2°) the border of the RF (Born and Tootell 1991; Li et al. 2000; Nothdurft et al. 1999). The amplitude of our modulations was indeed comparable to what was observed by Knierim and van Essen (1992) in the awake monkey and Nothdurft et al. (1999) in the anesthetized monkey.

Levitt and Lund (1997) have studied the spatial extent of the surrounds of monkey V1 neurons by using gratings. They found that the ratio between the diameters of the surround and the Minimum Response Field was on average 5.6. Our stimuli had a similar center/surround ratio and were therefore adequate to stimulate this "near surround." However, Levitt and Lund (1997) also found neurons for which the influences of the surround could extend further away. Whereas the near surround can be accounted by the monosynaptic spread of intrinsic interlaminar or horizontal connections, this is not the case for these far surround modulations (Levitt and Lund 1997). They are therefore more likely to depend on feedback connections. The spatial extent of our stimuli did not allow us to study such far surround influences.

OTHER SURROUND PROPERTIES. Many center/surround properties are present in V1 neurons (Li and Li 1994). It is not impossible that surround modulations other than the ones we have studied depend on feedback from V2. Results from an earlier study (Hupé et al. 1998) suggest that this is likely. We tested the role of feedback connections from MT onto the responses of V1, V2, and V3 neurons. We used moving stimuli of the figure/ground type, so direct comparisons cannot be done with this study. However, the suppressions induced by the moving background are akin to the surround suppression obtained with flashed stimuli. When the neurons were tested at high salience (high luminance bar over a low contrast background) and MT was inactivated by cooling, the background suppression of V1 and V3 neurons were still present and as strong as during the control period (Bullier et al. 2000; Hupé et al. 1998). But when low salience stimuli were used, the strong suppression by the moving background almost disappeared when MT was inactivated (Bullier et al. 2000; Hupé et al. 1998). The results obtained at high salience are comparable to those obtained in the present study: when a background stimulus modulates the response to a high contrast bar, inactivating the feedback connections produces no effect on this modulation. The effects observed at low salience may be specific for the feedback from MT, which is specialized for processing low contrast moving stimuli. This positive result suggests that some center/surround interactions that reflect specific properties of area V2 could be shown to be dependent on the feedback from V2.

ROLE OF FEEDBACK CONNECTIONS FROM V2 TO V1. We conclude that feedback connections from area V2 do not play a role in the center/surround interactions observed in V1 neurons, at least those generated with the present set of stimuli in the near surround and with variable orientation and spatial disposition of distributed bars. This negative result is important, since these interactions have been extensively studied, and since the temporal delay of their involvement had led several authors to suspect the role of feedback connections from V2. The surround orientation contrast property is supposed to play a role in *pop-out* properties, which are supposed to be due to a preattentive treatment of visual information. Such preattentive treatments have been described as *bottom-up* (Wolfe 1994). Our results suggest therefore that feedback connections are not involved in such a bottom-up treatment of information. As mentioned above, it is still possible that some center/surround interactions specific to the properties of V2 neurons will be shown to depend on feedback connections.

APPENDIX

Facilitation

Six neurons were classified F and not OC nor UF. This proportion is greater than the proportion found by Nothdurft et al. (1999), but these neurons presented also a small response to the surrounds presented in isolation, which could explain the response to the C/S and C/S′ condition almost by a linear summation. The timing of the facilitation corresponded to the latency of the surround-only condition (facilitation observed in the 2nd bin of response, 20–40 ms). No effect of V2 inactivation was observed on these neurons (see Fig. A1, *A* and *B*).

Uniform field

Only four neurons were found in this category. It seemed that the orientation-dependent modulation was delayed. There was a strong transient response to the surround-only stimuli, which interestingly enough was not orientation selective, and could not therefore explain the orientation-specific surround modulation by a linear mechanism. Both phasic responses to C/S and C/S′ were even a little smaller than the response to the bar alone (see Fig. A1, *C* and *D*).

Not modulated cells

Twenty neurons showed no statistically significant modulation when tests were done on the whole response. However, it appeared that in the average there was a nonorientation-specific suppression of the early response (see Fig. A2*A*). This suppression seemed to decrease during V2 inactivation (Fig. A2*B*). To address the question of a possible effect on the early modulations of the response, we computed the response over the first 100 ms of response and made the classification again. Over the 20 NM neurons, 6 had a significant early surround suppression (Fig. A2*C*). GABA injections in V2 had, however, no effect on this modulation (Fig. A2*D*).

We also computed the late part of the responses, from 100 to 500 ms, and made the classification tests again. We specifically looked at the significant late enhancements of response. Then we selected the neurons for which the early response (0–100 ms) was not modulated by the surround (precisely the early response did not increase more than 5% if ever it increased for the given surround). Thirteen neurons matched these criteria. No effect of V2 inactivation was found on this late modulation (Fig. A2, *E* and *F*).

End-stopped cells

The modulations of the iso-oriented surround (S) were compared with the modulations originating from the regions aligned with the axis of preferred orientation of the neurons (stimulus L, for "line").

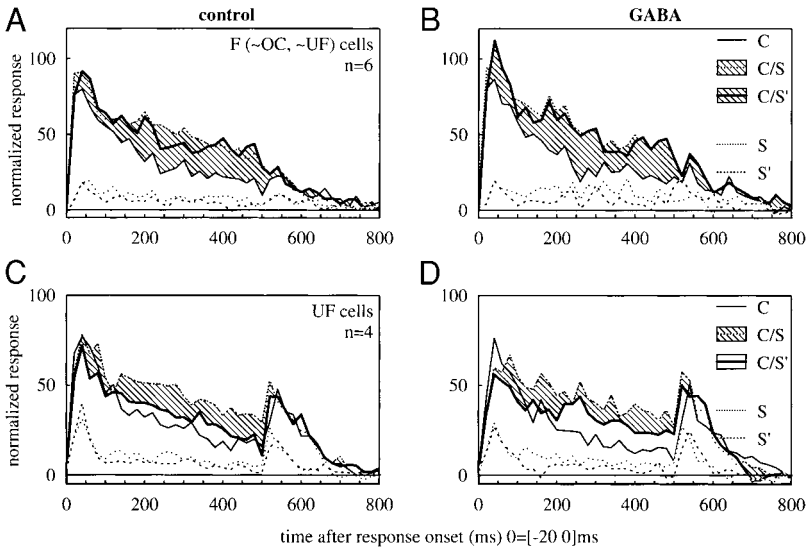

FIG. A1. No effect of V2 inactivation on other surround modulations. See text. Same conventions as in Fig. 7. *A* and *B*: population histograms for the neurons for which the responses to the center/surround stimuli are significantly larger than the response to the center-only stimuli. *C* and *D*: population histogram for the neurons for which the response to C/S is significantly larger than the response to C/S′.

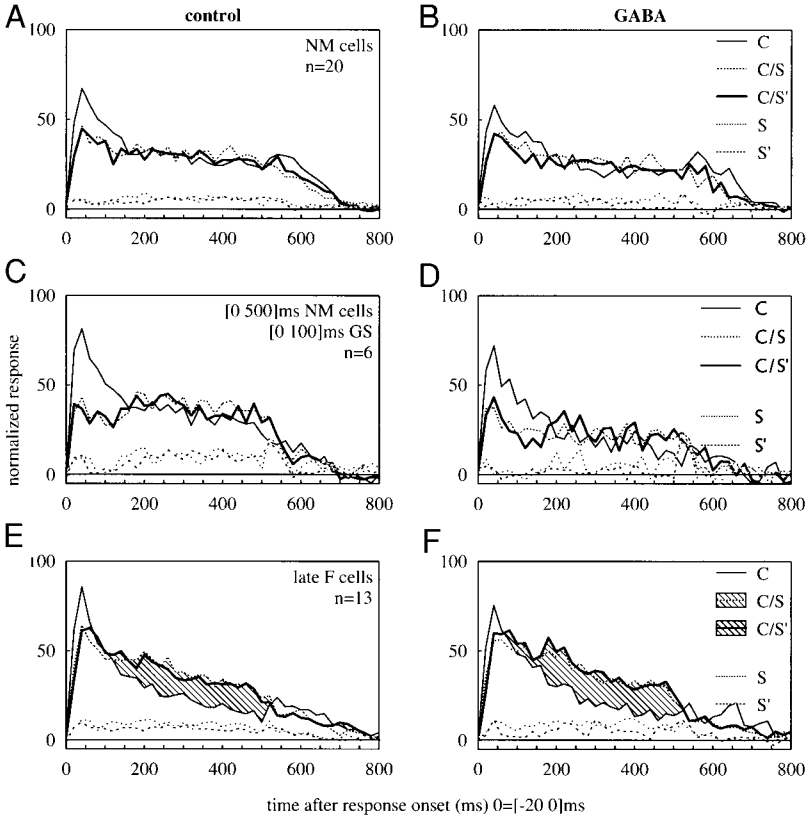

FIG. A2. No effect of V2 inactivation on the neuron responses that are not modulated by the surround. See text. Same conventions as in Fig. 7. *A* and *B*: population histogram for the 20 NM neurons. *C* and *D*: population histogram for NM neurons for which the first 100 ms of response is significantly suppressed by the surround. *E* and *F*: population histogram for the neurons for which only the late part of the response (after 100 ms) increased with the surround stimuli (note: these neurons were not necessarily NM when tested over 500 ms).

For the 15 neurons classified End-Stopped in the control condition, the response to the whole surround C/S was also always significantly suppressed. The suppression originated from the beginning of the response, as for the GS, and there was no effect of V2 inactivation. Ten of 15 neurons were still significantly E-S during V2 inactivation. Among the five neurons not significantly E-S anymore during the GABA injection, only one of them had been significantly E-S for both controls. On the other hand, one neuron was classified E-S only during V2 inactivation. Population PSTHs were simular during the control and when V2 was inactivated (not shown).

To target the neurons for which the suppression originated predominantly from the end-zones of the RF, we selected the neurons for which at least 70% of the total inhibition obtained for C/S was already present with the stimulus C/l, i.e., $C/l < C - 0.7*(C - C/S)$. Seven neurons fulfilled this requirement; the population PSTHs obtained this way were very similar to the previous ones, and no effect of V2 inactivation could be observed (not shown).

Thirty-six neurons were neither E-S nor SI; the population histograms showed superimposed traces for the response to stimuli C and C/l both in control and GABA conditions (not shown).

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