Modulation of neuronal responses in macaque primary visual cortex in a memory task

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Abstract

The primary visual cortex, a relatively early station in the visual pathway, has long been considered mainly as a site of basic feature detection but evidence is emerging that is consistent with the existence of feedback influences from higher cortical areas. We show that in a delayed match-to-sample memory task, where the monkey needs to remember both the visual pattern and its location, there is significant modulation of neuronal activity in the primary visual cortex suggestive of a feedback signal. Responses to identical patterns are remarkably different depending upon their place in the memory task. These modulatory influences are significantly less when the same visual patterns are shown during a simple fixation task, where these stimuli can be ignored and not attended to. The results indicate that neural processing specific to attentional and mnemonic functions can involve even primary sensory areas.

Introduction

Four decades of neuroscientific research have firmly established the role of the primary visual (striate) cortex in the processing of basic stimulus features such as orientation, contrast, colour, binocular disparity and movement but recently there has also been evidence for modulation of its activity by feedback influences related to attention (Motter, 1993; Roelfsema *et al.*, 1998; Vidyasagar, 1998; Brefczynski & DeYoe, 1999; Somers *et al.*, 1999; Gandhi *et al.*, 2001; Super *et al.*, 2001a; Di Russo *et al.*, 2003; Li *et al.*, 2004; Boynton, 2005; McAdams & Reid, 2005) and contextual processing (Zipser *et al.*, 1996; Hupe *et al.*, 1998; Super *et al.*, 2001b). Although such modulation may be expected on the basis of models of early attentional selection (Wolfe, 1994; Treisman, 1988; Vidyasagar, 1999), memory functions have so far been mostly considered as a preserve of brain regions higher up in the hierarchy, such as the inferotemporal (IT) cortex, hippocampus and frontal cortex (e.g. Squire, 1987; Fuster, 1995; Ishikawa *et al.*, 1996; Miller *et al.*, 1996). This belief is, however, based upon human clinical studies, and lesion and neurophysiological studies on macaques conducted using simple, isolated (i.e. sparse, uncluttered) sensory stimuli. However, a necessary constraint of the extrastriate, IT regions usually held responsible for object recognition is the large receptive field (RF) sizes of their neurones (Boussaoud *et al.*, 1991). Although the large RFs form the basis of the useful property of position invariance (i.e. being able to recognize objects irrespective of their locations), many real-life situations involve simultaneous encoding of objects and their locations in a highly cluttered visual world. This may require that regions subserving object recognition link dynamically with one or more higher brain regions that encode spatial locations of objects or interact

with a region that has a fine grain topographic representation of the visual scene, such as the primary visual cortex. There is indeed some evidence for mnemonic effects in primary visual (Super *et al.*, 2001a) and somatosensory (Zhou & Fuster, 1996) areas. To explore this issue, we trained monkeys in a delayed match-to-sample (DMS) memory task (Fig. 1), where the animal needed to remember both the visual pattern and its location and we recorded the activity of striate cortical cells during the performance of this task ('active' task). The responses of the cells were compared with those in a 'passive' task, in which identical visual patterns were shown during a simple fixation task, where the monkey could ignore these stimuli. This task was introduced as a control to test for effects due to the visual stimuli themselves, such as adaptation (Müller *et al.*, 1999) or paired-pulse facilitation (Volgushev *et al.*, 1997), which are known to occur in the striate cortex and can potentially confound the results obtained in the memory task.

In our study we have primarily attempted to assess possible contributions from attention and memory functions in the striate cortical response. While acknowledging that there are more possibilities, we have focused our data analysis on the following six types of cell responses that are theoretically possible and of interest in the experimental paradigm (Fig. 2). (A) Visual responses unmodulated by attention, memory or other contextual factors, giving similar responses to sample [first grating stimulus in each trial of the DMS task (S1)] and test [second grating stimulus in each trial of the DMS task (S2)] stimuli in both tasks. (B) Responses that depend upon whether the monkey is paying general attention to the visual stimuli, thus showing enhanced responses to both S1 and S2 in the active DMS task compared with the passive task. (C) Cells showing increased neuronal activity during the delay period between the two stimuli in the active task but not in the passive task, indicating that some sort of memory trace is coded in the neurone's firing rate (retention), as in a recent report (Bisley *et al.*, 2004) on middle temporal (area MT) neurones. (D) Responses to the same visual stimulus may be different depending upon whether it

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FIG. 1. Delayed match-to-sample (DMS) experimental paradigm. Typically, 200 ms after the appearance of the fixation spot (0.1° diameter; not drawn to scale), the first grating is flashed for a period of 80 ms (in this example) with the same presentation time within any one block, which consisted of 100 trials. After a delay, which was around 1 s, a second grating is flashed for the same duration as the first. After a minimum of 300 ms after the offset of the second grating, the fixation spot was dimmed for 700 ms and then extinguished. (b) The four possible combinations between the two gratings. The monkey was required to release the bar as soon as the spot dimmed if the two gratings matched for both stimulus orientation and location in the visual field. The monkey had to wait until the spot disappeared entirely to release the lever if it was a non-match trial (NM). M, match trial. (c) Raster and peristimulus time histogram (PSTH) of a primary visual cortex or striate cortex cell in the active DMS task is shown for the match stimuli. This and the spike density functions in Fig. 3 (binwidth 25 ms) all show only the responses for the match trials, where the grating stimuli (first and second grating stimuli in each trial of the DMS task and second grating stimulus in each trial of the DMS task) were identical and for the grating orientation that evoked the better response. The bottom panels show the times of grating presentation, period of obligatory eye fixation and presence of the fixation spot (dimming of the spot not shown).

happens to be the first (S1) or second (S2) stimulus in the active task, but not so in the passive task, indicating that the neurone discriminates between stimuli that are to be stored in memory (encoding) and stimuli that are being matched with images already stored in memory (recognition). (E) Cell responses similar to D in the active task but also generally poorer responses in the passive task, thus showing both an attention and a memory component. (F) Cells that show increased responses to repeated (match) stimuli, only in a mnemonic context but not for simple repetition of a stimulus, similar to those found by Miller & Desimone (1994) in IT cortex. Such cells will show an enhancement to S2 in the match trials but not in non-match trials and will actually show a suppression of S2 response in the match trials of the passive task. Although response type B is likely to be purely related to attention (as in Vidyasagar, 1998; McAdams & Reid, 2005), response types C–F indicate possible memory-related influences. We report here that, apart from simple visual cells (type A), a substantial number of neurones in the striate cortex exhibited the type of modulation in the active, matching task shown in panels D and E (Fig. 2). The responses in the active and passive tasks will be analysed with a view to throwing light on whether the differences are due to a mnemonic component in addition to any attentional component.

Materials and methods

Behavioural training

Two male macaques (*Macaca nemestrina*) were trained on a special version of a DMS task (Fig. 1a). Stimuli were presented on a monitor (Barco Industries, Belgium) at 57 cm from the monkey and driven by a Truevision Vistaboard from a PC. Each trial was started by the monkey pressing a lever that caused a small grey fixation spot (0.1° diameter) to appear on the monitor. While the animal was maintaining fixation, a patch of sine wave grating (stimulus 1, sample or S1), either horizontal or vertical and usually subtending $8^\circ \times 8^\circ$, was flashed at a location in the parafoveal region for a period of 150 ms and a second grating of the same size (stimulus 2, test or S2) was flashed for a similar duration after a delay of 900 ms. We used different stimulus durations in 11 cells (down to 80 ms) and shorter delays in eight cells (down to 200 ms) among our sample of 52 cells tested on both behavioural tasks to look for any prominent effects from these parameters on the main findings reported here. These were not seen, however, and so these results are pooled with the main body of data. Either grating (S1 or S2) could appear in one of usually five different, spatially non-overlapping locations around the fixation point but one

FIG. 2. Schematic diagram (not to scale) of the six types (A–F) of cell responses that are theoretically possible in our experimental paradigm and at which the data analysis was directed. The horizontal bar below each trace showing cell spikes indicates the time of presentation of the sample [first grating stimulus in each trial of the delayed match-to-sample (DMS) task (S1)] and test [second grating stimulus in each trial of the DMS task (S2)] stimuli. This was usually 150 ms, and the delay period between S1 and S2 usually 900 ms. Each panel is described in detail in the text.

location was centred over the RF and covered it entirely. The centres of the grating patches usually constituted five of the nine points of a 3×3 array, leaving out the centre (the location of the fixation point) and the three locations falling on the side ipsilateral to the hemisphere being recorded from (see Supplementary material, Fig. S1). The centres of the gratings were separated from each other in the X- or Y-axis by $8-9^\circ$. All recordings in both monkeys were from the left hemisphere, with the right hemispherical sites being reserved for later experiments to study processes underlying transfer of the learning to new locations. During recording sessions, the black and white sine wave gratings (illuminant C; 30% contrast with a mean luminance of 15 cd/m^2 on a background of the same luminance) were optimized for spatial frequency and phase during the passive task. The optimal spatial frequency was usually within the range of $0.5-2 \text{ cycles/}^\circ$ at the eccentricities that we recorded ($4-10^\circ$). In this rather difficult task (a covertly attended DMS task for pattern and place with maintained central fixation) it was not easy to train the monkey to generalize for orientation, i.e. to present any two orthogonal orientations as the pair of orientations to be used in a block. Therefore, we took the approach of using only two orientations, namely vertical and horizontal, and we analysed only cells whose preferred stimulus orientation was within 10° of vertical or horizontal. In practice, this was not a serious impediment in obtaining adequate number of cells, as we could target the same orientation column in subsequent penetrations with our implantation technique. It was, however, easier to train the monkey to generalize for spatial frequency, i.e. it could still perform the orientation and location matching task if presented with gratings of a different spatial frequency. Therefore, we were able to optimize the

spatial frequency for each cell. The monkey needed to compare both the orientation and location of the two gratings in each trial and respond in one of two ways to indicate whether the gratings matched for both of these parameters. Thus, it would be a 'match' trial only if the second grating had the same orientation as the first and also appeared at the same location (Fig. 1b). At the end of the fixation period, the fixation spot was first dimmed for 700 ms and then extinguished. If the two gratings were matched for both orientation and location ('match' trials), the monkey was required to release the lever as soon as the fixation spot dimmed but if the gratings were not matched for either of the two parameters ('non-match' trials), it was required to wait until the spot disappeared entirely before releasing the lever to obtain fruit juice reward. The monkey was allowed a reaction time window of 200–650 ms. The total duration of the fixation spot until it dimmed was usually 1500 ms. However, to avoid the monkey getting used to a rhythm and to make sure that it fixated during the whole period and maintained attention in the task, the duration of the fixation spot was varied between 200 and 1700 ms. Both sample and match grating stimuli were presented only in those trials where the fixation spot lasted long enough to include a period of 200 ms before the onset of the first grating and a period of at least 200 ms after the offset of the second grating, thus usually for more than 1400 ms. Match and non-match trials summed across all locations were nearly 50% each but the different match and non-match stimuli at different locations were pseudorandomized within each block to enable sufficient numbers of critical trials (match trials of optimum or near optimum stimulus orientation on the RF) to be presented within the available time. We did this by increasing the probability of the stimuli

over the RF so that ultimately around 10–15% of the total trials were match trials of optimal or near optimal orientation on the RF (see Supplementary Appendix S1A for the logic used in pseudorandomization). This slightly increased the probability of stimuli appearing at the RF location but there were no differences in performance between retinal locations to indicate a significant bias in spatial attention due to this pseudorandomization. Any tendency of the monkey to allocate more spatial attention to the RF location was partially offset by periodically transferring, in some blocks, the increased probability to other locations.

The monkeys were trained to maintain eye fixation during learning of the DMS task by a number of procedures, such as 'catch trials' that included either no gratings or only the first grating. The fixation spot disappeared at the end of its randomly varied duration and the monkey had to simply release the lever within the usual reaction time window to obtain reward, ignoring any grating. In all trials, the onset of the first grating was also randomly varied from trial to trial (100–300 ms). For further details of these training procedures, see Vidyasagar (1998) and Pigarev *et al.* (2001). These procedures helped to train the monkey to avoid any eye movements during the time that the fixation spot was on. After the implantation surgery (see below), eye movements could be monitored to provide the feedback for fixation by aborting trials when fixation was lost. It was then observed that the monkeys were fairly well trained in fixation by the above pre-surgical fixation procedures and needed only about a week to attain satisfactory fixation within the defined window (40' of arc in radius) to permit single-unit recordings. The window for obligatory eye fixation started at least 50 ms before the first stimulus and lasted at least 300 ms after the offset of the second stimulus.

The monkeys were also trained on a simple fixation task. During the period of fixation in this task (to be referred to as the 'passive task' in contrast to the DMS task above, which will be referred to as the 'active task'), grating stimuli similar to those in the active task were presented. However, in the passive task the monkeys could ignore the presented gratings and were rewarded just for maintaining fixation. The monkeys initiated each trial by pressing a lever, which brought on the fixation point and they had to release the bar within 650 ms when the spot disappeared; there was no dimming period. A slight red tinge to the fixation spot indicated to the monkey right from the beginning of the block that this was the passive task and not the active memory task. The same gratings were presented at the same locations and with the same probabilities of presentation as in the active task. Thus, visual responses to identical visual stimuli could be recorded during either the active memory task or the passive fixation task. Despite the incorrect responses and pseudorandomization, most of the data used in the analysis had at least 10 trials for the condition of interest, with an average of 14 for the active task and 15 for the passive task. At the time of the recordings, the monkeys were well trained in both tasks. The mean correct response rate for the blocks included in the analysis here (after exclusion of eye fixation errors) was 82% in the active task and 89% in the passive task (paired *t*-test, $P < 0.0001$), the passive task being, understandably, easier. Although there was no difference between performance in match and non-match trials in the passive task (paired *t*-test, $P > 0.7$), there was a small difference in the active task (85% for match and 79% for non-match trials, $P < 0.01$). This deficit in non-match trials is probably due to the extra time that the monkey has to wait (the fixation spot dimming period of 700 ms) before it could release the bar to receive reward because most errors were a slightly earlier release of the bar. The correct reaction times themselves were similar between active and passive tasks for each monkey (*t*-test, $P > 0.3$). In 17 of the 52 cells reported here, data were first collected for the passive task but the main effect reported here was seen in

roughly the same proportion of cells there (4/17) as in the rest of the sample (11/35).

Surgery and electrophysiology

When the monkeys had been trained in the DMS task to reach consistent performance at a minimum of 80% correct responses, they were fitted with a frame around the head under ketamine (10–15 mg/kg, i.m.) plus xylazine (0.5–2 mg/kg, i.m.) anaesthesia. The surgery followed a variation of the technique described elsewhere (Pigarev *et al.*, 1997), with a rigid metal frame fitted around the head 'like a halo' and attached to the skull by five posts that just jut against the bone. As the forces along these posts counterbalance each other, the system does not need to be screwed into the skull. This technique allows easy access to most of the scalp surface for electrode penetrations. The frame was used in immobilizing the monkey's head during the recording period and for carrying the Kopf hydraulic microelectrode holder. Small holes (1.5–2 mm) were drilled into the skull under anaesthesia and fitted with short (20–25-mm-long) conical plastic guide tubes for insertion of lacquer-coated tungsten electrodes. These craniotomies were located close enough to the posterior pole and well away from representations of the vertical and horizontal meridians, and usually at a retinal eccentricity of 3–8° in the inferior visual field in primary visual cortex (striate cortex or area V1). In one of the two monkeys used in these experiments, most eye movement recordings were performed using a scleral search coil (Judge *et al.*, 1980) in 1.8-m field coils (CNC Engineering, Seattle, WA, USA). For some recordings in this monkey and for all recordings in the other monkey, we used a non-invasive high-resolution infrared system with an analogue output (Dr Bouis, Karlsruhe, Germany) to monitor eye movements. The outputs were passed through a low-pass filter with a cut-off frequency of 400 Hz and digitized at 1 kHz. Both systems had a minimum resolution of 3' of arc. The monkeys had to maintain fixation within 40' of arc and any eye movements outside this window during a period starting at least 50 ms before the onset of the first grating and extending for at least 300 ms beyond the second grating led to the trial being aborted. The response to each grating was calculated within a window of 200 ms starting 50 ms after stimulus onset. In comparing response rates either between sample and match stimuli or between active and passive tasks, we used non-parametric tests because the distributions were not always normal. All results shown are only the correct responses for match trials for the grating orientation (vertical or horizontal) that gave the better response at the RF location of the cell. As we searched for visual cells while the monkey was performing the memory task, cells that were unresponsive to the two orientations were rarely encountered. Orientation tuning was tested, usually using hand-held stimuli, and only cells with optimum orientation within 10° of the vertical or horizontal orientation were further recorded from.

The experiments were approved by the Australian National University's Animal Experimentation Ethics Committee and conformed to NIH guidelines and the Australian Code of Practice for the Use of Animals for Scientific Purposes.

Results

We present below our results from the cells recorded from the striate cortex of the two trained monkeys by comparing their responses in the two tasks in accordance with the predictions made earlier in Fig. 2A–F.

Comparison of visual responses between the memory task and passive fixation

A total of 78 striate cortical cells were recorded from two monkeys during the performance of the active DMS task (see Materials and methods for details). Figure 1c shows the responses of one of these cells for the match trials of the presentation of a horizontal grating on the cell's RF. The responses to S1 and S2 are significantly different (Mann–Whitney U -test, $P < 0.015$). Figure 3 shows the responses for three more cells and compares the responses in the active and passive tasks. In all three cells, the differences between S1 and S2 responses in the active tasks were statistically significant (Mann–Whitney U -test, $P < 0.05$), whereas for the passive task there was no significant difference in any of the three cells. Responses of the cell shown in Fig. 3a were also significantly poorer in the passive

task (Mann–Whitney U -test, $P < 0.05$) compared with the active task.

Figure 4 compares the responses for the first and second gratings for all of the cells in our sample in the active and passive tasks. Forty-three (55%) of the 78 cells tested in the active task (Fig. 4a) showed a significant difference (Mann–Whitney U -test, $P < 0.05$) between responses to S1 and S2. The responses were also recorded in a passive task in 52 of these 78 cells (39 from Monkey 1 and 13 from Monkey 2). The main effect that we report here (i.e. the difference between the two tasks) was seen in both monkeys and so the data from the two animals are pooled. Figure 4b compares the responses for S1 and S2 in the passive task. In only six (11.5%) of these 52 cells was there a difference between S1 and S2 that reached statistical significance (Mann–Whitney U -test, $P < 0.05$). Figure 4c compares the degree to which each cell of the sample discriminates between S1

FIG. 3. Responses of three different cells (a–c) are shown as spike density functions (with 2 SEM, thin lines) in both the active delayed match-to-sample (DMS) task and the passive task. Responses are to the same grating stimuli in both tasks. Spatial frequency and orientation of the gratings used were near optimum for each cell. The bar below each peristimulus time histogram shows the timing of the two gratings (first grating stimulus in each trial of the DMS task and second grating stimulus in each trial of the DMS task).

FIG. 4. Responses for the first and second grating stimuli are compared in the active task (a) (78 cells) and in the passive task (b) (52 cells). Filled circle represent cells where the difference between responses to the first and second grating was statistically significant. open triangle represent the cells where the difference was not significant (Mann–Whitney U -test, $P > 0.05$). (c) Comparison of the actual difference in response between the first and second gratings in the active and passive tasks. This includes the 52 cells that were tested in both active and passive tasks. For each cell and for each condition (active and passive), the first grating stimulus in each trial of the delayed match-to-sample (DMS) task–second grating stimulus in each trial of the DMS task (S1–S2) response was calculated for each trial and then averaged ($\pm$ SEM shown as error bars). The dashed line is the identity line of slope 1.

and S2 in the active and passive tasks. Such discrimination in spike rate is more in the active task (mean $15.3 \text{ spikes/s} \pm 1.51 \text{ SE}$) than in the passive task (mean $6.13 \text{ spikes/s} \pm 0.79 \text{ SE}$). This difference between active and passive tasks is statistically very significant (paired t -test, $P < 0.0001$). Applying a non-parametric test to compare sample and match responses on a cell-by-cell basis (Mann–Whitney U -test, $P < 0.05$), 32 cells showed a significant difference in the active but not in the passive task, three cells showed a difference in the passive but not in the active task and three cells showed a difference in both. 14 cells showed no significant difference between S1 and S2 in either task.

Furthermore, the slope of the regression line (solid line) in Fig. 4c was only $0.19 \pm 0.056 \text{ SE}$ ($r = 0.44$; $P < 0.002$), with 95% confidence limits (0.079–0.304) not including the identity line. However, as linear regression is not very appropriate to apply between two dependent variables, we also performed a non-parametric test between the absolute S1–S2 differences in the two tasks, which showed a significant difference between active and passive tasks (Wilcoxon signed-ranks test, $P < 0.001$). This suggests that discrimination between the stimuli S1 and S2 was far less in the passive task. We further examined whether the response difference between S1 and S2 itself differs significantly between the two tasks for each cell. However, this analysis can be confounded by differences in overall response level, as the active and passive tasks cannot be interleaved and were conducted in different blocks. Therefore, the response differences (S1–S2) in each trial were normalized to the average of all S1 and S2 responses in that block and then a comparison was performed between the active and passive blocks. This analysis showed that 15 (29%) of the sample of 52 cells in Fig. 4c showed a significant difference (Mann–Whitney U -test, $P < 0.05$) in the stimulus discrimination between the two tasks, i.e. departing significantly from the identity line of slope 1 (dashed line in Fig. 4c). We also calculated a normalized index for stimulus discrimination for each cell for both tasks $[(rS1 - rS2)/(rS1 + rS2)]$, where $rS1$ is response to S1 and $rS2$ is response to S2, which gives a value between -1 and $+1$, with -1 indicating response only for S2, $+1$ indicating response only for S1 and 0 indicating equal response for S1 and S2. Figure 5 plots the index in the passive task against that for the active task for each cell. This figure also shows that stimulus discrimination was much less for the passive task. The linear regression has a slope of $0.32 \pm 0.07 \text{ SE}$ ($r = 0.54$, $P < 0.001$), with 95% confidence limits (0.178–0.459) not including the identity line. Again, we performed a non-parametric test between the absolute S1–S2 differences, which showed a significant difference between the active and passive tasks (Wilcoxon signed-ranks test, $P = 0.002$). The above results indicate that a high proportion of cells in striate cortex fall in the category that discriminate between S1 and S2 much more in the active task than in the passive fixation task (i.e. category D in Fig. 2).

The overall response level between the active and passive tasks showed small but significantly higher responses in the active task (see Supplementary Appendix S1B). As the tasks were run in separate blocks, it may not be easy to interpret this (to test whether some of the cells may be in category E rather than D of Fig. 2) but, more importantly, comparing the means of all 52 cells for S1 and S2 in the two tasks, there was no statistically significant trend (repeated-measure ANOVA, $0.1 > P > 0.05$) towards a shift of the population response to higher S1 or S2 activity depending upon the task. There was also no indication that in one monkey the responses to S1 were more and in the other monkey responses to S2 were higher in either the active or passive task (repeated-measure ANOVA, $P > 0.1$).

FIG. 5. Comparison of stimulus discrimination in the active and passive tasks. A normalized stimulus discrimination index was calculated for each cell as a measure of the degree to which the cell discriminates between the first and second grating stimuli $[(rS1 - rS2)/(rS1 + rS2)]$. The regression line (continuous line) is shown as well as the identity line (dashed line).

Analysis of delay period responses

In a delayed response task, where the monkeys needed to remember the target position during a delay phase before they made an eye movement to it, striate neurones have been reported to show increased activity during the retention phase (Super *et al.*, 2001a). In our sample of 78 cells from the primary visual cortex, we had no indication that there was a significant increase in maintained activity during the delay period in our memory paradigm beyond the initial 100 ms during which there are often off responses to the first stimulus. The mean maintained activity during a 100-ms interval prior to S1, when the monkey was already fixating, was 8.5 spikes/s (± 1.3 SE) in the active task and this was not significantly different (paired *t*-test, $P > 0.5$, $n = 52$) from the maintained activity (8.6 spikes/s ± 1.1 SE) during the delay period between the two stimuli, starting 150 ms after offset of the first grating. Mean spontaneous activity during the passive task (7 spikes/s ± 0.9 SE) was also not significantly different from that during the active task (paired *t*-test, $P > 0.1$). Thus, in our paradigm, there seems to be no indication of a memory-related activity during the delay period.

Control for eye movements

Although it appears that the responses of many of our striate cells could be modulated by the task demands related to attention and/or memory, it is first necessary to consider the possibility of artefacts due to subtle eye movements. This is a serious possibility in recordings in area V1 due to the small sizes of RFs and the marked effects that eye movements, particularly drifts and microsaccades, can have on striate cortical responses (Leopold & Logothetis, 1998; Martinez-Conde

et al., 2000). We have considered four possible artefactual effects that can lead to differences between sample and match stimuli in the active but not in the passive task. (i) A change in mean eye position between presentations of S1 and S2, that might happen only or mainly in the active task and is large and consistent enough, can potentially produce the main effect reported here. (ii) If there is poorer fixation stability during the passive task, it may mask consistent differences between responses for sample and match that may otherwise be present in both tasks. (iii) The frequency of microsaccades may change between S1 and S2 for the active but not for the passive task. (iv) There could be vergence changes between the presentation of sample and match stimuli that are consistently more in the active task. In the case of neurones sensitive to disparity, this could make a significant difference in the cells' responses to S1 and S2.

Detailed analysis was undertaken on 37 cells (25 from Monkey 1 and 12 from Monkey 2) where complete eye movement data were available for offline study. The results (reported in detail in the Supplementary Appendix S1C and Figs S2 and S3) indicate that none of the four factors mentioned above could explain the findings reported above. In summary, only about 10.8% of the observed variance in the difference between sample and match stimuli seen in the active task could be attributed to eye position differences. There was also no difference in the fixation stability between the active and passive tasks, and nor was there any significant degree of correlation between microsaccades and the responses that could explain the main effect. Our results also suggest that vergence changes were unlikely to have produced the results.

These control studies are consistent with the finding that attentional capture by a transient onset of a peripheral stimulus, whether abrupt (Tse *et al.*, 2002) or predictable (Kowler & Steinman, 1979), does not cause any changes in the pattern of eye movements during fixation; changes are seen only if the task requires a saccade to be made (Tse *et al.*, 2002), which is not the case in our paradigm. Furthermore, attentional capture itself by the task-irrelevant grating stimuli in the passive task would have been weak (Folk *et al.*, 1992; Most *et al.*, 2005).

Is there match vs. non-match differentiation?

Apart from the differentiation between sample and match stimuli shown above, we also investigated whether there could be any discrimination between match and non-match trials by striate cortical cells as a genuine component of the memory task (as shown for the active task in category F in Fig. 2). This may be seen as a difference in the response to an optimum S2 stimulus flashed on the RF, depending upon whether it was part of a match or a non-match trial or, in other words, depending upon whether S1 was of the same orientation as S2 or was of the orthogonal orientation. Such a difference, particularly a greater S1–S2 difference for match than for non-match stimulus pairs, may also be a consequence of feature-based attention (Motter, 1994a,b) operating at the level of the primary visual cortex. We performed this analysis by comparing the responses of striate cells to the same optimum stimulus on the RF that was either S2 in a match trial or S2 in a non-match trial. As our pseudorandomization procedure distributed the non-match trials among a greater number of conditions than the match trials, there were generally fewer relevant non-match trials, i.e. those with S2 on the RF. We could, however, analyse 43 cells that had a minimum of four non-match trials in both active and passive tasks (mean of 8.5 ± 0.5 SE trials for active and mean of 9.4 ± 0.6 SE trials for passive tasks). We have included in this analysis only those non-

match trials where both S1 and S2 were flashed on the RF, as the randomization led to very few trials where optimum S2 was on RF but the S1 grating was elsewhere. As reported earlier, this subgroup of cells also showed a distinction in the responses to match trials between active and passive tasks, with 67% (29 cells) showing a significant difference (Mann–Whitney *U*-test, $P < 0.05$) between S1 and S2 responses in the active task, whereas it was down to 11.6% of cells (five cells) in the passive task. However, with the active task it was apparent that a distinction between match and non-match trials was far from common. Overall, only 14% (6/43 cells) showed a significant difference (Mann–Whitney *U*-test, $P < 0.05$) between the responses to S2 stimuli preceded by a matching or a non-matching grating, whereas 40% (17/43 cells) showed a significant difference between the responses to the non-matching but optimum S2 stimulus and the response to the optimum S1 stimulus from match trials. In other words, responses to optimum S2 stimuli were generally the same regardless of the S1 orientation; once attention was drawn to the spatial location, the response was affected in the same way and not much influenced by the orientation of S1. Of the 29 cells that showed a significant distinction between S1 and S2 in match trials, only four showed a significant difference between match and non-match S2 responses. These results show only mild, if any, feature-based attention in our paradigm.

Discussion

The major finding of our study is the significant response discrimination by a large proportion of neurones between the sample (S1) and match (S2) stimuli in the active memory task but not in the fixation task. Although a major difference between the two tasks is that the monkey has to pay attention to the gratings in the active task, we interpret the greater stimulus discrimination observed in the active task to be related at least partially to a mnemonic component specific to that task. This is not to deny the role of attention in this task. In fact, attention probably functions as a 'gate-keeper' for working memory (Awh *et al.*, 2006) and any mnemonic modulations seen in area V1 are likely to be driven by an attentional feedback from higher areas such as the posterior parietal cortex. However, our finding that the increased response could be either for the first or the second grating stimulus suggests that the modulation seen in the striate cortex is not a simple non-specific facilitation of the striate cortex due to attention or other factors during either encoding of the sample stimulus (in which case responses for S1 should always be greater than for S2) or during recognition (when S2 responses should always be greater). It is more likely that the modulation is directed at two different populations of neurones during encoding and recognition, and that these cells may well be segregated in separate layers or columns. Our present techniques cannot throw any light on the possibility of such segregation. A related interpretation is that tasks such as these, and even perception in general, involve matching incoming sensory inputs with re-entrant feedbacks to the primary sensory areas from a higher cortical area that stores the information during the delay period and endows it with behavioural significance (Di Lollo *et al.*, 2000).

Our results are consistent with an early study (Haenny & Schiller, 1988) of possible feedback effects in the striate cortex in a DMS memory (Konorski) task, even though their effects in area V1 were milder and often non-specific. Two methodological factors could have led to our more marked and specific effects. (i) As Haenny & Schiller (1988) used a stimulus paradigm where the monkey could be performing the task using foveal RFs, modulation of the cell under study, whose RF could often be extrafoveal, need not be strong.

(ii) There is reason to believe that modulatory effects in area V1 are more likely to be seen when there is a clutter of objects in the scene (Motter, 1993; Vidyasagar, 1998; Brefczynski & DeYoe, 1999) and information on spatial location is essential for task performance (Sharma *et al.*, 2003). Although only one grating was flashed at any one instant of time, our paradigm is specifically designed to involve location information, which was not the case in the paradigm of Haenny & Schiller (1988). Furthermore, we performed controls to exclude eye movements as a possible artefact and incorporated the control passive task to exclude simple sequence effects of the visual stimuli and investigate pure task-related factors. These make it more likely that the effects seen by us and possibly those seen by Haenny & Schiller (1988) are due to feedback effects related to performing the memory task. Although many pattern-selective IT neurones also show memory-related responses (Fuster & Jervey, 1982; Miyashita & Chang, 1988; Chelazzi *et al.*, 1993; Miller *et al.*, 1993; Miller & Desimone, 1994), their large RFs (Boussaoud *et al.*, 1991) have poor location information. Therefore, tasks such as our DMS task, for which location and pattern are both important, may require the involvement of the striate cortex to provide the spatial focus essential for the task.

Alternatively, could the results be explained as all due to general attentional engagement or arousal in the active task? Such an interpretation may sound consistent with recent reports of attentional effects at early visual stations (Motter, 1993; Roelfsema *et al.*, 1998; Vidyasagar, 1998; Brefczynski & DeYoe, 1999; Somers *et al.*, 1999; Gandhi *et al.*, 2001; Casagrande *et al.*, 2005; McAdams & Reid, 2005) and with the role that attention could potentially play in encoding items into working memory (Awh *et al.*, 2006). However, although attention is vital for successful performance of the task and might be gating the responses in area V1, there are several lines of argument against a purely attentional explanation for our findings.

(i) The monkey does not know beforehand either the location or orientation of the first grating, so neither spatial nor featural attention can operate effectively in our task to modulate the responses to S1. (ii) In any particular cell in our sample, the difference in the responses between the first (S1) and second (S2) stimuli in the active task could go either way ($S1 > S2$ or $S2 > S1$), whereas the reported attentional effects in macaque area V1 are mostly facilitatory at the locus of attention (Vidyasagar, 1998; Brefczynski & DeYoe, 1999; McAdams & Reid, 2005), unlike parietal areas (Robinson *et al.*, 1995; Constantinidis & Steinmetz, 2001) or the superior colliculus (Fecteau *et al.*, 2004), where effects could often be suppressive. (iii) It has been reported that attentional modulation in area V1 is apparent mainly when there is a clutter of competing stimuli that are simultaneously present in the visual field (Motter, 1993; Vidyasagar, 1998; Brefczynski & DeYoe, 1999) or in other tasks that also require serial attentive processing (Roelfsema *et al.*, 2003). Our paradigm presents only one stimulus at any one instant of time. It is more likely that it is the mnemonic requirement in our task that the location of the grating pattern also needs to be coded that leads to the observed modulation.

It was, however, interesting to note that, even in the passive task, there was some degree of modulation in most cells. Even though it was to a much milder extent than in the active task (a slope of only 0.19 in Fig. 4c), the modulation was generally in the same direction as in the active task (i.e. either $S1 > S2$ or $S2 > S1$ in both tasks). This indicates that, even in the passive task, the salience of the grating presentations could have led to some mnemonic processing similar to what happens in the active task but just weaker. The modulatory influence could have arisen in areas such as the posterior parietal cortex, where salient visual stimuli that have no behavioural

significance can still evoke neuronal responses (Constantinidis & Steinmetz, 2005).

Our results also bear upon the issue of feature-based attention in area V1. Although spatial attention has already been shown to operate in area V1 (Motter, 1993; Roelfsema *et al.*, 1998; Vidyasagar, 1998; Brefczynski & DeYoe, 1999; Gandhi *et al.*, 2001; Super *et al.*, 2001a; Di Russo *et al.*, 2003; McAdams & Reid, 2005) and even in the dorsal lateral geniculate nucleus (Casagrande *et al.*, 2005), feature-based attention has been demonstrated mainly in the extrastriate areas V4 (Motter, 1994a,b; McAdams & Maunsell, 2000; Reynolds *et al.*, 2000), MT (Treue & Martinez Trujillo, 1999; Martinez-Trujillo & Treue, 2004) and IT (Chelazzi *et al.*, 1993). In the striate cortex, a mild effect (Roelfsema *et al.*, 2003) has been reported but this can be explained by lateral connections within area V1 without recourse to a featural feedback. Our results are not in support of feature-based attention in striate cortex. The modulation seen in the response to the second stimulus (whether $S2 > S1$ or $S1 > S2$) seems to follow simply the spatial allocation of attention to that region of the visual field. If a featural component was present, non-match trials should have yielded a general depression of optimal $S2$ responses when preceded by an orthogonal, non-optimal $S1$. Thus, the main effect in our sample of area V1 neurones seems to be to distinguish between two classes of cells, those where the $S2$ response is less than the $S1$ response and those where it is more, which cannot be explained either as a general attentional engagement or as feature-based attention.

An intriguingly similar dichotomy of cells, suppressed or enhanced by the matching stimulus, was reported in the IT cortex by Miller & Desimone (1994) in a DMS task. In their version of the task, in each trial, the sample and match stimuli were separated by 0–4 intervening non-match stimuli. Some of these non-match stimuli were repeated between sample and match stimuli, allowing Miller & Desimone (1994) to test whether IT neurones distinguished between automatic repetition and mnemonically relevant repetition. They found that some of their IT cells exhibited enhanced responses to match stimuli and others showed suppressed responses but the cells showing enhancement to the match stimulus did not show the enhancement to repeated non-match stimulus. In other words, although all cells showed suppression to a repeated non-match stimulus, some cells showed suppression and others enhancement to the relevant match stimulus. The behaviour of these two types of cells in the mnemonic condition is very similar to the two types of cell responses for repeated match stimuli observed in our active DMS task but, notably, in the match trials of our passive task, the $S2$ responses are not always a decrement. The two types of area V1 cells that we have seen may thus be the first stage in a system where a distinction is made between primary encoding of a stimulus that enters short-term working memory and recognition of a stimulus that matches one already in working memory.

Rapid changes in the sensitivity of area V1 neurones after brief presentation of an optimum stimulus have been reported in the anaesthetized macaque (Müller *et al.*, 1999). However, it is unlikely that our data represent such changes, as the change observed by Müller *et al.* (1999) was always reduced sensitivity, representing an adaptation of the cell, whereas in about half of our cells, the changes were facilitatory. Furthermore, our routine delay period (900 ms) was much longer than the 13–215-ms period used by Müller *et al.* (1999) to obtain the data shown in their Fig. 2C.

Can our results still be explained as reward or response related or as an effect of expectation? Such effects have been reported not only in the IT cortex and in the medial temporal lobe (Vidyasagar *et al.*, 1991; Ringo & O'Neill, 1993; Salzmann *et al.*, 1993; Colombo & Gross, 1994) but recently also in the responses of some striate cells (Dragoi

et al., 2002). This is, however, highly unlikely in our case for two reasons. First, the increased responses that we report were not always for the second stimulus but often for the first stimulus, which is not associated with reward. Second, any reward-related facilitation or even inhibition of response for the second stimulus should also be evident in the passive task but this was not the case either.

The present results are consistent with our earlier suggestion from behavioural studies (Pigarev *et al.*, 2001) that the primary visual cortex plays an important mnemonic role in the early stages of learning our DMS task, when the monkey had learned to perform a DMS task in only one retinal location. We found that, at this stage, the learning was highly retinal position specific and also did not show size constancy, suggesting that at least a component of the learning occurs at an early visual area that has a fine-grain topographical representation. However, our present electrophysiological studies were performed when the monkey had fully learned the task and had generalized the learning to other retinal locations and for different sizes. Despite this generalization, the fact that the monkey had to remember the location along with the orientation of the grating is perhaps the reason for the marked modulatory effects that we have observed in striate neurones.

Among the many studies of single-unit responses in temporal (Fuster & Jervey, 1982; Miyashita & Chang, 1988; Fuster, 1990; Vidyasagar *et al.*, 1991; Chelazzi *et al.*, 1993; Miller *et al.*, 1993; Salzmann *et al.*, 1993; Miller & Desimone, 1994; Suzuki *et al.*, 1997), parietal (Bodner *et al.*, 2005) and frontal (Levy & Goldman-Rakic, 2000; Fuster, 2001) cortices and the hippocampus (Cahusac *et al.*, 1989; Vidyasagar *et al.*, 1991; Salzmann *et al.*, 1993), some have shown specific mnemonic responses either during the delay period or during encoding or recognition in a DMS memory task. However, our results show that in a DMS task, especially when place and pattern both need encoding, significant task-related responses can be observed even as early as the primary visual cortex. Thus, it is most likely that a distributed mode of processing underlies the performance in this memory task, similar to that proposed by many others as the neural substrate of memory (e.g. Edelman, 1987; Fuster, 1997). As human amnesics perform poorly in tasks such as that used by us (Holdstock *et al.*, 1995), it will be interesting to see whether lesions in primary sensory areas could indeed contribute to specific mnemonic difficulties in some cases of amnesia.

Supplementary material

The following supplementary material may be found on www.blackwell-synergy.com

Fig. S1. Five possible locations where the two stimuli in each trial could appear.

Fig. S2. Graze position changes and response differences between sample and match stimuli in the active and passive tasks.

Fig. S3. Response ratio versus gaze changes in active and passive tasks. Appendix S1. (A) Pseudorandomisation used for the stimulus presentation. (B) Comparison of cell responsiveness between active and passive tasks. (C) Eye movement controls.

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Abbreviations

Area V1, primary visual cortex or striate cortex; DMS, delayed match-to-sample; IT, inferotemporal; MT, middle temporal; RF, receptive field; S1, first grating stimulus in each trial of the delayed match-to-sample task; S2, second grating stimulus in each trial of the delayed match-to-sample task.

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