specified as the desired final positional standard deviation, was taken as $(W + w)/r$, where $r$ was taken as 1.96 to achieve a 95% success rate. The movement duration was calculated as the shortest possible time that could achieve this accuracy constraint, given that the signal-dependent noise on the entire motor-neuronal pool had a 1% coefficient of variation.

**Nonlinear model.** For the nonlinear two-jointed planar arm, we used two linear second-order muscles, as described above, acting on the shoulder and elbow joint of a two-link arm moving in the horizontal plane (arm parameters from ref. 29). The trajectories were parametrized as cubic splines with the knots evenly spaced in time. For the point-to-point movements, 7 cartesian $(x,y)$ knots were used with the first and last points fixed at the start and target locations with zero velocity. 500 movements (650-ms duration, sampled at 10 ms) were simulated with signal-dependent noise to determine the trajectory that minimizes the post-movement variance. The optimal trajectory was found using the simplex algorithm to adjust the knot locations.

For ellipse-drawing movements (duration 600 ms, sampled at 20 ms), the knots represented the proportion of the distance travelled around the ellipse as a function of time. Seven knots were used with the first knot at zero and the last at one. This spline determined the velocity profile of the movement which was confined to an elliptic path. The simplex algorithm was used to find the optimal trajectory.

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# Cortical feedback improves discrimination between figure and background by V1, V2 and V3 neurons

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**A single visual stimulus activates neurons in many different cortical areas. A major challenge in cortical physiology is to understand how the neural activity in these numerous active zones leads to a unified percept of the visual scene. The anatomical basis for these interactions is the dense network of connections that link the visual areas. Within this network, feedforward connections transmit signals from lower-order areas such as V1 or V2 to higher-order areas. In addition, there is a dense web of feedback connections which, despite their anatomical prominence[1–4], remain functionally mysterious[5–8]. Here we show, using reversible inactivation of a higher-order area (monkey area V5/MT), that feedback connections serve to amplify and focus activity of neurons in lower-order areas, and that they are important in the differentiation of figure from ground, particularly in the case of stimuli of low visibility. More specifically, we show that feedback connections facilitate responses to objects moving within the classical receptive field; enhance suppression evoked by background stimuli in the surrounding region; and have the strongest effects for stimuli of low salience.**

We recorded single units and multiunits (114 single units and 54 multiunits) in areas V1, V2 and V3 of anaesthetized and paralysed macaque monkeys. To study the role of feedback connections from area V5, a small region of the superior temporal sulcus (STS) containing this area was reversibly inactivated by cooling; we then compared the neuronal responses before, during and after STS inactivation. We used visual stimuli consisting of an optimally orientated bar moved across the centre of the receptive field on a background of irregularly distributed, half light and half dark, but lower luminance, square checks (Fig. 1d). In a sequence of interleaved stimulus conditions, the bar and background moved one at a time, or together, in the preferred direction for the cell or its opposite.

Figure 1a–c illustrates a spectrum of effects of the V5 inactivation for single neurons recorded in areas V1, V2 and V3, and stimulated by a bright bar moving in front of a stationary background of lower luminance contrast. A substantial and highly significant decrease in the response to the moving bar is observed in each case during V5 inactivation. Figure 1e, f gives the population data. It is clear that diminution of responses is by far the most frequent effect of V5 inactivation, as observed before for other feedback connections[6,8]. Of the total sample of sites tested, 33% showed a significant decrease ($P < 0.01$) and 6.5% an increase. Similar effects were observed in infragranular and supragranular layers. No effect was observed in layer 4C of area V1.

The role of feedback connections in figure–ground discrimination was suggested to us when we found that the strength of the effect of V5 inactivation depended on the visibility of the stimuli used for testing neurons in area V3, an area that receives a particularly large feedback input from MT/V5 (ref. 9). We com-

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pared the effects of V5 inactivation on the responses of V3 neurons for different luminances of the central moving bar and the stationary background. We quantified the visibility of the bar against the background by a salience index that corresponds to the ratio of the contrasts of the central bar and the background. Figure 2 shows that the suppression of the response during cooling for V3 neurons is stronger for low-salience stimuli than for middle- and high-salience stimuli. For the low-salience stimuli, the bar is barely visible when both bar and background are stationary or moving coherently. The movement of the bar on the stationary background makes it clearly visible. Feedback from V5 could therefore provide the information on motion contrast to V3 neurons. As shown in Fig. 2 (right box), there were also response reductions in areas V1 and V2 for high-salience stimuli. It is important to mention that, for the whole sample in areas V1, V2 and V3, response increases were observed only for high-salience stimuli (not shown).

Because of the high degree of convergence of feedback connections[10] and the larger receptive fields in higher-order areas, we suspected that feedback connections are involved in the integration of information concerning different parts of the visual field. We therefore compared the responses of neurons to the central bar moved on a stationary or moving background. As expected from the inhibitory interactions between centre and surround in receptive fields of many visual cortical neurons[11–13], the response to the bar and background when moved together was usually much weaker than when the bar moved on the stationary background (Fig. 3a, hatched histograms). For a number of V3 neurons, inactivating V5 had a differential effect on the responses to these two stimuli. When the central bar moved alone, the inactivation of area V5 decreased the response, as already shown in Fig. 1. In contrast, it enhanced the response when the central bar and background moved coherently (Fig. 3a, open histograms). In most cases, the response to the background moving alone was null or very small (Fig. 3a).

The salience was also found to be important in determining the strength of effects elicited by inactivation of area V5. When V5 was inactivated, there was a marked increase in the response to the bar and background moved together (BM stimulus), which was significant at the population level only in the case of low-salience stimuli (Fig. 3b). This suggests that the suppression of the response induced by the moving background is under the influence of area V5. For the low-salience stimuli (Fig. 3c), when area V5 was inactivated, there was a substantial decrease in background suppression for all the neurons except one, as shown by the positions of most points well below the line of no change in suppression. In most cases (5/7), this decrease in background suppression corresponded to a statistically significant increase in the response to the BM stimulus. An effect on a smaller proportion of the neurons was observed for middle-salience cases and no effect was seen for the high-salience cases (Fig. 3d). Thus, feedback afferents from V5 specifically increase the surround-induced suppression of the centre-mechanism response in V3 neurons in the case of low-salience stimuli. Note that the bar contrast is not the determinant variable: when classifying the neurons with respect to bar contrast, the effects are no longer clustered (not shown).

Feedback projections from area V5 also contribute importantly to the direction selectivity of lower-order neurons when salience is low. As for the surround suppression, changes in direction selectivity in V3 neurons were observed for low-salience stimuli (increases as well as decreases in direction selectivity were observed; not shown) and no effect was observed for middle and high salience. These results suggest that, at least for low-salience stimuli, the deficits in discrimination of stimulus direction after lesions in area V5 (refs 14, 15) are not necessarily due solely to the elimination of the numerous direction-selective units found in this area.

The results show that cooling the depth of the STS decreases the responses of many neurons in areas V1, V2 and V3. In addition to direct controls (see Methods), several indirect arguments contradict the possibility of a direct effect of the cold on the recorded regions or the radiations fibres. (1) There was no statistically significant correlation between the incidence or the strength of the response decrease and the depth of recording or the temperature of the probe. (2) Neurons showing response increases or no changes were mixed

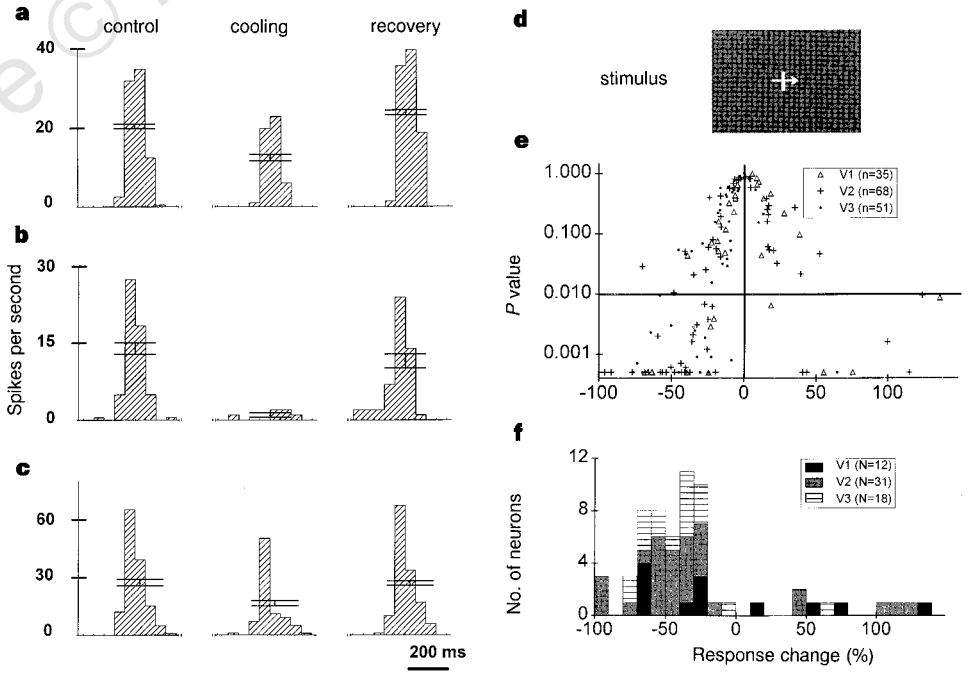


**Figure 1** Effect of V5 inactivation on responses of neurons in areas V1, V2, V3. The stimulus was a light bar moving on a stationary background of lower contrast. **a–c**, Points and bars over each histogram represent the mean and s.e.m. Bin width = 50 ms. **a**, Area V1, 39% decrease of the response, case lca21. **b**, Area V2, 91% decrease, case kas11. **c**, Area V3, 40% decrease, case lck21. **d**, Illustration of the stimulus. **e**, Scattergram of statistical significance (*P*-value) versus percentage change in response. The horizontal bar indicates the level of significance used ($P < 0.01$). **f**, Distribution histogram of the percentage change in response for significant effects ($P < 0.01$).

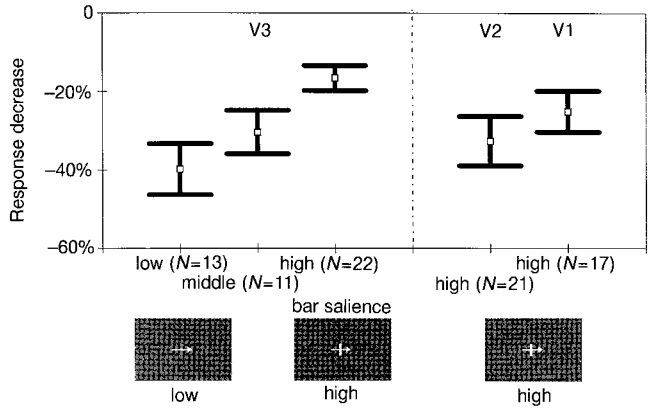


**Figure 2** Effect of bar salience. Left box, effect on the response decreases due to V5 inactivation for V3 neurons stimulated with a moving bar on a stationary textured background (mean values ± s.e.m.; calculated for all the neurons showing response decreases). Strongest effects are observed for low salience of the bar (Kruskal–Wallis test, $P = 0.003$). A similar, but nonsignificant trend was observed in areas V1 and V2. Right box, values of response reductions for high-salience stimuli in areas V1 and V2. The reductions at high salience were not significantly different in the three areas ($P = 0.13$ in a Kruskal–Wallis test). The salience is defined as the ratio of the contrasts of the bar and the background. Low salience, 1–7; medium salience, 7–15; high salience, >15.

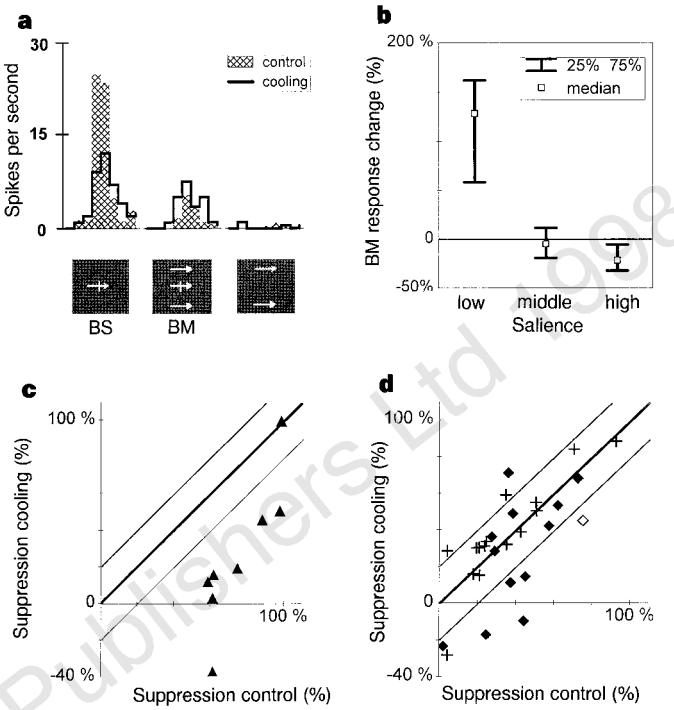


**Figure 3** Effect of V5 inactivation on foreground–background interactions in V3 neurons. **a**, Responses before and during V5 cooling to a central bar moved on a stationary background (BS), to the same central bar moved coherently with the background (BM), and to the background alone. Case lcj21, area V3, salience 13.1, bin width 100 ms. **b**, Percentage change in response for the BM stimulus (bar and background moving together) during V5 inactivation. Only cases in which BS > BM activity were included. The difference between groups is highly significant ($P = 0.0086$ in a Kruskal–Wallis test; salience as defined in Fig. 2: low, $n = 8$; middle, $n = 13$; high, $n = 15$). **c**, Scattergram of the background-induced response suppression ($100 \times (BS - BM)/BS$) during V5 cooling versus control (mean value) for low salience. Central diagonal line indicates no change; the flanking lines indicate changes within 20% which include practically all the points in a similar scattergram between the two control runs. Values below the line of no change (central dark line) correspond to a decrease in response suppression. **d**, The same as (**c**) but for middle-salience stimuli (filled diamonds) and high-salience stimuli (+ symbols). Open symbol corresponds to example in (**a**). The cooling-induced changes in suppression for different groups of salience was highly significant (Kruskal–Wallis test, $P = 0.0004$; there was no significant effect between the controls: Kruskal–Wallis test, $P = 0.45$).

among neurons showing response decreases in the same penetrations. (3) Most effects were stimulus specific: besides the mentioned dependence on salience, we found that for most neurons showing a significant response decrease for the moving central bar, there was an increase or no change in response to at least one other stimulus presented in an interleaved fashion (Fig. 3a).

It is clear, however, that areas of the V5 complex that surround V5, such as areas MST, FST and V4t, are partly affected by the cooling. We believe that the effects we observed were mostly due to inactivation of area V5, as this area provides the strongest contingent of feedback connections to areas V1, V2 and V3 (refs 2–4, 9, 16). This conclusion is supported by the observation that no effect was observed in another animal in which the probes were placed rostral to V5 in the STS.

Our results show that feedback connections from area V5 have a facilitatory effect on the responses of neurons in areas V1, V2 and V3 to a bar moved on a stationary background. This agrees with known anatomy showing feedback projections terminating mainly on spiny, excitatory neurons, presumably of pyramidal type, and much less so on sparsely spinous inhibitory neurons[17]. The boosting effects of feedback connections can be quite strong, particularly for low-salience stimuli: some neurons in V1, V2 and V3 are completely silenced in the absence of a feedback input from V5 (Fig. 1b, f). This means that the activity of a neuron in a given cortical area is not simply shaped by its feedforward inputs and the local network of horizontal connections, but depends crucially on the activity of neurons located in higher-order areas and transferred through feedback connections.

Although inactivation of feedforward[18,19] as well as feedback connections produce mainly a decrease of neuronal responses, there are clear differences between the roles of the two pathways. For example, when V1 is inactivated, all activity is abolished in area V2, despite the fact that most neurons remain active in V5 (refs 18–20). In other words, in the absence of a drive from V1 through feedforward connections, feedback connections from V5 are unable to drive neurons in V2. Similar conclusions on feedforward/feedback differences have been reached from experiments using cats, where deactivation of the middle suprasylvian cortex, a possible homologue of V5, has little effect on neural activity revealed in areas 17 and 18 by 2-deoxyglucose (2DG)[7]. It is therefore likely that, at least in anaesthetized preparations, feedback connections act more as a gain enhancer, or gater, of activity already present, rather than as an activator of otherwise silent neurons, a role presumably reserved for feedforward connections.

Inactivation in V5 usually had opposing effects on figure–ground stimuli of low salience, decreasing the response to the central bar and increasing the response to the bar and background moved coherently. Thus, feedback connections may act in a push–pull fashion, amplifying the response to the optimal stimulus for the centre mechanism and decreasing that to stimuli activating centre and surround (Fig. 3a). These push–pull interactions are at their strongest for low-salience stimuli. This interesting specificity implies that feedback projections serve to improve the visibility of features that activate the receptive field centre in the stimulus and may thus contribute to figure–ground segregation, breaking of camouflage, and psychophysically demonstrated 'pop-out' effects. □

## Methods

**Physiology.** Recordings were obtained from two anaesthetized, paralysed cynomolgus monkeys. Procedures were similar to those reported earlier[21]. For analgesia, we replaced fentanyl by suffentanil (usually $4\,\mu g\,kg^{-1}\,h^{-1}$). A spike discriminator (MSD from Alpha Omega) was used to extract single units from our recordings and to monitor neuronal identity during periods of control,

cooling and recovery. The receptive fields of recorded neurons were located in the central 4° of visual field. Electrolytic lesions were used to aid reconstruction of electrode tracts on histological sections stained for Nissl substance, cytochrome oxidase and Cat301. We relied principally on Cat301 labelling[22] to identify V3 and MT/V5.

**Cooling.** The general procedure was similar to that described earlier[23]. Several months before the experiment, two probes, consisting of a 7 mm × 3 mm loop of hypodermic tubing, were placed side-by-side in the depth of the STS at the level of area V5, ipsilateral to the recordings. The proper placement of the probes was verified post-mortem on histological sections stained as above. Cooled methanol was circulated simultaneously through both probes. Probe temperatures (mean value 7.2 °C, range 2.5–12 °C) were monitored by thermocouples at the base of the cooling loops.

Runs usually lasted for 3.5 min. Two control runs were done before cooling was applied. Recording during the cooling run was started once the probes reached constant temperature, a few minutes after the chilled methanol began circulating. After a pause of 15–30 min after the end of the cooling run, one or several recovery runs were done.

It is important to determine to what extent the tissue is affected by the cold. It was shown earlier that the average temperature gradient created by the probe is 10 deg mm$^{-1}$ and that neuropil beyond 3–3.5 mm from the cooling probe is at physiological temperature (Fig. 1 of Lomber *et al.*[23]). This was confirmed by 2DG mapping showing that the metabolic activity of cortex located 3 mm away from the cooling probe was totally unaffected by the cooling[7]. From earlier anatomical publications[2], we measured the following shortest distances between retinotopically corresponding regions in STS and V1, V2, V3 and V4: 7, 5.7, 7 and 3.4 mm. Thus it is highly unlikely that these areas are affected by the cold. This was confirmed by measuring in two instances the temperature from the surface of area 17 down to a depth of 8 mm (corresponding to our recordings in V3). In one experiment there was no change in temperature throughout the cortical depth and in the other case the temperature dropped by less than 2 °C when the probes were cooled.

Furthermore, because fibres of the optic radiations travel 1–2 mm below the STS grey matter[24], even for the lowest temperature of our probes (2.5 °C), these fibres did not reach temperatures lower than 27 °C. Because fibres have a blocking temperature at least 10 deg lower than cell bodies that are inactivated below 20 °C[25,26], it seems very unlikely that direct blocking of LGN fibres could explain our results.

**Visual stimuli.** Visual stimuli were presented on a computer monitor driven by a Truevision Vista Board under the control of a Matlab program. Stimuli were presented twenty times in an interleaved fashion. The bar was approximately optimized in size and velocity for each neuron site studied. Orientation was optimized to within 15° by measurement of an orientation tuning curve. The background covered a field that was 12.7° wide and 8.4° high and that comprised randomly distributed checks of a size equal to the bar width. The background had the appearance of a set of bars of variable length and similar orientation as the central bar, which was only visible against the background if it differed in contrast or relative movement. One set of luminance values was used at each site, with mean background luminance, $L_0$, being in the range 9–24 Cd m$^{-2}$. The contrast of the bar relative to this luminance, $C_{bar} = (L_{bar} - L_0)/L_0$, was in the range 0.72–12.6. The contrast of the light background checks relative to $L_0$, $C_{check} = (L_{check} - L_0)/L_0$ (equal to the Michelson contrast of the light–dark checks) was in the range 0.06–0.98. The salience is equal to $C_{bar}/C_{check}$. Selection of different luminance combinations for the bar and background was not systematic.

**Data processing.** To limit the presence of false positive results due to poor stationarity of the cortex, data were analysed only when the responses to the first two control runs were not significantly different ($P > 0.01$). Responses were measured as the mean number of spikes over the stimulation period for 20 repetitions of the stimulus. Because of the non-gaussian distribution of the data and occasional changes in variance between conditions, we used a bias-corrected and accelerated-bootstrap Student-*t* procedure[27] to assess the statistical significance of differences in the mean number of spikes across the different runs.

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# Stress and glucocorticoids impair retrieval of long-term spatial memory

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**Extensive evidence from animal and human studies indicates that stress and glucocorticoids influence cognitive function[1–11]. Previous studies have focused exclusively on glucocorticoid effects on acquisition and long-term storage of newly acquired information. Here we report that stress and glucocorticoids also affect memory retrieval. We show that rats have impaired performance in a water-maze spatial task after being given footshock 30 min before retention testing but are not impaired when footshock is given 2 min or 4 h before testing. These time-dependent effects on retention performance correspond to the circulating corticoster-**