

The Representation of Stimulus Familiarity in Anterior Inferior Temporal Cortex

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SUMMARY AND CONCLUSIONS

1. The inferior temporal (IT) cortex plays an important role in both short- and long-term memory for visual patterns. Most previous studies of IT neurons have tested their responses in recency memory tasks, which require that the memory lasts only the length of a single behavioral trial, which may be <1 s. To determine the role of IT neurons in longer lasting memories, we measured their responses to initially novel stimuli as the stimuli gradually became familiar to the animal.

2. Two rhesus monkeys were trained on a delayed matching to sample (DMS) task with several intervening stimuli between the sample and the final matching stimulus on each trial. The purpose of the task was to ensure that the animal attended to the stimuli and held them in memory, at least temporarily. Unlike in several previous studies, the focus was not on within-trial effects but rather on the incidental memories that built up across trials as the stimuli became familiar. Each cell was tested with a set of 20 novel stimuli (digitized pictures of objects) that the monkey had not seen before. These stimuli were used in a fixed order over the course of an hour-long recording session, and the number of intervening trials between repetitions of a given sample stimulus was varied.

3. The responses of about one-third of the cells recorded in anterior-ventral IT cortex declined systematically as the novel stimuli became familiar. After six to eight repetitions, responses reached a plateau that was ~40% of the peak response. Virtually all of these cells also showed selectivity for particular visual stimuli and thus were not "novelty detectors" in the sense of cells that respond to any novel stimulus. Rather, the responses of these cells were a joint function of familiarity and specific object features such as shape and color. A few cells showed increasing responses with repetition over the recording session, but these changes were accompanied by changes in baseline firing rate, suggesting that they were caused by nonspecific effects.

4. The decrement in response with familiarity was stimulus specific and bridged >150 presentations of other stimuli, the maximum tested. For some cells the maximum decrement in response occurred for those stimuli that initially elicited the largest response. There was no significant change in response to stimuli that were already familiar.

5. The same cells that showed familiarity effects also showed reduced responses to the matching stimuli at the end of each trial, compared with the responses to the samples. The responses to these matching stimuli declined with familiarity in parallel with the decline in responses to the samples over the session. Recency and familiarity effects appear to summate within IT cortex.

6. We examined the time course of responses to novel and familiar stimuli. The population of cells took 100 ms after response onset to distinguish between a novel stimulus and the same stimulus seen once previously, possibly reflecting feedback to IT cortex. However, after a single additional presentation, cells distinguished between novel and familiar stimuli within 10 ms of response onset, that is, by nearly the first action potential. Thus there is virtually no time for the effect of familiarity on the initial

phase of the response to be caused either by lengthy temporal processing with IT cortex or by feedback from other structures.

7. The results support the proposal that a subpopulation of IT cells functions as "adaptive mnemonic filters" for both short- and long-term memories. A high level of activation in IT cortex may provide a feedback signal to orienting systems that the current stimulus is new and deserving of attention. Because increased contact with a stimulus drives down activity in IT cortex, this feedback between memory and attentional systems may result in an organism driven to seek out contact with new stimuli.

INTRODUCTION

Primates have a remarkable ability to retain visual information. People shown thousands of different pictures a single time each can later recognize an individual one as familiar (Shepard 1992; Standing 1973). Clearly, the neural circuitry underlying visual recognition employs powerful storage and retrieval mechanisms, and inferior temporal (IT) cortex appears to be an important component of that circuitry (Gross 1973; Mishkin 1982).

IT cortex is at the culmination of a cortical pathway underlying the recognition of visual objects (for a review, see Desimone and Ungerleider 1989) and is interconnected with other structures important for memory (Aggleton et al. 1980; Amaral and Price 1984; Baizer et al. 1991; Desimone et al. 1980; Insausti et al. 1987a,b; Martin-Elkins and Horel 1992; Ungerleider and Mishkin 1982; Van Hoesen and Pandya 1975a,b; Webster et al. 1991). Accordingly, IT neurons have large receptive fields and complex properties (Desimone et al. 1984; Gross et al. 1972; Schwartz et al. 1983; Tanaka et al. 1991). Some IT neurons appear to extract information about the overall shape of objects, whereas others are selective for specific stimuli such as faces and hands. Although posterior IT cortex is most important for visual discrimination, anterior IT cortex is particularly important for memory for visual form (Mishkin 1982).

The mnemonic tasks on which animals with IT lesions are impaired include two variants of the delayed matching to sample (DMS) paradigm, one of which requires recency memory and the other recognition memory. In the typical recency variant, a small set of familiar stimuli is used repeatedly. On a given trial, a sample stimulus is followed by two test stimuli, and the animal indicates which one matches the sample. Because both test stimuli is familiar, the task requires that the animal judge which of the two test stimuli was seen most recently. In the typical recognition variant, the stimuli used are all initially novel; a given stimulus is used on only a single trial ("trial unique"). A novel stimulus is presented as the sample, and, after a delay last-

ing up to several minutes, it is presented again as a (familiar) test stimulus, together with a new novel stimulus. Although the animal must indicate which of the two test stimuli matches the sample, as in the recency design, it may also base its choice on the relative novelty or familiarity of the two test stimuli.

Several neurophysiological studies have investigated recency effects in IT cortex with the use of the DMS paradigm with familiar stimuli and with delays of up to several seconds. These studies have reported that many IT neurons respond differently to a test stimulus depending on whether or not it matches the sample (Baylis and Rolls 1987; Eskandar et al. 1992; Gross et al. 1979; Mikami and Kubota 1980; Miller et al. 1991b; Riches et al. 1991; Vogels and Orban 1990), and this difference is maintained even when several other stimuli intervene in the retention interval (Miller et al. 1991b, 1993). Because the responses of many cells to a current stimulus are suppressed according to its similarity to the sample held in memory, we have suggested that IT cells function as "adaptive mnemonic filters."

Whether IT neurons might also play a role in recognition memory has been less clear. Studies of IT neurons in anesthetized or passively fixating monkeys report that the responses of some cells "habituate" to repeated presentations of a stimulus (Gross et al. 1972; Pollen et al. 1984; Richmond et al. 1983) with effects lasting no more than 12 s (Miller et al. 1991a). Recognition memory, however, requires a neural mechanism that is both stimulus specific and longer lasting than 12 s. Baylis and Rolls (1987) studied neurons in the lateral portion of IT cortex in animals performing a serial recognition memory task. They found that the responses to novel stimuli decreased with repetition, but this effect was eliminated if more than two other stimuli intervened in the retention interval. By contrast, Riches et al. (1991) recorded from a few cells in the anterior ventral portion of IT cortex and found changes in response to novel stimuli that were maintained over at least several intervening stimuli. Finally, Rolls et al. (1989) reported that the responses of some face-selective cells in IT cortex systematically increase for some faces and decrease for others as initially novel faces become familiar. However, it is not known if this phenomenon is specific to faces.

To explore further the role of IT cortex in visual recognition memory, we studied IT neurons in fixating monkeys performing a version of the DMS task. There were two critical differences in the methods of the present study compared with those used in our study of recency memory in IT cortex (Miller et al. 1991b, 1993). First, whereas the stimuli in the recency study were all familiar to the animal, most of the stimuli used for each cell in the present study were initially novel. Second, whereas the focus in the recency study was on within-trial modulation of responses to matching and nonmatching stimuli, the focus of the present study was on across-trial effects, namely the responses to the initially novel stimuli as they gradually became familiar to the animal during the recording session. Because we did not require the animal to distinguish novel from familiar stimuli, any effects of increasing familiarity on the cells' responses would be due to incidental memories that accrued during the session. In a previous preliminary report we described how IT neuronal responses decline with stimulus

familiarity (Miller et al. 1991b). In the present study we describe several manipulations that help define how this familiarity mechanism operates in IT cortex.

METHODS

Subjects

Two rhesus monkeys weighing 8–9 kg were used. These were the same animals used in the study of recency memory in IT cortex (Miller et al. 1993), and the surgical, recording, and histological methods were also the same.

Behavioral task

The task was a modified version of the DMS task used to study recency memory (Miller et al. 1993). The monkey began each trial by grasping a metal bar and fixating a small (0.2°) fixation target, which remained on throughout the trial. Trials were aborted if the monkey's gaze deviated from the fixation target $>1\text{--}1.5^\circ$ at any time during the trial (fixation typically varied much less than 1°). A sample stimulus was presented 300 ms after the animal achieved fixation. The sample was followed by two to five test stimuli. When one of the test stimuli matched the sample, the monkey was required to release the bar within 900 ms of stimulus onset to receive an orange juice reward. Each stimulus was presented for 500 ms, and there was a 700-ms delay between the disappearance of one stimulus and onset of the next. The match stimulus was the last stimulus presented on each trial, and this stimulus was extinguished as soon as the monkey made its response, typically ~ 350 ms after stimulus onset. The time between trials was $\sim 1\text{--}3$ s, depending on how long the animal took to drink the juice and initiate the next trial. We searched for cells while the animal performed the DMS task, with the use of a set of familiar sample and test stimuli. Once a cell was isolated, we switched to the novel set and initiated the data acquisition.

A new set of 20 initially novel stimuli were used as the samples and matching test stimuli for each cell, and a fixed set of four highly familiar stimuli were used as the nonmatching ones (the same nonmatching items were also used in the task used to search for cells). Thus the initially novel stimuli appeared only at the beginning (sample) and end (matching test) of each trial, never as an intervening nonmatching stimulus. This design was chosen because it greatly simplified the analysis of repetition and temporal order effects for the initially novel stimuli. Although the use of familiar nonmatching stimuli allowed the animal to possibly use relative novelty within a trial as a cue to whether a test stimulus was a match or nonmatch, our major interest was in the changing response to the sample stimuli rather than match-nonmatch effects. The main purpose of the behavioral task was to ensure that the animal attended to the stimuli and held them in memory, at least temporarily.

The stimuli were complex, multicolored pictures digitized from magazine photographs and presented on a computer display. The images were of faces, bodies, natural objects, and complex patterns that did not appear in the laboratory setting. We did not attempt to find "optimal" stimuli for any of the cells. Rather, we randomly selected a wide variety of complex pictures for each set, which previous studies indicated would elicit a full range of responses from any given cell (Desimone et al. 1984; Gross et al. 1972; Tanaka et al. 1991). The stimuli ranged between 1 and 3° on a side and were presented at the center of gaze. Most of the stimuli were used for only one cell, but a few were reused after a minimum of 3 mo.

The initially novel sample stimuli were presented in a particular

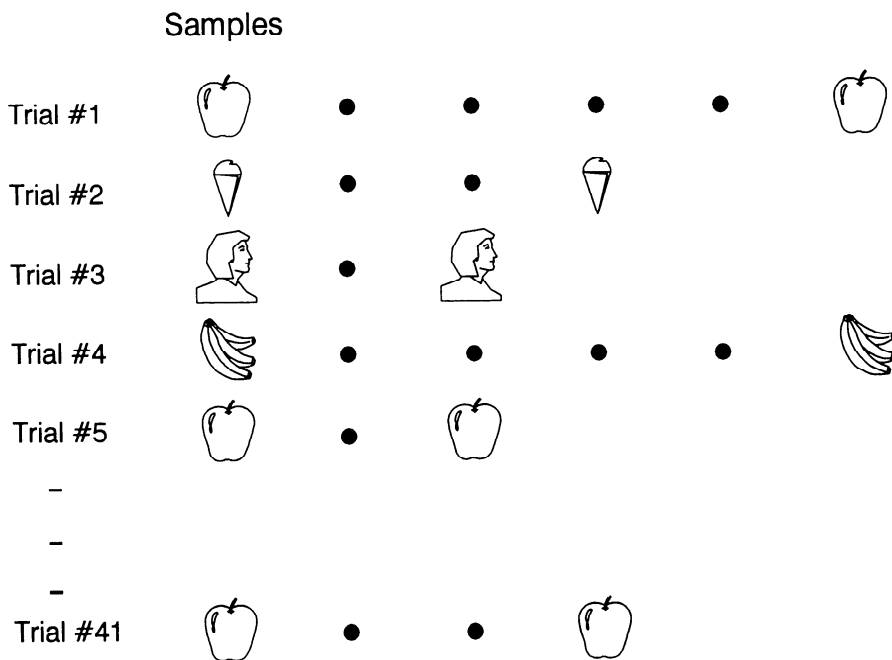


FIG. 1. Schematic representation of trial sequence. Initially novel stimuli were used as samples and matching test stimuli. Nonmatching stimuli are represented by dots. A given sample stimulus is repeated after 3 or 35 intervening trials, in alternation. The apple, for example, appears on trials 1, 5, 41, 45, 81, etc.

fixed order, allowing comparison of the responses to stimuli repeated after either a small or large number of intervening trials, as follows. The 20 stimuli were randomly divided into 5 blocks of 4 stimuli each. The first block of four stimuli was used as the samples on the first four trials of the session, and then this same block of stimuli was repeated in the same order for the next four trials of the session. We then switched to the second block of stimuli, which was also used for two sets of four trials, and so on. After all 20 stimuli appeared in 2 blocks (i.e., on 2 trials) each, we then repeated the whole series several times, for a total of 11–20 trials per stimulus. Thus the number of intervening trials between repetitions of a given sample alternated between 3 and 35, and each sample stimulus appeared on an intervening trial for every other sample stimulus. The sequence of trials is illustrated in Fig. 1.

Across all types of trials, the average number of stimuli presented per trial was 4.3. Thus, in the blocks with 4 trials, a given stimulus was repeated, on the average, after 13 intervening stimuli (3 intervening trials), which took ~ 25 s. In blocks with 35 intervening trials, a given stimulus was repeated, on the average, after 152 intervening stimuli, which took ~ 5 min. A complete session with a single cell typically lasted ~ 1 h.

Data analysis

Responses to stimuli were appraised by the use of analysis of variance (ANOVA), t tests, and linear regression, evaluated at the $P < 0.05$ level of significance. Responses to match stimuli were always calculated over a 200-ms time interval beginning 75 ms after stimulus onset. The beginning of this time interval was chosen to coincide with the typical minimum response latencies of IT neurons, and the end was chosen to occur well before the animal's behavioral response (mean reaction time was 359 ms). To facilitate comparison with the match responses, responses to the samples were also calculated over this 200-ms interval, except for the linear regression computed on sample responses over the session. For this latter test, we utilized the full neuronal response for the sample, which was measured over a 425-ms interval beginning 75 ms after stimulus onset. To compare response histograms averaged from multiple cells, the individual spike trains for each cell were first "smoothed" by convolution with a Gaussian with a standard deviation of 10 ms (Richmond and Optican 1987).

RESULTS

Anatomic location of penetrations

As shown in Fig. 2, all of the recording sites were located on the inferior temporal gyrus, just lateral to the rhinal sulcus and medial to the anterior medial temporal sulcus.

General properties

A total of 72 visually responsive neurons were recorded. All neurons gave excitatory responses. To determine whether the response to a sample stimulus was significantly different from the neuron's spontaneous activity, we compared the firing rate during the presentation of each sample stimulus with the prestimulus firing rate with the use of a paired t test. Of the 1,440 stimuli used as a sample (72 neurons \times 20 stimuli), 967 (64%) elicited a visual response. To determine whether a given neuron was stimulus selective, we performed an ANOVA on the responses to the 20 sample stimuli. The ANOVA was significant ($P < 0.05$) for 89% (64/72) of the neurons.

Effect of familiarity on the responses to the sample stimuli

The responses of many IT neurons changed as the initially novel stimuli were repeatedly presented throughout the session. Figure 3 shows, for 1 cell, response histograms for the 1st through 6th presentations of all 20 sample stimuli averaged together. The responses to the stimuli were strongest when they were novel and became progressively weaker as they were repeated throughout the session, i.e., as they became familiar. We will refer to this change in response with stimulus repetition as the "familiarity effect."

For each cell, we determined whether there was a progressive change across the session in response to the samples by computing a linear regression on the response to the first 12 presentations of the 20 sample stimuli. Responses to all samples were used in the regression, including samples that may not have elicited any significant response (relative to

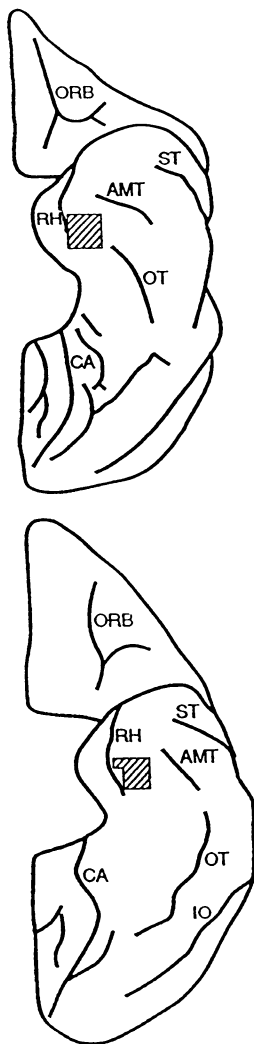


FIG. 2. Location of recording zones (□) in both monkeys. AMT, anterior middle temporal sulcus; CA, calcarine sulcus; IO, inferior occipital sulcus; OT, occipitotemporal sulcus; ORB, orbital sulcus; RH, rhinal sulcus; ST, superior temporal sulcus.

the spontaneous firing rate) during the session. On the basis of this regression, about one-third of the neurons (25/72) exhibited a significant decrease in response across the session, and 18% (13/72) exhibited a significant increase in response. We will first describe some of the properties of the cells showing a decrement in response with familiarity and then consider the cells that appeared to show an increase.

Decrement of response with familiarity

Of the 25 cells with a significant decrement of response with familiarity, 24 of them (96%) were stimulus selective according to the ANOVA described above. These cells did not simply respond equally to all novel stimuli and thus were not "novelty detectors" in that sense. An optimal response seemed to require a stimulus that was both novel and of the appropriate color, shape, and so on.

Figure 4A shows the responses to the first 11 presentations (the minimum number of presentations per cell) of all 20 sample stimuli, averaged from all the responses of the 25 IT neurons that showed a significant overall decrease in response with repeated presentation of the sample stimuli

(according to the linear regression described above). The trial number on the abscissa is the absolute trial number in the session, with the numbering beginning with trial 0. Thus a stimulus appeared as a sample for the first time on trial number 0, for the second time on trial number 4, for the third time on trial number 40, for the fourth time on trial 44, and so on. Across the population of cells, there is a waning of response that reaches a plateau after six to eight sample presentations (because each stimulus also appeared as a match at the end of a trial, this corresponds to 12–16 stimulus presentations). For comparison, the figure also indicates the neurons' average baseline, or spontaneous, activity for the same trials. The response to the first presentation of a stimulus was ~ 20 spikes/s above the baseline rate, whereas the plateau was only ~ 8 spikes/s above the baseline, or $\sim 40\%$ of the initial response. This reduction to 40% of the initial response is probably an underestimate of the size of the familiarity effect, because the average is based on the response to all stimuli, some of which elicited little or no response throughout the session. The baseline rate did not show any significant change over the session.

The staircase appearance of the line relating response magnitude to trial number in Fig. 4A is due to the two different numbers of trials intervening between presentations of a given sample stimulus. The number of intervening trials between repetitions of a given sample alternated between 3 and 35 throughout the session (see METHODS). Figure 4A shows that the decrement in response was greater when only 3 trials intervened than when 35 trials intervened between presentations of the same sample stimulus. The response to a specific novel stimulus "A," for example, declined more when the animal had seen A 4 trials ago (3 intervening trials) than 36 trials ago. Closely spaced repetitions are apparently more effective at "stamping in" the memory trace. However, even though there was no further decrement after 35 intervening trials, the response did not

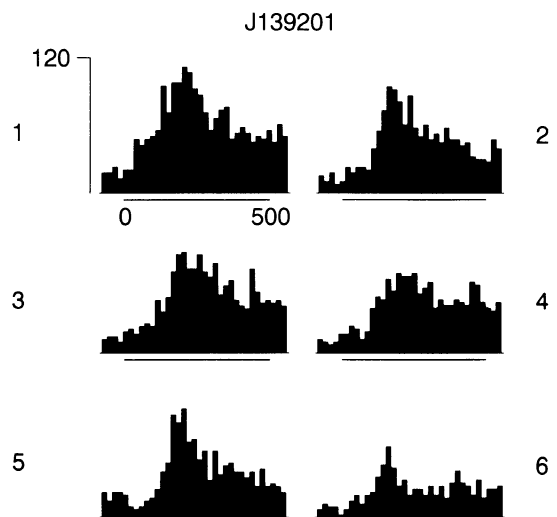


FIG. 3. Example of responses of an individual inferior temporal (IT) neuron to a set of 20 initially novel sample stimuli. Responses to all 20 stimuli have been averaged together into single composite histograms. The 6 histograms show the average response to the 1st 6 presentations of all stimuli. Horizontal line under the histograms indicates when the stimuli were on. The vertical scale indicates firing rate in spikes/s, and the bin-width is 10 ms.

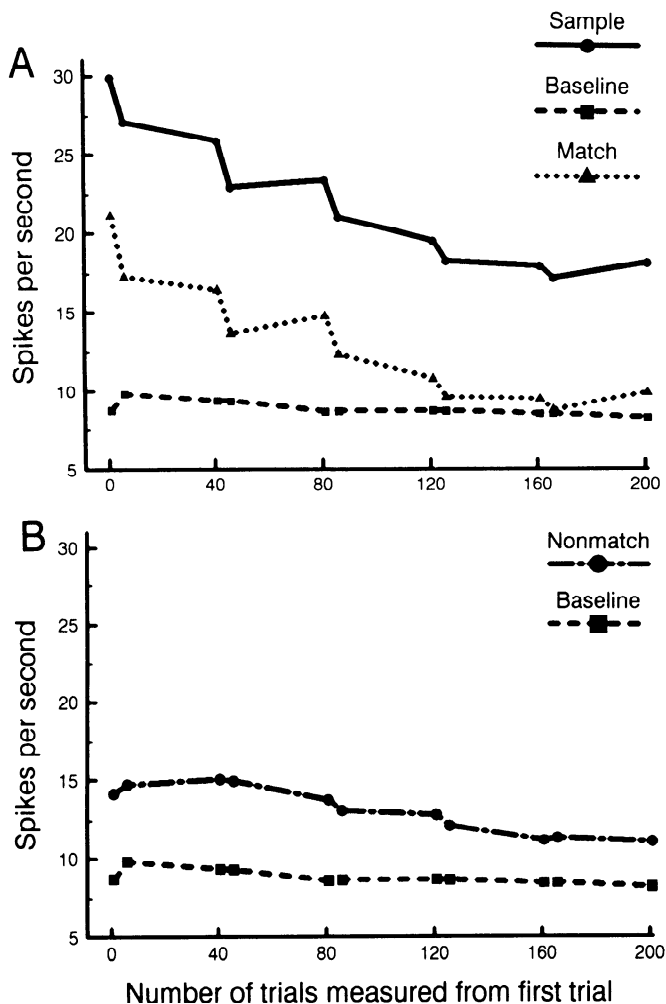


FIG. 4. *A*: average responses of 25 neurons whose responses declined significantly with increasing stimulus familiarity over the session. Solid line indicates responses to the sample stimuli, dotted line indicates responses to the match stimuli, and dashed line gives baseline (prestimulus) firing rate. Trial number is measured from 1st trial of a given stimulus. *B*: average responses of the same cells to a set of 4 familiar nonmatching stimuli. Baseline rate is also shown, for comparison.

recover to its initial value. Thus the cells “remembered” a stimulus even after 152 intervening stimulus presentations (35 intervening trials with an average of 4.3 stimuli per trial), or a retention interval of ~ 5 min.

The larger decrement in response after 3 trials than after 35 trials establishes that the response decrement is stimulus specific and cannot be due to neuronal “fatigue” or other nonspecific changes that might have occurred during the session. If the neurons were simply becoming fatigued (or if the decrement were not linked to specific stimuli), there should have been a larger response decrement after 35 intervening trials than after 3 intervening trials, because more time elapsed, more stimuli appeared, and more responses occurred with the larger number of intervening trials.

To determine how many cells showed a significant drop in response after just three intervening trials, we performed a paired *t* test on the responses to each sample stimulus before and after each block of three intervening trials. For this comparison, any overall changes that occur over the entire recording session are discounted. On the basis of the *t*

test, 13 (18%) of the 72 total cells showed a difference in response to the same stimuli repeated after 3 intervening trials. All of these cells were in the group of 25 that showed a significant trend in response over the session based on the linear regression, and all of the response differences were decrements. Thus the only consistent “short-term” change in response to repetition in IT cortex was a decrement. The fact that fewer cells showed a significant short-term change in response than a significant overall trend is presumably due to some cells showing consistent, but not statistically significant, short-term decrements in response that accumulated over the course of a session, resulting in a significant trend.

If the decrement in IT neuronal responses was due to increasing familiarity, we would expect that the responses to the four familiar *nonmatching* stimuli presented on most trials would show little decrement. The same nonmatching stimuli were used for several months over the course of the experiment, and they had also been seen by the animal at the start of each recording session when we searched for cells. Figure 4*B* shows the average responses to the nonmatching stimuli, for the same 25 neurons that showed a decrement in response to the samples. The population response to the familiar nonmatching stimuli declined only slightly over the session, and none of the cells showed a significant trend.

Because the nonmatching stimuli were already familiar to the animal at the start of each recording session, we might also expect the response to these stimuli to be smaller, on the average, than those to the first few presentations of the initially novel stimuli used as samples and matches. This comparison is complicated by the fact that IT responses to familiar stimuli are typically largest to samples, followed by nonmatching and then matching stimuli (Miller et al. 1991b, 1993). However, it can be seen by comparing *A* and *B* of Fig. 4 that, on the initial three presentations of the novel stimulus set (through trial 40), responses of the population of cells to the familiar nonmatching items were not only smaller than those to the novel sample but also smaller than to the novel matching test stimuli. This reversal of the order of responses to matching and nonmatching stimuli that had previously been seen in studies with familiar stimuli is likely due to the novelty of the matching stimuli in the present study. After the first three presentations of the stimulus set, when the initially novel stimuli were now somewhat familiar, responses to the matching stimuli fell below those to the nonmatching, which is the typical order of responses to familiar stimuli.

Stimulus selectivity of the familiarity effect

As described above, the fact that the familiarity effect was larger when 3 trials intervened between repetitions of a sample than when 35 trials intervened indicated that the familiarity effect was stimulus specific. As an additional test of stimulus specificity, we tested 10 cells with a 2nd set of novel stimuli after completing a session with the 1st set. Figure 5 shows an example of a single IT neuron’s responses to presentation of 1 set of 20 novel stimuli and the neuron’s subsequent responses when a new set of stimuli was intro-

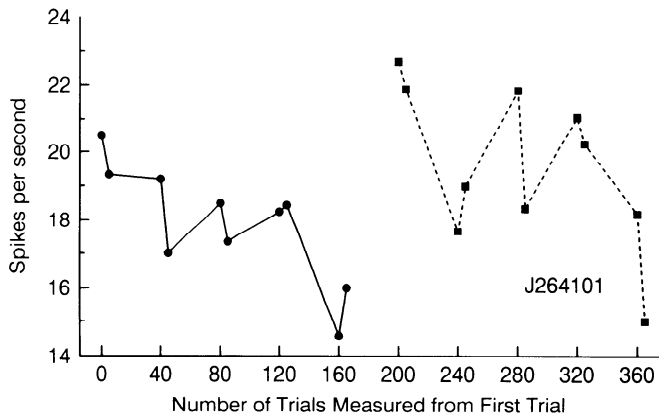


FIG. 5. Average responses of an individual IT neuron to 2 sets of initially novel stimuli. After the neuron's response to the 1st set had significantly declined (—), a new set of stimuli was introduced. The response rebounded (---) and then declined again as the new set became familiar.

duced. The responses of this neuron declined as the first set of stimuli became familiar. When a new set of novel stimuli was then substituted for the first, the neuron's response recovered to a high rate, followed by a progressive decrement in response as the new stimulus set became familiar. Thus the response decrement was tied to the familiarity of specific stimuli, and it did not generalize to other, unseen, stimuli. This recovery of response to new stimuli was seen for all 10 cells tested with a 2nd set.

Relationship between familiarity effect and matching effects

In our previous study of IT cortex in monkeys performing a DMS task, we found that responses to test stimuli that matched the sample held in memory on a given trial were suppressed in comparison with the responses to samples and nonmatching stimuli (Miller et al. 1991b, 1993). To determine whether the neurons that showed the (across-trial) familiarity effect also showed the (within-trial) suppression of response to matching stimuli ("matching effect"), we examined the average responses to the matching stimuli at the end of each trial. As shown in Fig. 4A, the average response to matching stimuli was weaker than the average response to sample stimuli throughout the session. Furthermore, the responses to the matching stimuli declined across the session, in parallel with the decline in responses to the samples. The within-trial matching effect appeared to add to the across-trial familiarity effect. Thus an IT neuron appears to be capable of coding both types of mnemonic information: the matching status of a stimulus within a trial and the relative familiarity of the stimulus that builds up across trials.

A relationship between familiarity and recency is further suggested by the fact that the 25 cells showing a decrement in response with familiarity had a larger matching effect than the remainder of the population of cells. The response to the match stimulus was only 67% of the sample response in these 25 cells, compared with 94% of the sample response for the remainder of the population. This suggests that information about both familiarity and recency may be carried mostly by the same subgroup of IT cells.

Cells showing an increase in response with familiarity

The stimulus specificity of the familiarity effect, the stability of the baseline activity across the recording session, and recovery of response with a new set of stimuli (for the 10 neurons so tested) all indicate that the response decrement over the session was not caused by nonspecific changes in the cortex, such as damage or irritation to the recorded cells or surrounding neuropil. By contrast, the 13 cells showing a significant increase in response over the recording session could well have been due to such nonspecific factors. Figure 6A shows the average response to the 1st 11 presentations of all 20 samples for these 13 cells, as well as their baseline activity. The responses and baseline activity of the 25 cells with a response decrement are also shown, for comparison. Unlike the cells showing a decrement, whose baseline activity was constant, the cells whose responses increased over the session showed parallel increases in their baseline firing rates, suggesting some change in overall excitability, possibly due to damage or irritation. This conclusion is supported by the shape of the curve showing the average response over the session for these cells. The curve has a negative staircase appearance, superimposed on a larger, more gradual, increase. That is, with three intervening trials between presentations of a given sample, repetition actually appeared to cause a decrement in response of these cells,

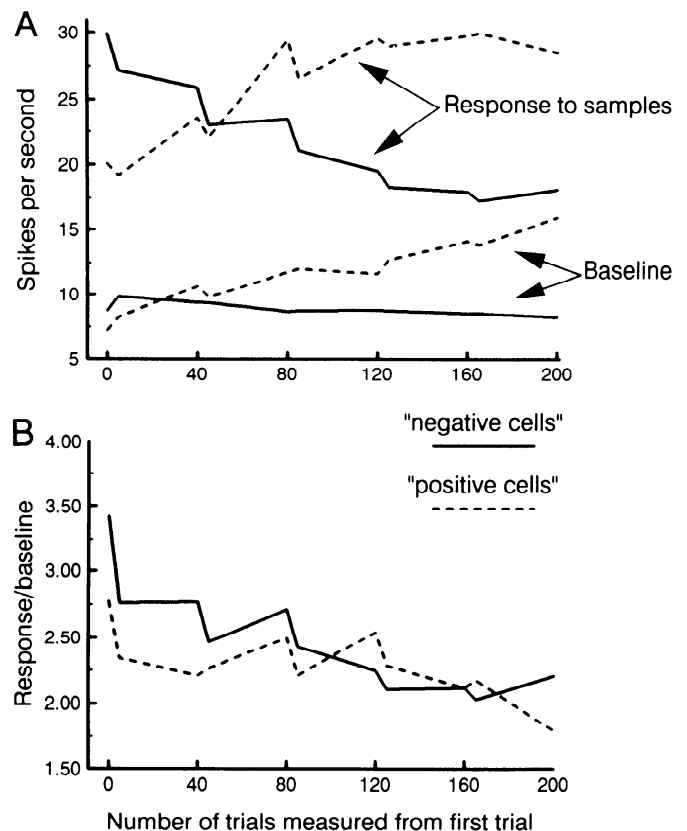


FIG. 6. A: average response of 13 IT neurons whose response increased significantly over the course of the recording session, or positive cells (top ---) and, for comparison, the average response of the 25 cells whose response significantly decreased, or negative cells (—). The prestimulus baseline activity for the 2 groups is shown by the 2 bottom lines. B: average response of the same cells, but with the response divided by the baseline firing rate.

whereas there was a net increase in response over the longer number of intervening trials.

To control for nonspecific changes in excitability, as measured by changes in the baseline activity, we divided the response to each stimulus by the average baseline firing rate on each trial for both the "positive" and "negative" cells. Figure 6B shows the stimulus responses, which are now expressed as multiples of the baseline firing rates. Although the "negative cells" still show a decrease in response over the session, the "positive cells" no longer show an increase but actually show a slight decrease. If the responses of these few cells with increments are indeed due to nonspecific changes, then the only change in response with familiarity in IT cortex may be a decrement.

This conclusion is further supported by the results shown in Fig. 7, which shows the average responses of the entire population of recorded cells, excluding the 25 cells with a significant decrement in response. There is no tendency for the remaining neurons to show any increase in response over the session. Interestingly, the average response of the cells unaffected by familiarity was 15.24 spikes/s, which was only about one-half the response of the 25 "decrement" cells to the initial presentation of a novel stimulus. In fact, the average response of the unaffected population was about equal to the "plateau" response of the decrement cells, after the initially novel stimuli had become familiar for that group.

Effects of familiarity on responses to individual stimuli

Even though there was little or no evidence for a subpopulation of IT cells whose average response to all stimuli increased with familiarity, it is still possible that the responses of some cells increased for just a few of the stimuli tested, but did not change, or even decreased, for other stimuli. Such cells might have been missed in the regression analysis, which was based on the average response across all stimuli.

To test whether the change in response over the session was different for different stimuli, we computed a multiple linear regression for each cell, with number of repetitions as a linear factor and the particular stimulus tested as a classifi-

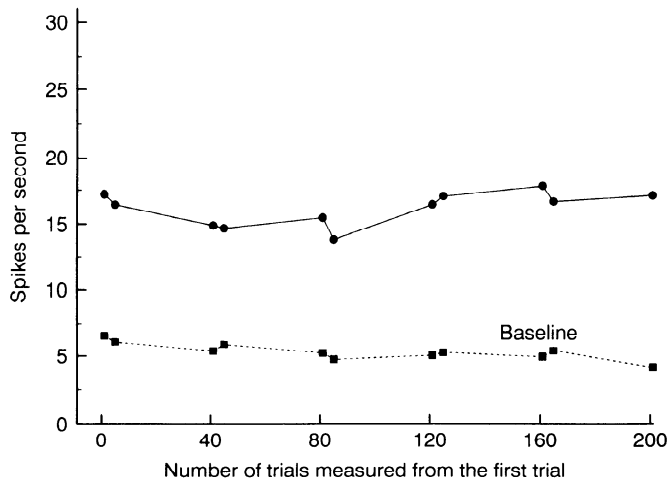


FIG. 7. Average response of the entire sample of IT neurons, excluding the cells that showed a significant decrease in response with familiarity.

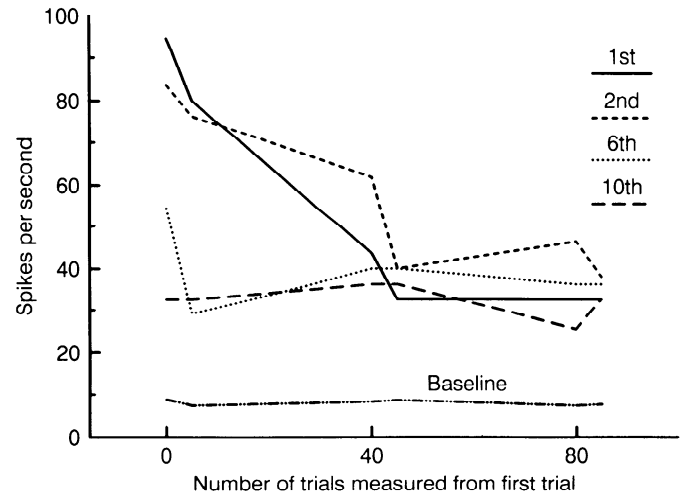


FIG. 8. Responses of an IT neuron to 4 stimuli. The 20 novel stimuli tested were ranked according to their initial response, and the lines indicate the responses to the 1st, 2nd, 6th, and 10th best of the 20.

cation factor. We then asked whether there was a significant interaction between the stimulus (stimulus factor) and the rate of change of response (repetition factor). Because stimuli that elicited no response could not show a response change over the session, we limited this test to the 10 "best" stimuli for each cell. These stimuli were determined by rank ordering the stimuli on the basis of the average response to the first two presentations.

The interaction was significant for eight cells (out of the 72 total). That is, the rate of change in response across the session for these cells was different for different stimuli. One of the eight showed a significant overall increase in response with familiarity, which was correlated with a change in the neuron's baseline firing rate. We did not include this cell in further analyses. For the remaining seven cells, we computed a simple linear regression of the response across repetitions, for each stimulus separately. Of the 70 stimuli used (7 cells \times 10 stimuli), the regression was significant for 24, and all of these showed a decrease in response across the session. No individual stimulus showed a significant increase in response over the session.

Inspection of the responses for the seven cells with significant interactions between the stimulus factor and the rate of response change indicated that these interactions were caused by differences in the initial responses to the stimuli. Specifically, the stimuli that elicited a stronger initial response showed a greater response decrement over the session than did less effective stimuli. The significant interaction in the regression was apparently due to a "floor" effect for the stimuli that initially elicited poor responses. An example of 1 cell exhibiting an interaction is shown in Fig. 8, which shows the responses of the cell to the 1st, 2nd, 6th, and 10th best stimuli. The initial responses to all four of the stimuli were well above the neuron's baseline firing rate. However, the responses to the 1st and 2nd best stimuli showed sharp declines with repetition, whereas the responses to the 6th and 10th best stimuli showed little or no change. Because the decrement in response was largest for the stimuli that initially gave the best response, the responses of the cell showed greater selectivity among the

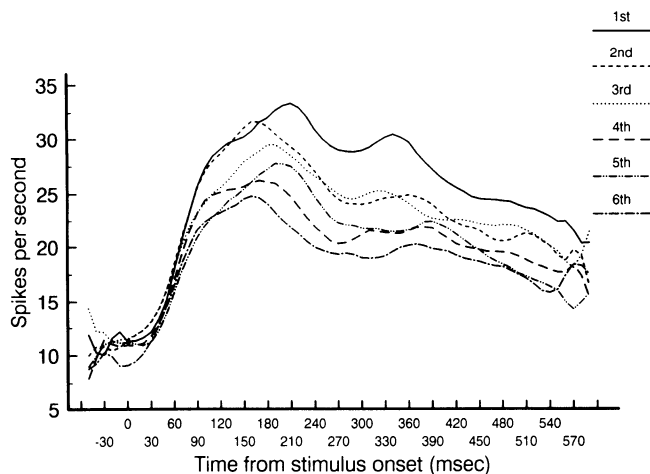


FIG. 9. Time course of the response to novel stimuli as they became familiar. Curves show the responses to the 1st–6th presentation of all 20 initially novel stimuli, for the 25 cells that showed a significant decrement in response with familiarity. The stimulus was turned on at *time 0* and turned off 500 ms later.

stimuli when they were still relatively novel than when they were familiar, i.e., after four to five presentations.

Time course of the familiarity effect

To determine how soon after the onset of the visual response IT cells distinguished among novel and familiar stimuli, we computed average response histograms for each of the 1st 6 presentations of all 20 sample stimuli for the 25 cells with a significant familiarity effect. Fig. 9 shows the response histograms for all 25 cells, averaged together. The responses to the first and second presentations of the same sample stimulus (with 3 intervening trials) have similar magnitudes and time courses until relatively late into the response, at which point the response to the second presentation appears to become suppressed. By contrast, the responses to the third through sixth stimulus presentation diverge from that of the first almost at the beginning of the visual response. Thus, by the third sample presentation, IT cells appear to distinguish between novel and familiar stimuli almost immediately. It should be noted that responses to the second versus third presentations as well as to the fourth versus fifth presentations show little or no divergence. This is due to the fact that 35 trials intervene between the 2nd and 3rd presentations and the 4th and 5th presentations, and IT cells show little or no additional decrement in response to a stimulus after 35 intervening trials. By contrast, responses to the third versus fourth and fifth versus sixth presentations do diverge, with three intervening trials.

To quantify these differences in the time course of the response, bin by bin paired *t* tests were computed for several pairs of presentations (1st vs. 2nd, 3rd vs. 4th, etc.). Response differences were taken to begin in the earliest bin in which the paired *t* test reached significance ($P < 0.05$). The latency of the visually evoked response was determined by a paired *t* test between the average response across the six presentations and the average baseline activity. For each presentation the response began ~ 70 ms after stimulus onset, that is, the paired *t* test first reached significance in the bin corresponding to 70–80 ms after stimulus onset. The

responses to the first and second presentations of the stimuli became significantly different 170–180 ms after stimulus onset, or 100–110 ms after response onset. By contrast, the difference in response between the first and fourth stimulus presentations became significant 80–90 ms after stimulus onset, which was only 10 ms after the start of the response. Thus, as the stimuli become increasingly familiar, the latency of the familiarity effect is reduced. The difference in response between the third and fourth and between the fifth and sixth presentations occurs 100–110 and 110–120 ms, respectively, after stimulus onset, or 30–50 ms after the beginning of the response.

We also computed average response histograms for the matching stimuli at the end of each trial, to compare with the time course of the familiarity effect for the samples. Figure 10 shows the average responses to the 1st and 2nd presentations of all 20 sample and matching stimuli, for the 25 cells showing a response decrement with familiarity. Although the response difference between the first and second sample presentations occurs relatively late, the difference between the sample and match responses occurs immediately from the onset of the visually evoked response. The immediate suppression of the match response is compatible with the results of our previous study of IT cells (Miller et al. 1993), in which we found immediate suppression of the match response compared with the nonmatch.

DISCUSSION

The responses of many IT neurons are determined by both the sensory features and familiarity of stimuli. About one-third of the neurons in our sample gave their strongest responses to specific novel stimuli and progressively weaker responses as the stimuli became more familiar over the course of an hour-long session. The cells are not novelty detectors, in the sense of cells that respond to any novel stimulus (Wilson and Rolls 1990). Rather, sensitivity to novelty seems to be accomplished in parallel with sensitivity to conventional visual features such as color, shape, etc. In a similar vein, we previously found that the responses of IT cells to otherwise effective test stimuli are suppressed according to their similarity to the sample stimulus held in

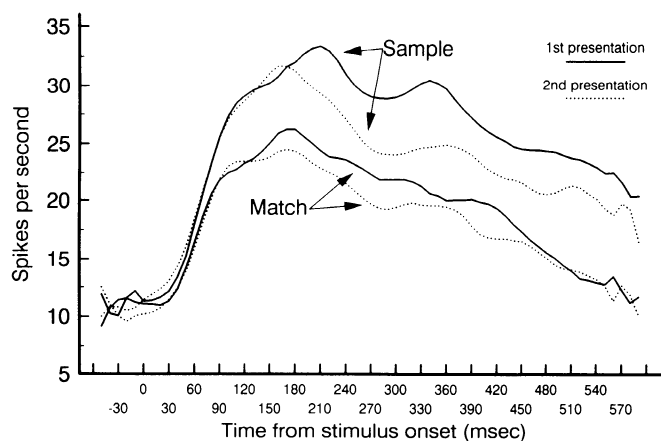


FIG. 10. Average response histograms to the 1st and 2nd presentations of the initially novel sample and matching test stimuli for the 25 cells that showed a significant decrement in response with familiarity. See Fig. 9 for conventions.

memory on a given trial of a DMS task (Miller et al. 1991b, 1993). Together with the results of the present study, the findings indicate that current stimuli are compared with both short- and long-term memory traces in IT. On the basis of this property, we have previously described IT cells as adaptive mnemonic filters.

We reached this conclusion about effects of stimulus familiarity in an earlier paper (Miller et al. 1991b), but the analyses of the present study allow us to expand on the previous one. We now have further evidence that the familiarity effect is stimulus specific; that it is largest for stimuli that initially cause the greatest response; that it is rarely, if ever, associated with an increase in response; that it affects responses to both sample and matching test stimuli in parallel; that it tends to occur in the same cells that show the largest repetition effects within a trial; that it has little effect on responses to stimuli that are already familiar; that it begins earlier in time as stimuli become increasingly familiar; and that it ultimately begins within 10 ms of response onset.

Relationship to prior studies

Although it has long been established that IT cortex is important for visual memory, recent studies suggest that the most anterior-ventral portion of IT plays the most important role. This region includes "perirhinal" cortex, which is comprised of area 35 in the lateral bank of the rhinal sulcus and area 36, located in the cortex between the rhinal and anterior middle temporal sulci and extending into the temporal pole (Amaral et al. 1987; Suzuki et al. 1993). Lesions that include perirhinal cortex have a devastating effect on performance of DMS tasks (Gaffan and Murray 1992; Horel et al. 1987; Meunier et al. 1990; Murray 1992; Murray et al. 1989; Suzuki et al. 1991, 1993; Zola-Morgan et al. 1989, 1993). Horel et al. (1987) directly compared the effects of cooling the anterior-ventral portion of IT cortex, including area 36 in the perirhinal region, with cooling lateral area TE and found a greater impairment on a DMS task from the ventral site. Although we were not able to localize recording sites precisely enough to distinguish ones in area 36 from those in TE, our recording region appears to span both regions. In future studies it will be important to compare cell properties in this region with those in adjacent areas such as lateral TE, area 35, TF/TH, and the hippocampus.

Although the role of IT neurons in recency memory has been investigated in a number of studies, there have been relatively few studies of the role of IT neurons in visual recognition. Baylis and Rolls (1987) tested the responses of IT neurons to novel stimuli in a serial recognition task and found that responses to novel stimuli typically declined when they were repeated. However, this effect was eliminated for most cells if even a single stimulus appeared in the retention interval and was eliminated for all cells with two intervening stimuli. They concluded that IT cortex "would be useful for short-term visual memory . . . but would not be useful in recency memory tasks in which one or more stimuli intervenes between the first and second presentations of a stimulus." Miller et al. (1991a) reported that the responses of IT neurons in both anesthetized and passively

fixating (awake) monkeys declined with stimulus repetition, but only if the stimuli were repeated at least once every 12 s. The failure to find long-lasting repetition effects in either of these two studies could be due to differences in either the task used or in the recordings sites. The latter seems more likely, because neither of these two studies included cells in the anterior-ventral portion of IT cortex included in the present study.

Riches et al. (1991) did record in this anterior-ventral region and found that the response decrement to repeated stimulation survived intervening stimuli. However, the effect of intervening stimuli was tested in only a few cells, and the time course of the effect was not clear. Our data indicate that these familiarity effects can survive retention intervals lasting at least many minutes, filled with >100 stimulus presentations. Riches et al. (1991) also reported that some IT neurons gave stronger responses to a set of novel stimuli than to a set of highly familiar ones. Although this response difference might have been caused by featural differences between the stimuli in the novel and familiar sets, the fact that we found larger responses to the novel sample and match stimuli than to the highly familiar nonmatching stimuli suggests that the difference was in fact due to long-term memories of the familiar stimuli.

Finally, Rolls et al. (1989) recorded the responses of face-selective cells in the superior temporal sulcus and lateral portions of IT cortex to initially novel faces that were repeatedly presented. The responses of some cells gradually changed with repetition, even when repetitions of a stimulus were separated by several intervening items. This finding is consistent with the present results, except that neurons in anterior-ventral IT are not especially selective for faces. We found familiarity effects for a wide variety of stimuli, suggesting that this anterior-ventral region is a more "general purpose" recognition zone. Rolls et al. also found that the responses of face-selective cells decreased with repetition of some faces but increased with others, a result that we did not find for other objects in anterior-ventral IT cortex. This difference again could be due either to a difference in recording sites or to differences in the experimental design. Unlike in the present study, the monkeys in the Roll et al. study were not required to remember the faces for even a short period.

Adaptive memory cells and multiple memory systems

There have been many different types of memory defined at the behavioral level, which can generally be placed in two broad classes. One major class is explicit, or declarative, memory, which is the memory of specific facts and events. Another class is implicit, or nondeclarative, memory, which includes stimulus-response habit learning, skill learning, perceptual learning, and various types of nonassociative memory such as priming, habituation, sensitization, and so on. Behavioral studies suggest that IT cortex plays a role in both classes of memory. Lesions of IT cortex, particularly the anterior-ventral portion, impair performance of DMS tasks, which are thought to tap explicit memory (Gaffan and Murray 1992; Horel et al. 1987; Meunier et al. 1990; Murray 1992; Murray et al. 1989; Suzuki et al. 1991, 1993; Zola-Morgan et al. 1989, 1993). Likewise, IT lesions

impair visual discrimination learning, which is thought to involve implicit memory, at least in part (Mishkin 1982; Phillips et al. 1988).

As we have argued previously, adaptive memory filtering in IT might contribute to any or all of the memory systems defined in behavioral studies, depending on how the memory system is implemented neurally (Miller et al. 1993). Recently, we considered the possible contributions of IT neurons to performance of a recency memory task. We proposed that neurons in a hypothetical "decision network" downstream from IT receives opposing inputs from two different sets of IT neurons (Miller et al. 1993). One of the input sets (sensory cells) codes the sensory properties of the stimulus, with no influence of memory, and the other (adaptive cells) gives reduced responses to stimuli depending on how similar they are to stored memory traces. A difference in mean response between the two sets of cells signals that the current stimulus is a "match." The present results suggest that the same sort of decision network could support judgements of familiarity. A difference in response between the adaptive cells that show the familiarity effect and cells that do not could signal that the current stimulus is a familiar one. When both novel and familiar stimuli are used in a matching to sample task, the recency and novelty mechanisms may interact or even interfere. We found that responses to novel matching stimuli were larger than to familiar nonmatching stimuli early in the session, and a reversal of this relationship later in the session when the matching stimuli were more familiar. It is possible that the animal solved the task at the beginning of the session on the basis of relative novelty or familiarity (e.g., release the response bar to any novel test stimulus) and later switched to a recency strategy (e.g., release the bar to any stimulus repeated within a trial).

Because fewer IT cells respond strongly to a stimulus after it has become familiar, familiarity may cause a "focusing" of activity across IT cell populations. Cells that poorly represent the features of a given familiar stimulus may be winnowed out of the activated population through the adaptive memory mechanism, in much the same way that an excess of cells and connections are lost during development. Ironically, then, it may be the cells that do *not* show response decrements with familiarity that actually contribute to the long-term memory of a familiar stimulus. If these remaining activated cells have the appropriate association with cells coding contextual information (the circumstances in which the stimuli were seen, for example), they might mediate, in part, an "explicit" memory of the stimulus.

On the other hand, the adaptive memory mechanism might mediate priming phenomena, which reflects implicit memory. In a typical priming task for visual patterns, a subject is first shown a list of drawings, without any instruction to remember them. Later, they are given a picture recognition task, and their performance is usually faster or better for the stimuli that they had seen before, even if they have no conscious memory of having seen them (Schacter et al. 1990, 1991; Squire et al. 1992). It is commonly believed that priming is due to a tendency of neuronal populations to be more easily activated if they have been activated previously. For individual *cells*, we have shown that this is

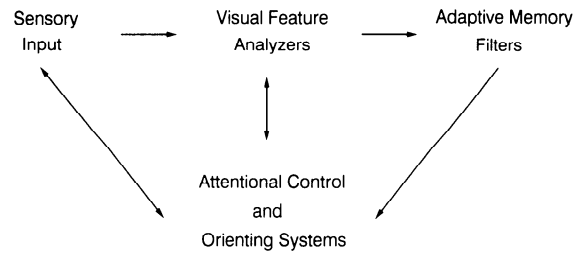


FIG. 11. Interaction between systems for memory and attention. In this scheme, a novel stimulus will activate adaptive memory filter cells in IT cortex, which in turn will drive attentional and orienting systems. This will lead to increased attention and contact with the new stimulus, causing adaptation of synaptic weights in IT cortex, reducing the activation of the cells. When the novelty of the new stimulus and the activation of IT cortex is sufficiently diminished, the system will be ready to process other competing stimuli.

not the case, at least in IT cortex. However, as we suggest above, it is the *elimination* of certain cells from the activated population that may be important in forming the underlying neuronal representation of a stimulus. Repetition may speed the construction of this critical population, resulting in faster and better recognition when a stimulus is repeated. Results from a recent positron emission tomography (PET) study of priming are consistent with the idea that priming is associated with a reduction of activity in the cortex. Subjects performing a word-stem completion task showed less activation of temporal cortex when they had previously seen the words before (Squire et al. 1992).

Finally, the fact that neuronal responses decreased with familiarity suggests a link to orienting responses and behavioral habituation. Although no individual cells in IT cortex appeared to be novelty detectors, the summed activity of IT cells could provide a signal to other systems that the current stimulus is new and deserving of attention. As the organism orients and attends to the new stimulus, activated IT cell populations shrink to the critical set necessary for representing the stimulus. This shrinkage reduces the overall activity in IT cortex, reducing the drive on the orienting system and freeing the organism's attention for other, competing, stimuli. One could view this as a negative feedback system for incorporating knowledge about new stimuli into the structure of the cortex (see Fig. 11). A similar negative feedback system is an essential component of Carpenter and Grossberg's (1987) adaptive resonance theory (ART) of memory and attention. Gochin and colleagues (Gochin 1990; Gochin and Lubin 1990; Gochin et al. 1991) have pointed out similarities between characteristics of ART and IT neuronal properties and have suggested that ART may serve as a useful model of memory storage in IT cortex.

Related structures

Anterior-ventral IT cortex has direct or indirect connections with rhinal cortex, entorhinal cortex, the hippocampal formation, parahippocampal gyrus, amygdala, the basal forebrain, and the prefrontal cortex (Aggleton et al. 1980; Insausti et al. 1987a,b; Turner et al. 1980), all of which have been implicated in recognition memory. Thus anterior-ventral IT cortex is in a position to supply other structures with information critical for visual memory formation and to be influenced by those structures in return. On

the basis of our analysis of average response histograms, it takes IT cells >100 ms after response onset to distinguish a novel sample stimulus from one that has been presented just once before. This is clearly enough time for the response difference to be caused by feedback from other structures. However, after just a few repetitions, IT cells distinguish novel from familiar stimuli within 10 ms of the onset of the visual response (or ~80–90 ms from the onset of the visual stimulus), which is probably not enough time for the response difference to be caused by feedback from memory circuits beyond IT cortex. Thus, although feedback may be necessary to initiate the processes that ultimately result in memory formation in IT, after a few repetitions IT networks appear to be capable of distinguishing novel from familiar stimuli on their own. It is not known whether IT cortex is the only structure in the visual system with this capability. Although neuronal responses are known to be affected by repeated presentations of a stimulus over very short time intervals in areas posterior to IT cortex, including V4 (Haenny et al. 1988; Haenny and Schiller 1988; Maunsell et al. 1991) and V1 (Nelson 1991), it is not yet known to what extent neurons in these areas can distinguish familiar stimuli from novel ones.

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