Feedback Connections Act on the Early Part of the Responses in Monkey Visual Cortex

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Hupé, Jean-Michel, Andrew C. James, Pascal Girard, Stephen G. Lomber, Bertram R. Payne, and Jean Bullier. Feedback connections act on the early part of the responses in monkey visual cortex. *J Neurophysiol* 85: 134–145, 2001. We previously showed that feedback connections from MT play a role in figure/ground segmentation. Figure/ground coding has been described at the V1 level in the late part of the neuronal responses to visual stimuli, and it has been suggested that these late modulations depend on feedback connections. In the present work we tested whether it actually takes time for this information to be fed back to lower order areas. We analyzed the extracellular responses of 169 V1, V2, and V3 neurons that we recorded in two anesthetized macaque monkeys. MT was inactivated by cooling. We studied the time course of the responses of the neurons that were significantly affected by the inactivation of MT to see whether the effects were delayed relative to the onset of the response. We first measured the time course of the feedback influences from MT on V1, V2, and V3 neurons tested with moving stimuli. For the large majority of the 51 neurons for which the response decreased, the effect was present from the beginning of the response. In the responses averaged after normalization, the decrease of response was significant in the first 10-ms bin of response. A similar result was found for six neurons for which the response significantly increased when MT was inactivated. We then looked at the time course of the responses to flashed stimuli (95 neurons). We observed 15 significant decreases of response and 14 significant increases. In both populations, the effects were significant within the first 10 ms of response. For some neurons with increased responses we even observed a shorter latency when MT was inactivated. We measured the latency of the response to the flashed stimuli. We found that even the earliest responding neurons were affected early by the feedback from MT. This was true for the response to flashed and to moving stimuli. These results show that feedback connections are recruited very early for the treatment of visual information. It further indicates that the presence or absence of feedback effects cannot be deduced from the time course of the response modulations.

INTRODUCTION

Figure/ground discrimination based on motion cues involves two operations: the integration of points moving at the same velocity and in the same direction, and hence sharing a "common fate" (Wertheimer 1923), and the precise segmentation of the object from its background. Both extracellular recordings (Britten et al. 1992; Newsome et al. 1989) and lesion experiments (Newsome and Paré 1988; Rudolph and Pasternak 1999) highlighted the role of the visual area MT/V5 in the global process. Another lesion experiment showed that the discrimination of shapes based on a kinetically defined boundary (border between 2 random dot fields moving in different directions or at different speeds) was specifically impaired when MT was removed in macaque monkeys (Marcar and Cowey 1992), suggesting that the local process would also depend on MT. However, MT neurons do not code the orientation nor the position of kinetically defined boundaries (Marcar et al. 1995), implying that whereas MT is necessary for indicating the presence of a motion-defined figure and establishing a reliable indication of its direction of motion, it has to send this information to other cortical visual areas where further local processing of the kinetic boundary would be performed. Feedback connections from MT to areas V3, V2, and V1 may be involved, as selectivity for the orientation of kinetically defined boundaries has been observed in V2 (Marcar et al. 1994) and selectivity to motion-defined contours exist in V1 (Lamme 1995). Low-order areas are in fact quite a logical locus for registering (Mumford 1993) the precise position and orientation of kinetically defined contours, as the neurons have small receptive fields and are sensitive to high spatial frequencies, thus coding contours with high resolution. Further evidence comes from psychophysics, as the motion segmentation mechanism shares its speed tuning with that of V1 neurons, whereas that of motion detection mechanisms corresponds to MT neurons (Masson et al. 1999). In a previous study, we indeed showed that figure/ground information based on motion cues is fed back to areas V1, V2, and V3 of the anesthetized macaque monkey (Hupé et al. 1998).

Figure/ground coding has been shown to influence the late part of the neuron responses to visual stimuli in V1 (Lamme et al. 1999; Lee et al. 1998), and it has been suggested that these late modulations could depend on feedback connections (Lamme et al. 1998a,b). Whereas it is well documented at the anatomical level that feed-forward projections are matched by reciprocal feedback connections that have distinctive lamination patterns (Felleman and van Essen 1991), the functional role of these connections has been poorly studied and is not yet really understood (Salin and Bullier 1995). Conspicuously absent from all studies is an analysis of the time course of the feedback influences. Higher order areas contain neurons whose

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responses tend to lag behind those of lower order areas (Nowak and Bullier 1997), so a delay for the involvement of feedback connections would seem logical. In this study, we tested whether it takes time for MT figure/ground information to be fed back to lower order areas. Such a delay would have consequences for the timing of the perception of shapes and contours from motion, and would be consistent with the longer time course for motion segmentation compared with motion discrimination (Masson et al. 1999).

In this paper, we directly address the question of the timing of the influences of feedback connections on the responses of low-order area neurons. We measured the latencies of the effects of MT inactivation on the responses of V1, V2, and V3 neurons to the moving stimuli used in our previous experiment (Hupé et al. 1998), to determine whether motion-based figure/ground segmentation modulates the late part of the responses of neurons in areas V1, V2, and V3. For some neurons, we also measured the latency of the effects of MT inactivation on the responses to flashed stimuli. Indeed, one could argue that responses to moving stimuli are not the appropriate way to examine the timing of feedback influences because a moving bar activates MT neurons with receptive fields larger than that of the recorded neuron, and therefore the influence of the feedback may already be present before the lower order neuron has started to respond as the bar enters its receptive field (RF) center. We compared the time course of the responses of individual neurons to moving and flashed stimuli when MT was active or inactivated, and failed to find any substantial delay for the feedback influences in both cases. At the level of the population, it is important to know the latency of the neurons that are affected by removal of feedback input, as a delayed modulation could either express itself on the late part of the responses of neurons with short latencies, or on the early response of late responding neurons. In the Lamme et al. experiments, the question could not be addressed as large clusters of neurons were recorded simultaneously (Lamme et al. 1999) or the responses of several units with maybe different latencies were pooled together to see the timing of the modulations (Lamme 1995). We measured the latency to flash stimuli and found that feedback connections act on the early part of the response even in the case of neurons with short latencies.

METHODS

Animals and recording procedures

Recordings were obtained from two anesthetized, paralyzed cynomolgus monkeys, which were tested with a series of moving and flash stimuli while area MT was inactivated. Monkeys were initially anesthetized by an intramuscular injection of ketamine hydrochloride (Imalgene, 15 mg/kg). An intravenous catheter was placed in the cephalic vein, and an endotracheal tube was positioned. During surgery, the animals were anesthetized by repeated intravenous injections of 0.1–0.2 ml of alphadolone and alphaxolone (Saffan). During recording, they were paralyzed by a continuous infusion of pancuronium bromide (10 $mg \cdot kg^{-1} \cdot h^{-1}$, in a solution of lactated Ringer and glucose 5%) and artificially ventilated with N_2O/O_2 (70%/30%). Anesthesia and analgesia were supplemented by a continuous infusion of suffentanil (usually 4 $\mu g \cdot kg^{-1} \cdot h^{-1}$). The end-tidal CO_2 level and the heart rate were monitored and maintained at proper levels.

A device sealed to the skull with screws and dental cement held the animal head. The pupils were dilated by corneal application of 1% atropine. Refractive lenses were used to focus the eyes at a distance of 1.14 m from a tangent screen. A craniotomy was performed above area V1, just below the lunate sulcus, whose blue trace could be detected through the skull. Penetrations were made in V1 through the dura matter, to achieve a better stability of single-unit recordings. We used a device made of two microelectrodes glued together (inter-tip distance, 300 μm). Recording microelectrodes were tungsten-in-glass type (Merril and Ainsworth 1972) with typically 10-μm tips, which could provide multi-unit as well as single-unit recording of cortical neurons. 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, MT inactivation, and recovery. Spike activity was recorded with a PC-based system (CED 1401 interface and Spike2 software). Analyses were done on-line, but all the recordings were also stored on videotapes for off-line analysis. All the recordings were replayed to check the identity and the stability of the studied neurons. In addition, isolation index (II) of the spike traces were systematically calculated for each testing period. The isolation index is the ratio of the peak value of the histogram of errors (between the spike template and the recognized spikes) over the value of the histogram at the rejection threshold. It is now implemented in the MSD software.[1] A value of one indicates a perfect isolation; a value of zero indicates multi-unit activity with no possibility of isolation of a single neuron. Examples of the use of the MSD and of the isolation index were published elsewhere (Guenot et al. 1999).

At the end of the experiment, the animals were killed by an overdose of pentobarbital sodium and perfused with normal saline followed by 4% paraformaldehyde in phosphate buffer. The posterior part of the brain was removed and, after cryoprotection in 30% sucrose, cut at 50 μm on a freezing microtome in the parasagittal plane. On histological Nissl-stained sections, penetrations were reconstructed from lesions placed during the recording (typically 7 μA for 7 s).

Feedback inactivation

Area MT and adjacent cortices were inactivated by circulating chilled methanol through chronically implanted hypodermic loops that induce a localized hypothermia and block synaptic function and activity of neurons (Lomber et al. 1999). We implanted the probes in the superior temporal sulcus prior to the experiment (Fig. 1). The method and the controls have been described in detail elsewhere (Hupé et al. 1998; Lomber et al. 1999). Each cooling session lasted less than 5 min. The total number of cooling sessions done over 4 days on each animal was 41 and 57. There was no correlation between the number of cooling cycles and the frequency or the strength of the effects.

Measurement of response latency

We adapted the method of Maunsell and Gibson (1992) and Nowak et al. (1995) to identify the beginning of the responses to the flashed and moving stimuli. Peristimulus time histograms (PSTHs) of responses were computed over 20 repetitions of the stimulus presented in control condition (before MT was inactivated). The binwidth was typically 5 ms, but binwidth values ranging from 2 to 20 ms were also used depending on the response strength. The histogram of the total number of spikes recorded during a spontaneous activity period (background distribution[2]) was fitted with a Poisson function. Then, for

[1] The II value produced by the MSD software is however not reliable when few spikes are recorded, as the binwidth of the histogram can then be too small. We systematically saved the whole error histograms and calculated the real isolation index from a smoothed histogram computed in Matlab.

[2] The spontaneous activity was estimated from the 500 ms periods between the stimulus presentations. This measure was not always very precise, as it could occasionally be contaminated by some late sustained response, or by some rebound from inhibition. It was checked however that this background activity was relevant to measure the onsets of responses to stimuli.

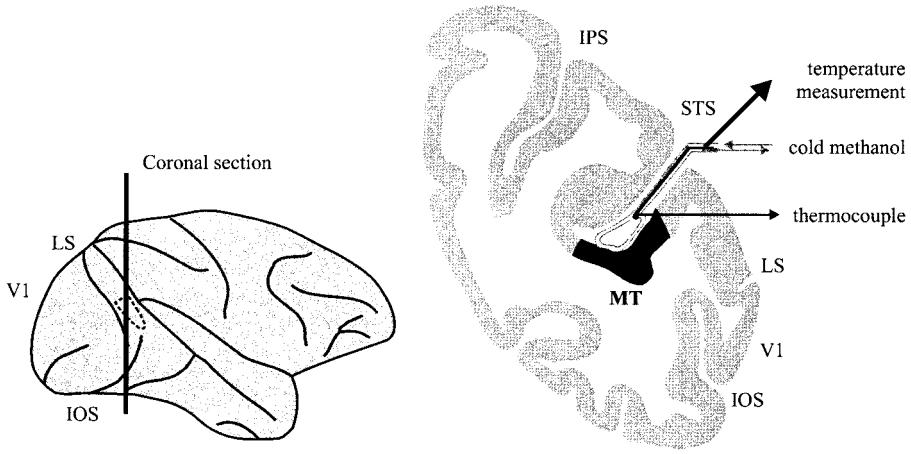

FIG. 1. Schema of a lateral view of the macaque brain (*left*) and of a coronal section (*right*) showing the cooling device placed in the depth of the superior temporal sulcus (STS), against the visual area MT. LS, lunate sulcus; IOS, inferior occipital sulcus; IPS, intraparietal sulcus.

flashed stimuli, the latency was taken to be the time corresponding to the center of the first bin after stimulus onset that *1*) exceeded a level corresponding to a probability of $P = 0.01$ with respect to the background distribution and *2*) was immediately followed by a bin that also reached this criterion and a third that exceeded a level corresponding to a probability of $P = 0.05$ (Maunsell and Gibson 1992). These criteria might appear stringent, and it could be argued that a first weak and transient component of the response, presumably due to feed-forward activation, would have been missed. That is the reason why we systematically used different binwidth sizes and chose the shortest latency, to include any first weak component in the response, as long at it was no more than 20 ms ahead of the sustained response. Also, if any early response component existed, it should have been visible on population histograms before the measured latency (see Fig. 8). We did not observe such an earlier component.

For moving stimuli, we used smaller P values: $P = 0.005$ and $P = 0.025$, respectively. The purpose of this modification was to identify specifically the onset of the main response to the moving stimulus. In fact, we observed that responses of some neurons started to slowly grow well before the peak response, suggesting that the bar moved across a region of the RF with low sensitivity.

Empirical controls of the method were carried out. The computed latencies were first visually checked for many neurons. We also took advantage of the fact that two sets of 20 repetitions were usually done in control condition, as a measurement of the stationarity of the response over time (Hupé et al. 1998). The latency was measured for both controls, and large differences between both measurements were systematically checked and documented: in a few obvious cases, the shortest latency was due to a burst occurring during the spontaneous activity period and was therefore discarded. Otherwise the minimal latency measured in both controls was used.

Analysis of effects of feedback inactivation on response strength

Visual stimuli were usually presented for 1 s on a computer monitor driven by a Truevision Vista Board under the control of a Matlab program. Intertrial was 0.5 s. Eight moving stimuli and one flash stimulus were presented 20 times in an interleaved fashion. A low-contrast textured background (12.7° wide and 8.4° high, 9–24 Cd/m^2) (see Hupé et al. 1998) was always present, either stationary or moving. The bar was therefore flashed against a stationary textured background. The bar was centered on the neuron receptive field (located in the central 4° of visual field) and approximately optimized in spatial phase, orientation, and size. The length of the bar was between 0.2 and 1° (mean = 0.65) and the width between 0.05 and 0.15° (mean = 0.09). Responses to the stationary bar were not always good, as the main purpose of the experiment was the effects of MT inactivation onto moving stimuli. One hundred five of the 169 neuron recorded in areas V1, V2, and V3 gave sizable ON responses to the flashing bars. (OFF responses were also measured but they are not described in this paper. The results were similar.) The selection of sizable responses was done first by observation of PSTHs with 100-ms binwidth. Latencies were then calculated as previously described.

Among the eight moving stimuli, four stimuli were made of the background moving alone and were used to check that the background alone was not sufficient to elicit a response of the neuron. The speed of the stimulus was optimized for each site, and was between 0.75 and 7.5°/s (mean = 2.9). As the flashed stimuli did not always elicit a response to the neurons that were studied, the responses to the four moving stimuli and the response to the flashed bar were analyzed separately. Spikes were counted during 500 ms for the flash stimuli or else during the whole period the stimulus was moving (typically 1 s). The mean spontaneous activity recorded during each run was then removed. We used the bootstrap Student *t*-test (Efron and Tibshirani 1993) with 10,000 bootstrap replications. This test allows the comparisons of the means of two distributions without making any assumptions about the shape of the distributions and is still valid when the variances and sample sizes of the two samples are different. (This is not the case of the classic Student *t*-test nor of its nonparametric equivalent, the Mann-Whitney *U* test.) As four responses to different moving stimuli were studied simultaneously, there was an increase of the type I error. The actual error was controlled thanks to the 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 therefore a controlled 5% type I error (see next section). The effect of MT inactivation on the mean responses of the V1, V2, and V3 neurons to the moving stimuli were described in a previous paper (Hupé et al. 1998) and are presented in detail elsewhere (Bullier et al. 2000). The ON responses to the flashed bar were tested independently, but the fact that responses to moving stimuli were tested in the same recording session increased the experimentwise type I error (Ludbrook 1991). We thus decided arbitrarily to take an individual nominal significance level of 1%, as we had done previously (Hupé et al. 1998), to protect us globally against the alpha risk at a level of about 5% (when the measures are independent).

A test was first done to compare the response strengths between two control runs of 20 stimulus repetitions each (Hupé et al. 1998). If the test was significant, the neuron was discarded, and the response was considered as not stationary. Ninety-five of the 105 neurons were kept after this first stage of analysis for the ON flash response, and 154 of the 169 neurons were kept for the analysis of the effect of cooling on the response to the bar moving across the stationary background. Tests were then done between the control runs and the cooling run.

Measurement of the latency of effects of feedback inactivation

There were too few repetitions of the stimulus presentation to allow a statistical measure of the latency of the effects on individual neurons, so we had to pool the responses of the neurons that behaved similarly to increase the signal/noise ratio. Population PSTHs were therefore computed from neurons being similarly affected (i.e., whose response was significantly increased or decreased) by feedback inactivation. Individual PSTHs were first computed with a 5-ms binwidth, then normalized to the peak response (100% of response, *arrow 1* on Fig. 2*A*) and aligned to the beginning of the responses (response latency, *arrow 2* on Fig. 2*A*). The PSTHs were then averaged. The latency and maximum response to the stimulus in control condition (before cooling) served as normalization for all the PSTHs (control, cooling, and recovery runs). Population PSTHs with binwidths of 10 and 20 ms were done from the 5-ms PSTH. The choice of a binwidth for further presentations and tests was done empirically with the criterion that once the response had started, then the PSTH was smooth enough. We preferred this method to the classical Gaussian convolution because we wanted to ensure that the mean responses obtained in each bin were reliable enough to allow statistical tests. In this way, we could also obtain an estimate of the temporal precision of a given data set.

Wilcoxon tests were done for each bin between the control and the inactivation condition. The choice of replacing the values by their ranks was justified by the previous normalization, which had already eliminated data of the absolute response. Repetitions of tests on the same set of data increase the type I error. Note, however, that these tests were done on responses that were already globally different, as the population histogram was computed only from neurons whose response was different when averaged over 500 ms or 1 s. The question was as follows: from when was this difference significant for the given sample? If for a given neuron, there was a difference of response from the beginning to the end of the response, then the differences in the bins should be highly correlated. If all the neurons behave this way, the type I error would be exactly the same regardless of whether the test was done on the whole response or on any part of the response. We therefore used a multiple comparisons procedure (MCP), which took into account the correlation of the measurements in the successive bins.

Manly (1997) proposed such a procedure for multiple randomization tests. We took advantage that the Wilcoxon test is just one kind of randomization test to adapt this test. For sample sizes up to $n = 16$, all the randomizations of possible signs were done (exact test), i.e., 2^n. For each set of data (one real, $2^n - 1$ randomized), the statistic of Wilcoxon was calculated simultaneously for x variables (x = the number of bins we wanted to test). {When the [2^n] set of data [ ] are ranked in order according to the minimum significance level obtained

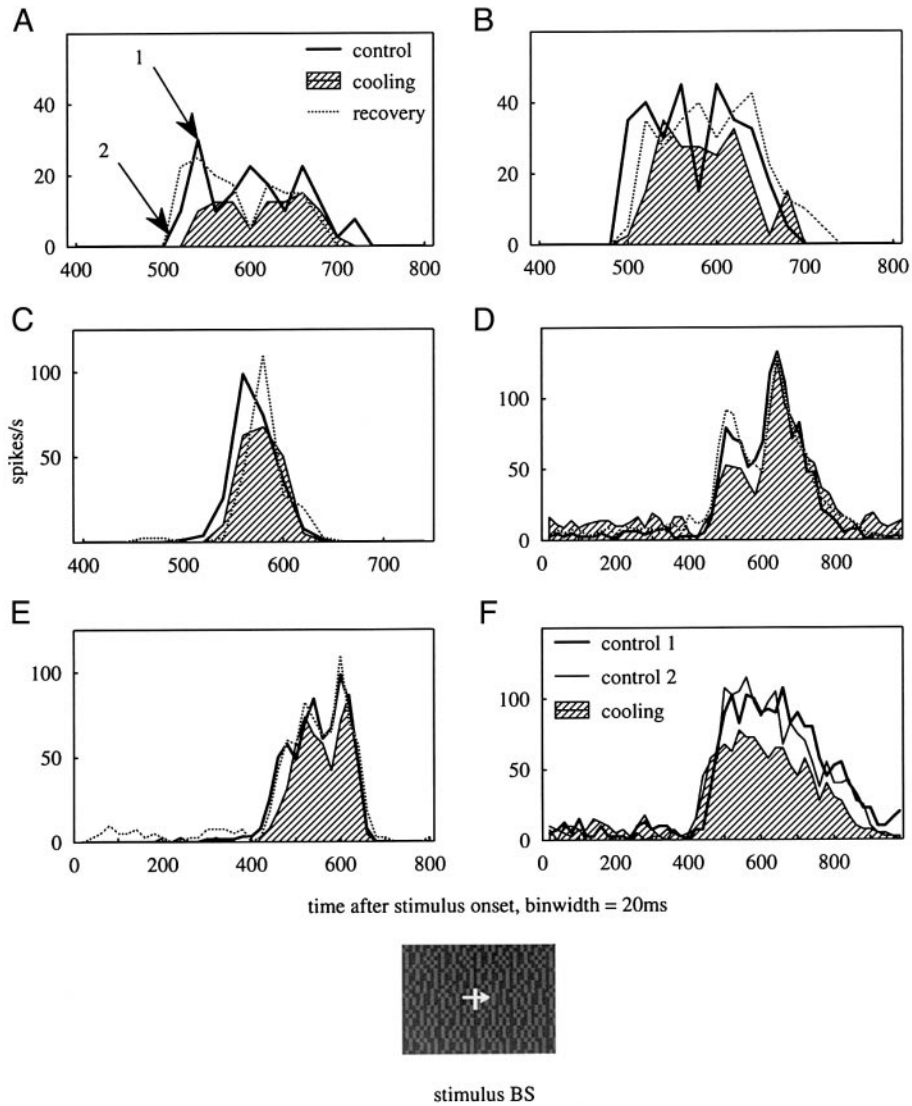

FIG. 2. Examples of neuron responses to a bar moving against a stationary textured background (stimulus BS) that are significantly decreased by MT inactivation. The tests were done on the mean number of spikes measured during the whole period of time the bar was moving (1 s). *A*: V1 neuron recorded in layer 2/3, tested with a low salience stimulus. The onset of the response measured in the control condition was 515 ms (*arrow 2*). The latency of response of this neuron when tested with a flash stimulus was 70 ms. Case lcc14, single unit, $P = 0.001$. *B*: same V1 neuron tested now with a middle salience stimulus. The effect of cooling MT was reproducible. The latency of response to the flash stimulus was now 62 ms. Case lcb14, $P = 0.000$. *C*: layer 4b V1 neuron. The response latency to the flash stimulus was 61 ms. Case lae14, single unit, $P = 0.010$. *D*: layer 5/6 V1 neuron. The spontaneous activity increased during cooling ($P = 0.00$), whereas the response to the moving bar decreased. No response to flash. Case kbd14, single unit, $P = 0.016$. *E*: layer 5 V2 neuron. The spontaneous activity was larger during recovery than during control, whereas the response to the moving bar was identical during control and recovery. Flash response latency = 63 ms. Case lbi14, single unit, $P = 0.002$. *F*: layer 2/3 V2 neuron. The isolation of the neuron was lost for the recovery. Flash response latency = 169 ms. Case kca12, single unit, $P = 0.001$.

from the [x] variables, it is found that 95% of these minimum significance levels exceed [P']%. In other words, if the variables are tested individually at the [P']% level, then the probability of obtaining any of them significant by chance is 5% (Manly 1997, p. 111)}. The P' value computed this way could be compared with the P value obtained with the classical Wilcoxon test. When the data for all the comparisons are perfectly correlated, then there is absolutely no difference between the two results. On the other hand, when there is absolutely no correlation, this procedure is equivalent to the Bonferroni procedure, which weights each significance threshold by the total number n of comparisons ($P' = P/n$). For samples larger than 16, all the possible randomizations were estimated by a random sample of 10,000 randomizations (including the observed one), the same sample being of course used for all the comparisons (Manly 1997).

All of these calculations were carried out in Matlab 4.2 (MathWorks).

RESULTS

Responses to moving stimuli

Responses of 154 neurons to moving stimuli were recorded in areas V1, V2, and V3 before, during, and after MT was inactivated by cooling. The mean response of the neurons was measured. The effects of MT inactivation on response strength have been described elsewhere (Hupé et al. 1998). Briefly, two major effects were observed. First, the response of neurons to a bar moving against a stationary textured background (stimulus BS) was decreased when MT was inactivated, indicating that motion information useful for the target segregation was fed back to these neurons. Second, responses were compared when the background was stationary and when it was moving together with the central bar. We were interested in the neurons for which the response was significantly decreased to the latter stimulus, as it meant that the neuron responded strongly when there was a motion contrast between the bar and the background. For such neurons, when tested at low salience, i.e., when motion was almost the only cue to detect the bar, the response to the bar moving together with the background (stimulus BM) was increased when MT was inactivated. This effect, significant for six neurons recorded in V3, lead to a loss of the ability of these neurons to perform figure/ground discrimination based on motion cues (Hupé et al. 1998).

In the present study, we first examined the latency of the significant decreases of response to BS (51 neurons). Figure 2 shows examples of the time courses of the responses of single neurons recorded in V1 and V2 in *1*) control condition before the inactivation, *2*) while MT was inactivated, and *3*) during the recovery after circulation of the coolant had been switched off. Examples of V3 neurons are presented in the *left part* of Fig. 4. Typically, the decrease of the response could be observed during the first 20-ms bin of response and could last up to the end of the response. This was most obvious for the cases where there was a total suppression of the response during cooling (Fig. 4*A*) and also for the majority of the significant but weaker response decreases presented here (Figs. 1, *A–F*, and 4, *C* and *E*).

The average PSTHs for control, cooling, and recovery blocks of trials were then computed after normalization of response strength and alignment of latencies (Fig. 3*A*). The difference between the average PSTHs during control and cooling is illustrated in Fig. 3*B*, with the bins showing significant differences indicated below (only the period between

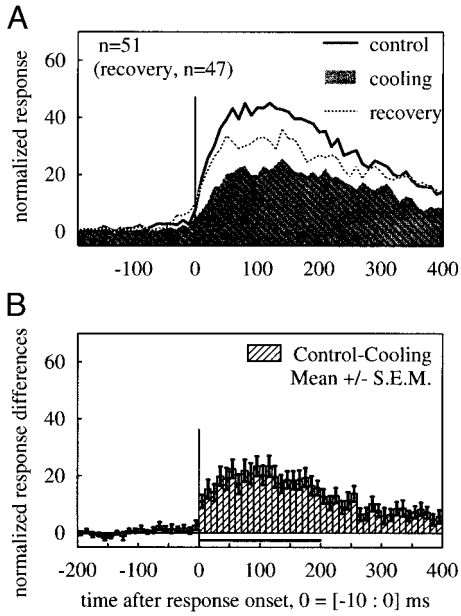

FIG. 3. Population histograms. *A*: the responses of the 51 neurons whose response to BS was significantly decreased by MT inactivation were pooled (see METHODS). The recovery was recorded for 47 neurons only. Binwidth = 10 ms. The tick-mark called ≪0≫ (vertical dark line) corresponds to the center of the last bin before response onset (mean normalized response between −10 and 0 ms). *B*: measure of the time course of the decrease of response due to MT inactivation. The difference of normalized response control-cooling was computed for each neuron, and then averaged in a population histogram. One SE is plotted below and above the mean response. The vertical dark line is placed here at the higher extremity of the last bin before response. The horizontal dark bar below the histogram indicates the bins that were significant ($P < 0.05$) when 2 multiple comparisons procedure (MCP) Wilcoxon exact tests (see METHODS) were done independently on the 20 bins (200 ms) before response onset and the 20 bins after response onset. This histogram shows the excitatory contributions of feedback connections from MT to the responses to a moving bar of V1, V2, and V3 neurons.

−200 and 200 ms with respect to the onset latency was tested; the period before the onset latency was tested independently of the response period). This shows that the response is affected by inactivation of MT during the first 10-ms bin following response onset and that the difference has an early peak, thus suggesting that the feedback effects are extremely rapid. Note that there is no significant change in spontaneous activity before the onset of the response (we will return to the issue of spontaneous activity below).

Figure 4 illustrates examples of neurons for which cooling MT decreased the responses to the bar stimulus (BS) while increasing the responses to bar moving together with the background (BM). For both response decrease and increase, the changes are observed from the beginning of the response. The examples of Fig. 4, *C–F*, are two of the six V3 neurons tested at low salience whose response to BM was significantly lower than the response to BS in control condition. This differential response (background suppression) allows the neurons to code the presence of the bar moving against a stationary textured background (segmentation based on motion cues). We did not compute a population histogram for these six neurons as in most of the cases we were not able to measure the latency of the very small response recorded in the control condition. The other four neurons showed, however, a similar pattern demonstrating an early increase in response when MT was inactivated.

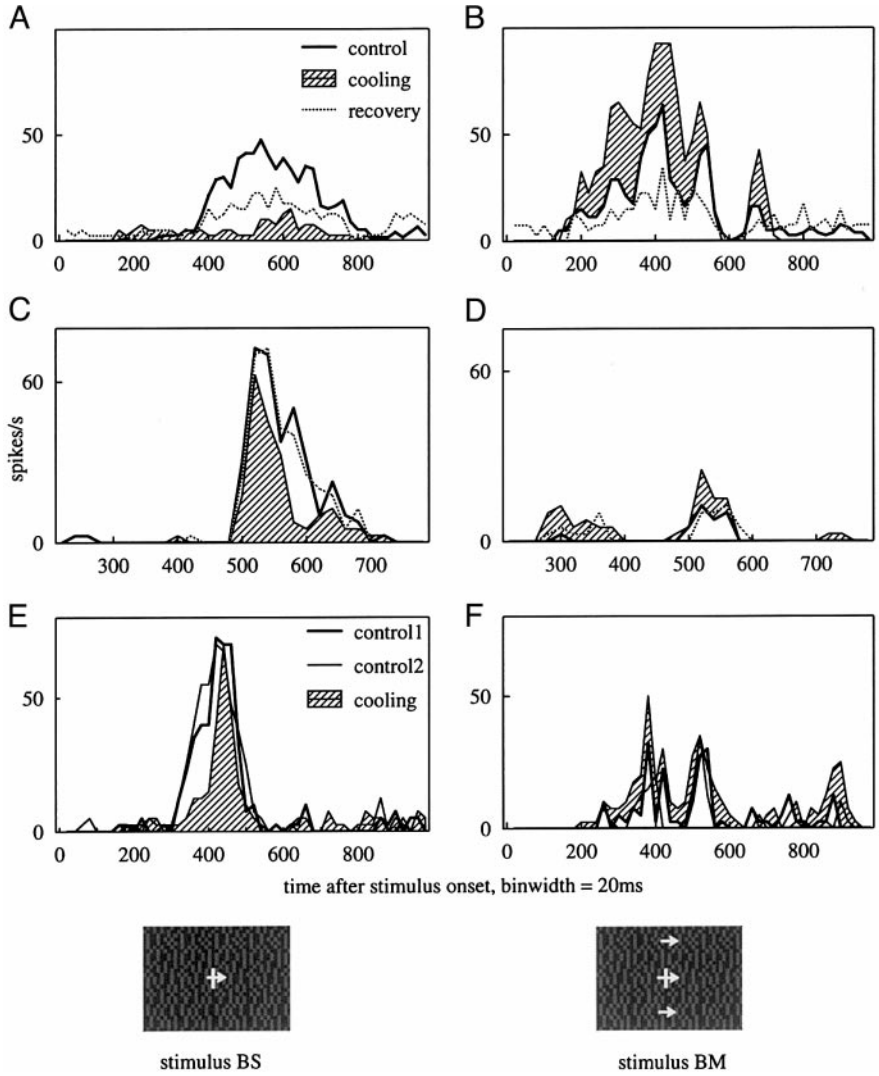

FIG. 4. Examples of neurons for which response to BS was decreased by MT inactivation, whereas response to BM (background moving coherently with the bar) was significantly increased. These neurons were tested with low salience stimuli. *A* and *B*: layer 2/3 V3 neuron. The mean response to the stimuli BS (*A*) and BM (*B*) in the control condition is the same. Case lch14, single unit. BS decrease, $P = 0.073$; BM increase, $P = 0.000$. *C* and *D*: layer 3/4 V3 neuron. The mean response to BM in the control condition was significantly smaller than the response to BM (background suppression, $P = 0.000$). Case lci11, single unit. BS decrease, $P = 0.053$; BM increase, $P = 0.002$. *E* and *F*: layer 4 V3 neuron. Background suppression in control, $P = 0.000$. Case lck14, single unit. BS decrease, $P = 0.000$; BM increase, $P = 0.008$.

One way to interpret such a rapid effect of feedback inactivation on the visual responses of neurons in areas V1, V2, and V3 is that it results from a change in the gain control of V1–V3 neurons because cooling decreases the spontaneous activity of MT neurons that send feedback connections to V1–V3 neurons. As a result, the spontaneous activity of V1–V3 neurons themselves should be affected by the inactivation of MT, and this should predict the changes of the evoked responses. To test this possibility we examined the relationship between changes in the spontaneous activity of the neurons in areas V1–V3 and the changes in the evoked responses. The spontaneous activity was measured during the 500-ms periods between the stimulus presentations, as described in METHODS. Figure 5*A* presents a scattergram of these two variables. In abscissa we plotted the change of V1–V3 spontaneous activity when MT was cooled. The "plus" (+) symbols indicate the neurons for which the change in spontaneous activity was significant (total = 24/155 neurons). Both significant increases and decreases of the spontaneous activity were observed. If a change in the gain control of neurons should explain the effects on the evoked response, then the direction of changes in spontaneous activity should be correlated with the direction of the effect on the response to the stimulus BS. It is clear from Fig. 5*A* that this is absolutely not the case. The neuron presented on Fig. 2*D*, and labeled 2D on Fig. 5*A*, illustrates a case for which a decrease of response is observed despite a strong increase in spontaneous activity. There appears to be a tendency for neurons with significant changes of BS responses to show a significant change of the level of spontaneous activity. However, the proportions are not significantly different between neurons with significant changes in BS and those that showed no changes (16/95 vs. 18/60,[3] $P > 0.05$).

In Fig. 5*B* we present the averaged PSTHs for 11 neurons for which changes in spontaneous activity were minimal (1 neuron with 6% change, the other cases below 1%). It is obvious that despite such a stable level of spontaneous activity, the response decrease is marked and is observed very early after the beginning of the response. Further arguments against the effect of cooling on the steady-state gain control of neurons in areas V1–V3 are presented in the DISCUSSION.

Although our results demonstrate an early effect of feedback

[3] The proportion of neurons for which the spontaneous activity changed significantly during cooling could seem important. However, the spontaneous activity already changed frequently (significantly for 25 neurons) between the two controls. This poor stationarity of the spontaneous activity may be due to the short period of measure used (see METHODS).

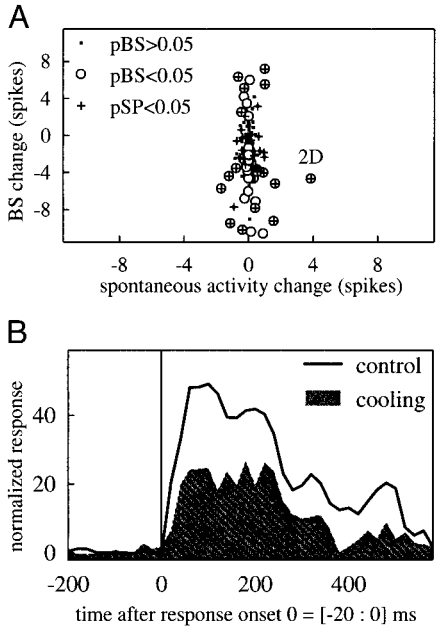

FIG. 5. *A*: relationship between the changes of spontaneous activity and the changes of the mean response to the stimulus BS. The mean number of spikes was counted during 1 s for the stimulus BS and during 1.5 s for the spontaneous activity. Symbols for the significant changes between control and cooling are indicated in the legend (SP, spontaneous activity; BS, stimulus BS). The point marked 2D is the neuron of Fig. 2*D*. *B*: population histogram of the responses of 11 neurons whose response to BS was significantly decreased by MT inactivation, whereas there was no change of the level of the spontaneous activity. Conventions as in Fig. 3*A*.

connections, this may simply reflect the fact that feedback connections preferentially target neurons with late responses to visual stimulation. This was tested by comparing the latencies to flashed stimuli of neurons that showed response decreases to the BS stimulus and neurons showing no significant effects. As evident in Fig. 6, there is no significant difference between these two populations, thus supporting the idea that even the earliest activated neurons may be influenced by feedback stimuli.

Responses to flashed stimuli

We then examined the timing of the effects of MT inactivation on the responses of neurons to stimuli flashed in the RF center. Among the 95 neurons for which the ON response was stationary enough to assess the effects of MT inactivation, 29 neurons were significantly affected. The effects were decreases of responses (15 neurons) as well as increases (14 neurons). As reported elsewhere (Bullier et al. 2000), whether increases or decreases are recorded depend on the area of recording and the salience of the stimulus. Two examples of significant decreases of the response of V1 neurons are shown in Fig. 7, *A* and *B*. The PSTH traces for control, cooling, and recovery (for *A*) are shown, using a binwidth of 20 ms. The decrease of response due to MT inactivation could be observed from the very start of the response (*A*, 60–80 ms; *B*, 40–60 ms). The neuron of Fig. 7*B* was recorded in layer 4b of V1, which is reciprocally connected with MT (Shipp and Zeki 1989; Ungerleider and Desimone 1986). This neuron had the shortest latency of our sample (42 ms). Similarly, two examples of significantly increased responses (Fig. 7, *C* and *D*) indicate that the effect of MT inactivation was present from the very start of the response. For the neuron of Fig. 7*C*, the increase could be observed in the first bin of response (60–80 ms). In the case shown in Fig. 7*D*, the latency of the response is shorter during cooling than in the control condition. For these four neurons, the effect was already significant when the first 100 ms of response were tested ($P < 10^{-4}$).

The effects were observed from the beginning of the response for most but not all the neurons: for 3 neurons among the 14 for which the response was significantly increased during cooling, the increase was only present after about 100 ms of response. Similarly, for 3/15 neurons, the response seemed to be decreased only after more than 50 ms of response.

Average PSTHs for flashed stimuli were computed with similar methods as described for moving stimuli and are shown in Fig. 8, *A* and *B*, for response decreases and Fig. 8, *C* and *D*, for response increases. Only 13 of the 15 significantly decreased responses (and 12 of the 14 significantly increased responses) were used to compute the population histograms; as for the other neurons, the flash response in control condition was too small or sluggish to measure the latency reliably. The mean decrease and increase of response during cooling was large and present from the beginning of the response. The recovery of the control activity was in average almost perfect, as can be seen from the superposition of the control and recovery traces. The differences between normalized control and cooling responses were computed (Fig. 8, *B* and *D)*. The level of significance for the response changes was computed between −120 and 120 ms with respect to the onset latency. Significant decreases are observed at the beginning of the response (the 1st 10-ms bin of response is significant, Fig. 8*B*). The mean increase is even seen and significant before the response onset (20-ms bin before the control response onset, Fig. 8*D*), since, as observed on Fig. 7*D*, the latency of response could be shorter during cooling than during the control. The effect lasts until the end of the response. As in the case of moving stimuli, no significant change was observed during the period of spontaneous activity.

One could imagine that only neurons with late latencies are affected by the feedback from MT, with the consequence that for the population of neurons of one area, the influences of feedback from MT would be late, even if the affected neurons were affected at the beginning of the response. This is not the

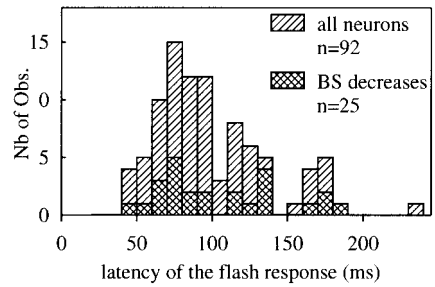

FIG. 6. Histogram of the ON-response latencies to a bar flashed in the receptive field (RF) center. The latencies were measured in the control condition. Ninety-two neurons of V1, V2, and V3 had a sizable ON response, and their response to BS could be recorded and tested during MT inactivation. The response to BS of 25 of these neurons was significantly decreased when MT was inactivated. The latencies of the flash response of these neurons are shown. There is no correlation between the latency of the flash response and the effect of MT inactivation on the response to the moving stimulus BS.

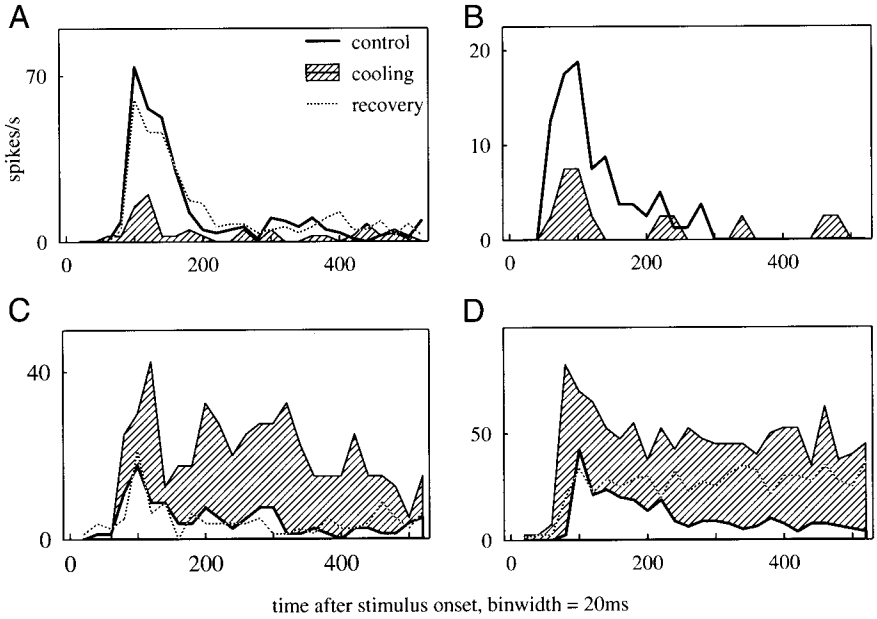

FIG. 7. Examples of neuron responses to a bar flashed against a stationary textured background that are significantly decreased or increased by MT inactivation. The tests were done on the mean number of spikes measured during 500 ms after the stimulus onset. *A* and *B*: 2 examples of significant decreases of the response. *A*: layer 2 V1 neuron. Latency = 70 ms (measured during the control condition). Case lba11, single unit, $P = 0.000$. *B*: layer 4b V1 neuron. Latency = 42 ms. Case lad15, single unit, $P = 0.000$. *C* and *D*: 2 examples of significant increases of the response. *C*: layer 3 V3 neuron. Latency = 75 ms (measured during the control condition). Case lbp15, single unit, $P = 0.000$. *D*: layer 4c V1 neuron. Latency = 78 ms (67 ms during cooling). Case laf14, single unit, $P = 0.000$.

case, as can be observed on the histograms of the latencies of the neurons tested in V1, V2, and V3 (Fig. 9). There is no tendency for neurons with late latencies to be more frequently affected by MT inactivation.

DISCUSSION

Our results show that effects of inactivating area MT on the responses of neurons in areas V1–V3 can be observed on the earliest part of the response, and they can last the whole duration of the stimulus response. We observed this result for both moving (Figs. 2–6) and stationary, flashed stimuli (Figs. 7–9). At the population level the increases and decreases of responses were always significant 10 ms at the latest after the response onset. This interval corresponds to the precision of our latency measurements, given the variability of the responses and the limited number of stimulus repetitions. One possibility that we explored is that feedback from MT acts on the early part of the responses of those V1–V3 neurons that generate longer latency responses to visual stimulation. While this possibility holds for some of our sample, there were several other examples of neurons that were very rapidly activated by visual stimuli, and their earliest activities were also influenced by the MT inactivation. Thus it appears that the effects of MT inactivation on neurons in areas V1–V3 are not or barely delayed with respect to visual responses. This conclusion is reached for both individual neurons and the population.

Absence of effects on the spontaneous activity

One possible mechanism to account for such a rapid onset of feedback influence is that the effect does not depend on the visual responses of MT neurons per se but acts through a gain control mechanism that is regulated in some way by the spon-

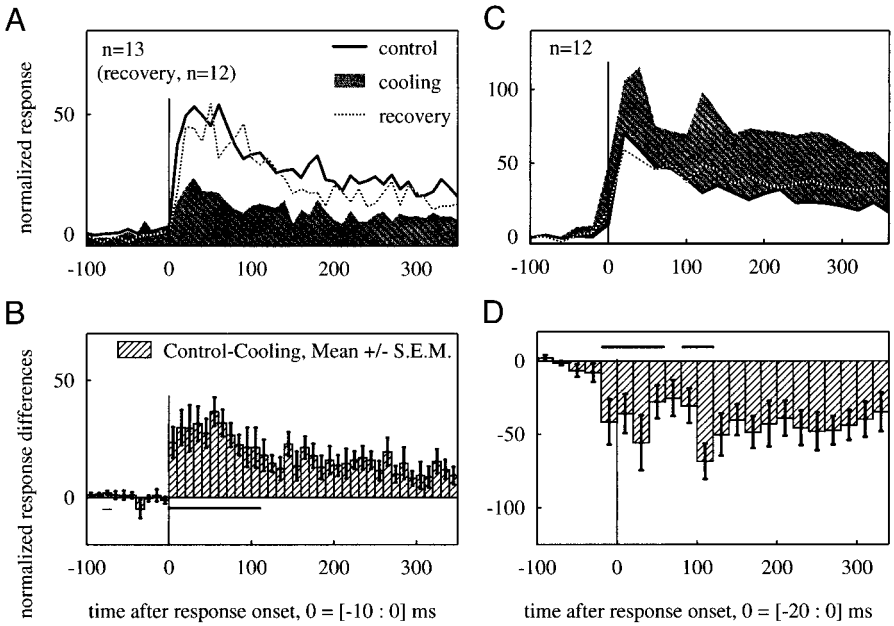

FIG. 8. Population histograms. *A*: the responses of 13 neurons whose ON response was significantly decreased by MT inactivation were pooled. The recovery was recorded for only 12 neurons. Conventions as in Fig. 3*A*. *B*: measure of the time course of the decrease of response due to MT inactivation. Conventions as in Fig. 3*B*. The horizontal dark bar below the histogram indicates the bins that were significant ($P < 0.05$) when 2 MCP Wilcoxon exact tests (see METHODS) were done independently on the 12 bins (120 ms) before response onset and the 12 bins after response onset. This histogram shows the excitatory contributions of feedback connections from MT to the ON responses of V1, V2, and V3 neurons. *C*: the responses of 12 neurons whose ON response was significantly increased by MT inactivation were pooled. Conventions as in *A*, except binwidth = 20 ms. *D*: measure of the time course of the increase of response due to MT inactivation. Conventions as in *B*, except binwidth = 20 ms. The horizontal dark bar above the histogram indicates the bins that were significant ($P < 0.05$) when 2 MCP Wilcoxon exact tests were done independently on the 6 bins (120 ms) before response onset and the 6 bins after response onset. This histogram shows the inhibitory contributions of feedback connections from MT.

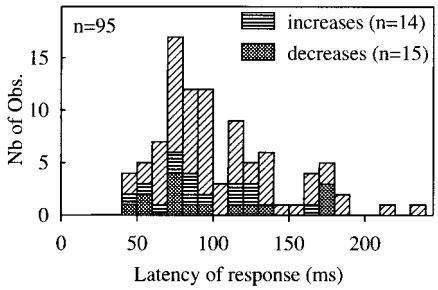

FIG. 9. Histogram of the latencies of the neuron ON responses to the flashed bar. Ninety-five neurons of V1, V2, and V3 were recorded and tested during MT inactivation. The latencies of the significantly affected neurons are shown. Note that there is no correlation between the latency of response and the effect of MT inactivation. Even responses with very short latencies can be modulated by the feedback from MT.

taneous activity in both MT and V1–V3. We think that such an interpretation is unlikely for five reasons. *1*) As demonstrated in Fig. 5, there is no relationship between changes in spontaneous activity and changes in evoked responses of neurons in areas V1–V3. If there was a relationship, we would expect to consistently study neurons that show a response decrease and exhibit a decrease in spontaneous activity during MT inactivation. However, we observed several examples of spontaneous activity increase conjoined to visual stimulation decrease in activity (Fig. 2*D*). *2*) For the subset of neurons for which there is no change in spontaneous activity, there is a clear early decrease of response to visual stimulation (Fig. 5*B*). *3*) In a number of neurons (e.g., Fig. 4), there was a decrease of the response to the BS stimulus and an increase of the response to the BM stimulus. If the results of cooling MT were due to a change in gain control related to the lowering of spontaneous activity in MT, it is difficult to see how this steady-state gain control could cause different effects for different visual stimuli. *4*) There were examples of neurons for which the initial and later phases of the response were differentially affected by MT inactivation (Fig. 2, *D* and *F*). This could result from the fact that the effect of the feedback was stronger for certain parts of the RF of the lower order neuron and weaker or nonexistent in other regions. Such observations are difficult to explain on the basis of a gain control change due to the decrease of spontaneous activity in MT neurons. *5*) Finally, there were examples of V1–V3 neurons for which the spontaneous activity changed between acquisition of two control measures, or between control and recovery, but there was no change at all in the response to the stimulus (when MT was active), even though MT inactivation induced a change in response (Fig. 2*E*).

We believe that these observations effectively counteract the suggestion that the MT influences over area V1–V3 neurons is mediated by changes in gain control based on spontaneous activity.

Mechanisms

For flash responses, when MT is inactivated, response increases of area V1–V3 neurons occur earlier than response decreases (Figs. 7 and 8). These observations suggest that disynaptic inhibitory influences are transmitted very rapidly from MT. This view is consistent with early inhibitory dips in neuronal responses in V1 and V2 (Nowak et al. 1999) and with the fact that inhibitory neurons appear to be the first activated neurons in sensory cortex (Swadlow 1995). Our extracellular recordings supposedly targeted preferentially excitatory neurons. In addition, this shortening of the latency during inactivation of the feedback could suggest that the MT feedback was present even before the feed-forward activation arrived. This could be also the case for neurons with longer latencies. However, our extracellular recording does not allow to test this hypothesis, and it could also be that the feedback is precisely timed with the feed-forward input.

For moving stimuli, a comparison of the effects of inactivation on the neuron activity before and after the stimulus has entered the RF center provides interesting clues as to the type of influences that feedback connections have over lower order area neurons. As is evident in the examples presented, hardly any change was observed in the neuron response before the stimulus activated the main discharge center of the V1–V3 RF. We know that feedback connections are strongly convergent (Perkel et al. 1986; Salin et al. 1992) and RF centers of MT neurons are much larger than those of neurons in V1–V3 (Gattass and Gross 1981). If we assume that the convergence is such that the RF of MT neurons overlap at least partially those of their target neurons (Salin et al. 1992), then the space-shift would be 3° (the average RF diameter of MT neurons at 2° eccentricity). With a maximal speed of 7.5°/s (typical speed was 3°/s), the time-shift in arrival time of feedback influences is $3/7.5 = 0.4$ s. When the bar stimulus moves toward the RF center of a neuron under study in V1–V3, this time-shift is long enough to activate many MT neurons that could provide feedback input to this neuron. Despite this presumably strong excitatory input (Hupé et al. 1998), no clear response is evoked in the neuron, as evidenced by the fact that the activity before the main response is hardly changed by MT inactivation (Figs. 2–5). This suggests that feedback connections act in a nonlinear fashion, boosting responses evoked by feed-forward inputs but not evoking responses per se. This conclusion is reminiscent of that made in an earlier publication (Salin and Bullier 1995) concerning the feedback connections from MT to V2. No response was evoked in V2 neurons when V1 was inactivated (Girard and Bullier 1989; Schiller and Malpeli 1977) despite the extensive feedback input from MT to V2 carrying strong residual activity in MT when V1 is inactivated (Girard et al. 1992; Rodman et al. 1989). A comparable amplification of convergent inputs has been demonstrated for multisensory neurons in the colliculus (Meredith and Stein 1983; Wallace et al. 1998). Interestingly enough, the potential for response amplification was greatest when responses evoked by individual stimuli were weakest (Meredith and Stein 1986), as in our case, responses to low salience stimuli most gain from the feedback from MT (Hupé et al. 1998).

How is such a rapid effect of feedback possible?

Based on hierarchical schemes of cortical connectivity and widely held beliefs on timing of top-down influences, rapid effects of feedback connections are unexpected. However, a number of arguments are consistent with rapid feedback effects. First, it is known that the spectrum of response latencies of neurons in higher-order areas overlap very broadly with the response latencies of lower order neurons, and many are not longer than the latencies of the lower order neurons. For example, single neuron studies and current source density

analyses show that neurons in area MT have latencies that, on average, are shorter than the latencies of neurons in V2, and only a few milliseconds longer than the latencies in areas V1 and V3 (Maunsell 1987; Nowak et al. 1995; Raiguel et al. 1989; Schmolesky et al. 1998; Schroeder et al. 1998). It is therefore possible that at least some of the MT neurons responding with short latencies are specifically involved in feedback connections. Another point of interest concerns the speed of feedback connections. Since feed-forward and feedback fibers have similar conduction velocities (Nowak et al. 1997), and feed-forward projections from V1 to MT are extremely rapid (Movshon and Newsome 1996), it could well be that some signals are transmitted from MT to V1–V3 in only 1 or 2 ms. Thus given the early activation of MT neurons by visual stimuli and the fast conduction velocity of feedback connections, it is not surprising that feedback connections could act very rapidly (within 10 ms) on the responses of neurons in lower order areas. In fact, given the strong pressure to reduce the number of thick (and thus rapid) rapid cortico-cortical axons in higher order vertebrates (Murre and Sturdy 1995), the very fact that feedback connections are fast conducting suggests that their actions must be rapid.

It has been argued that the early responses of neurons in area MT could be explained by a fast parallel pathway that bypasses V1 (Ffytche et al. 1995). Anatomical studies have revealed anatomical pathways that pass through the superior colliculus and pulvinar (Standage and Benevento 1983; Ungerleider et al. 1984), or directly through the lateral geniculate nucleus (Fries 1981; Yukie and Iwaï 1981), to reach the superior temporal sulcus. This pathway likely supports the persistent activity of MT neurons when V1 is inactivated (Girard et al. 1992) or lesioned (Rodman et al. 1989). Moreover, this pathway may be very fast because visual latencies as short as 30 ms have been reported in the inferior pulvinar (Benevento and Port 1995) and in its target layer 2 of area MT (Raiguel et al. 1999). It remains to be tested directly whether this transcollicular-pulvinar route supports the short visual latencies in MT/V5 to flashes and fast stimuli, as suggested by the studies of the human brain (Ffytche et al. 1995).

Knowledge of pathways and speed of transmission are important both for guiding interpretation of our results and for the generality of our conclusions. If the by-pass pathway to MT is shown to be fast, the significance of our results on feedback effects is attenuated because the results could equally well be interpreted in terms of blockade of one of two pathways that converge. Even though such results are interesting in their own right, they have little significance for signals interactions in other cortical areas. However, we are inclined to believe that the effects we have identified are mediated by true feedback pathways. In the following paper (Hupé et al. 2001), we show that a similar observation is made on the responses of V1 neurons when area V2 is inactivated by GABA: effects are observed on the early part of the responses to flashed stimuli, even for neurons with short latencies to visual stimuli.

Conclusion

The consequence of our results is that the visual cortex should be considered as temporally compact. One possible function of rapid feedback influences is to allow neurons to produce their most significant response (Heller et al. 1995; Tovee et al. 1993) after the signals have also been treated by higher cortical areas and fed back to the lower areas. The latter signals may be highly relevant to dynamic temporal and spatial aspects of RF properties (DeAngelis et al. 1995; McLean et al. 1994; Ringach et al. 1997). Thus the fast feedback connections ensure interactions between the activating and feedback signals and that include the early part of the response.

Other authors suggested that feedback effects be relegated to the later phase of the response (Lamme et al. 1998a,b). Our results do not preclude the possibility that feedback signals *also* influence the late part of the responses. In fact, we observed in a few neurons a late effect of MT inactivation. More surprising is the fact that Lamme and colleagues (Lamme et al. 1999; Lee et al. 1998) observed that the late part of the response of V1 neurons (beyond 100 ms after response onset) was modulated for the coding of figure/ground segmentation. Our stimuli tested also figure/ground discrimination (Hupé et al. 1998), and we did not observe such a delay. Several methodological reasons may explain these contrasting results. First, their experiments used awake monkeys. Some of the late modulations might be due to attention. The fact that anesthesia suppressed the late figure/ground component (Lamme et al. 1998a,b) indicates that we did not test similar properties of the neurons. Second, they used flashed stimuli, whereas we used a bar that was already moving before entering the RF of the neuron under study.

In our paradigm, we were in a situation where a moving target could be continuously identified when partly hidden in a background, a situation that often occurs. The fact that in any given part of the visual field the motion cue was always available to V1, V2, and V3 neurons as soon as they start to fire is an important result that helps us to understand why motion is such a powerful cue for precise and sustained segmentation. In our view, V1, V2, and in a lesser extent V3 neurons treat local information with their small RF. The early feedback influences from neurons with larger RF allow the V1 neurons to integrate also global information, as in the case of figure/ground discrimination (Hupé et al. 1998). This local/global integration by neurons of low level areas could also be involved in the processing of kinetic boundaries (Marcar et al. 1994, 1995). Our results further suggest that the time course for motion segmentation may not be longer than for motion discrimination, contrary to what was reported in a psychophysical study (Masson et al. 1999). But their task required the three-dimensional perception of multiple surfaces moving through or over each other, and involved therefore more complex and obviously different mechanisms than those addressed by our simple stimuli. Using a simpler figure/ground discrimination task, Moller and Hurlbert (1996) observed an improvement of motion segmentation with stimulus duration; yet with stimulus duration of $<60-80$ ms, their broadest segmentation targets (0.72°) were detected at a lower speed threshold than that required for motion detection, thus demonstrating a fast mechanism for detecting relative motion between target and background (Moller and Hurlbert 1996).

Our results are also very important for the interpretation of many physiological results. Briefly, when complex properties of neurons are found that lag the onset of the response, this does not mean that feedback connections are involved (Hupé et al. 2001). When complex properties do not lag the onset of the response, this also does not mean that these properties are

obligatorily shaped by their feed-forward inputs (Hupé et al. 1998). However, late modulations (Lamme et al. 1999) can be due to feedback connections. Some complex stimuli that we did not test in this study, or attention, could also lead to a delayed involvement of feedback connections. The role of feedback connections can therefore not be suggested by the temporal properties of lower order neurons. This further underlines the importance of reversible inactivation studies for understanding the logic of cortico-cortical connections (Wanduffel et al. 1997) in the visual cortex, that must be conceptualized as a network of interacting areas responding with near-simultaneity, rather than as a pipeline-type architecture.

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