Brain (1982), **105**, 611-646

NEURONAL RESPONSES RELATED TO VISUAL RECOGNITION

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SUMMARY

To analyse the neural basis of long-term memory, recordings were made from single neurons in monkeys performing a visual recognition task of the type impaired in anterograde amnesia in man. Each visual stimulus was shown twice per day, once as novel, and after 0 to 17 other intervening items in the recognition task, on a second trial, as familiar, when the monkey could lick to obtain fruit juice if he recognized the stimulus correctly. At the anterior border of the thalamus, a population of neurons was found which responded to the stimuli only when they were familiar. The activity of these neurons was not related to lick responses. Further, in a different, visual discrimination, task, a number of these neurons were found to respond both to the familiar rewarded stimulus to which the monkey always licked, and to the familiar aversive stimulus to which he did not lick. This shows that in a reward association task these neurons respond on the basis of familiarity, providing evidence for a dissociation of recognition and associative memories.

Analysis of the responses of these neurons in the continuous visual recognition task showed that the responses to familiar stimuli were time-locked to the onset and duration of the visual stimulation (brief exposures producing brief responses). The response latencies were in the range 100 to 200 ms. A 100 ms exposure of the stimulus was sufficient for the stimulus to be encoded, and a 100 ms exposure was also sufficient for a recognition related response. The magnitude of the neuronal response on trials with familiar stimuli decreased as the number of trials between the first (novel) and second (familiar) presentation of the same stimulus increased. The rate of this decay or 'forgetting' varied from cell to cell and was best described by an exponential function. Repeated exposure tended to slow the rate of forgetting, and two or three repeated presentations prolonged some cell 'memories' for more than 100 intervening trials. Although the majority of the neurons did not have such long 'memories', in that they responded as novel to stimuli seen on a preceding day, so that their responses could be related to recency but not to absolute recognition of ever having seen a stimulus before, 2 neurons did respond to stimuli which had not been seen for 24 h. The neurons showed some ability to respond to stimuli as familiar despite changes in viewing conditions and transformations such as 90 deg rotation.

These findings indicate that the responses of these neurons at the anterior border of the thalamus are activated during recency or longer term recognition memory processing, both of which are impaired in anterograde amnesia in man. Measurement of the responses of these neurons, which appear to have access to memory mechanisms, has allowed parameters affecting such memory mechanisms to be investigated.

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INTRODUCTION

Amnesia is produced by damage to the medial part of the temporal lobe in man (Scoville and Milner, 1957; Milner, 1972). The amnesia is devastating, in that such patients recognize or recall very little of items or events which have been seen or have occurred only minutes previously, and may not for example learn to recognize the physician who sees them daily. This anterograde amnesia, for events happening after the brain damage, is usually accompanied by at least partial retrograde amnesia, for events happening before the brain damage, although usually these patients do recognize people they knew and events which happened before the brain damage. Although damage to the hippocampus in both the temporal lobes and in structures connected to it such as the fornix may be critical in producing the anterograde amnesia (Scoville and Milner, 1975; Milner, 1972; Brion *et al.*, 1969; Heilman and Sypert, 1977), this has been questioned. Instead it has been suggested that damage to the fibre connections of the temporal lobe (in the temporal stem) leads to the amnesia (Horel, 1978). Other work suggests that damage to the mammillary bodies or a medial part of the thalamus is associated with the memory loss in Korsakoff's psychosis produced by chronic alcoholism or encephalitis (Victor *et al.*, 1977; Mair *et al.*, 1979). As there is such uncertainty about which brain structures are involved in this type of memory in man, in a series of studies we are recording the activity of single neurons while monkeys are performing a memory task of the type impaired in anterograde amnesia in man. The task is a serial visual recognition task developed from one shown to be disrupted by fornix lesions in the monkey (Gaffan, 1974, 1977) and comparable to a serial picture recognition task severely impaired in anterograde amnesia in man (Warrington, 1974). A serial recognition task is being used so that the type of memory impaired in anterograde amnesia in man can be studied in the monkey. In that long-term rather than short-term memory is usually considered to be impaired in human amnesia (*see* Baddeley, 1975), and also because the task requires memory which is resistant to intervening stimuli and occurs over time periods of at least minutes, the type of memory being studied can be considered in these respects to be long term. The recordings are being made in the different brain regions implicated in amnesia in man, and in connected systems, in order to trace the processing involved in long-term memory. The results for one brain region in which neuronal activity related to long-term visual recognition memory has been found are described here.

There is evidence that section of the fornix impairs performance in recognition tasks, but not in tasks in which the association of a stimulus with, for example, food reinforcement is required (Gaffan, 1974, 1976). To determine whether the responses of the neurons described here might be specifically related to recognition, independently of reward contingencies, their activity was also measured during the performance of a visual discrimination, in which one stimulus was always paired with reward, and the other with aversive saline. Then, in order to provide information on the neural representation of long-term memory, and on how the

responses of these neurons are related to long-term memory, the temporal factors related to the acquisition, retrieval and decay of the responses of these neurons were analysed in the continuous recognition task. Preliminary reports of this work have appeared (Rolls, Caan, Perrett and Wilson, 1980*a*, *b*, 1981; Perrett, 1981).

METHODS

The Serial Visual Recognition Task

Two male rhesus monkeys (*Macaca mulatta*) (weight 4-8 kg) were shown each of several hundred visual stimuli twice per day. The first time, when the stimulus was novel, the monkey had to withhold licking a tube positioned immediately in front of his mouth to avoid obtaining aversive hypertonic saline. The second time, when the stimulus was familiar, the monkey could lick the tube to obtain fruit juice. In order to ensure that the task required the relatively long-term memory which is impaired in anterograde amnesia, 0 to 17 trials intervened between the novel and the familiar presentation of a given stimulus. Thus on every trial, the monkey had to decide whether to lick for a stimulus which he might have seen in the preceding 0 to 17 intervening interfering trials. This task allowed measurement of the duration of any neuronal effects related to memory. The term novel is applied to stimuli on the first presentation of the day and the term familiar is used to refer to stimuli on their second or subsequent presentations of the day. It should be noted, however, that because of the large number of stimuli used on a given day (approximately 500), it was necessary to reuse some familiar objects from one day as novel objects on subsequent days. Thus the terms novel and familiar are in fact only descriptions of relative recency. To test the effects of absolute novelty of stimuli, on each day some stimuli that the monkey had never seen before were used. The trials were normally separated by 8 to 15 s. A 0.5 s signal tone preceded each trial to cue the monkey to fixate the wide aperture shutter which opened on each trial to reveal the visual stimulus for 1.5 s. The shutter aperture subtended 20 deg at the retina for one monkey, and 40 deg for the other monkey, and the objects 1 to 20 deg. The inside of the box on which the shutter was located was uniform matt black or grey, to minimize visual stimulation in the intertrial interval. Fruit juice was available (on familiar trials) for a time sufficiently long for the monkey to make up to 2 to 3 licks. This ensured that the monkey was fixating the shutter at the start of each trial in order to make the first lick quickly to obtain as many licks as possible in the reward availability period. The monkeys were fed and given water each day after the testing. The monkeys learned the visual recognition task by stages in up to four months, and could perform the task with 17 intervening stimuli at the 90 per cent correct level.

The majority of the stimuli used in this investigation were selected from a collection of about 1000 'junk objects'. These objects were chosen to be as visually distinct as possible and to vary in size, colour, surface texture and pattern, and three dimensional structure. For convenience of storage and visibility all objects were smaller than 15 cm but larger than 1 cm in their longest dimension. Foods and objects left overnight in the home cage were used to test the responsiveness of the neurons to stimuli with which the monkeys had had much prior experience. The foods included bananas, oranges, peanuts and raisins. The stimuli were either hand held with little or none of the hand visible, or were placed on a black platform immediately behind the shutter. The stimuli were presented in the same manner (orientation, distance, position, etc.) for the first and second presentation, except when variation of this parameter on the responsiveness of a neuron was being investigated.

During testing of how the responses of a neuron were related to recognition memory, lists of 50 trials were employed, which contained 25 stimuli each occurring on 2 trials, first as novel, and after a delay as familiar. The lists were constructed after Gaffan (1977) and had the following features. Novel and familiar trials (excluding the first and last 7 trials) occurred in pseudorandom order, that is, there were not more than 3 consecutive trials of the same type (all familiar or all novel). The

first 7 trials contained a preponderance of novel stimuli and the last 7 trials a preponderance of familiar trials. The average number of intervening trials between the first and second presentation of the same stimulus was 9 and the range was 0 to 17.

Visual Discrimination Task

In the visual discrimination task, the monkey was always rewarded for licking in response to the sight of one stimulus (the positive discriminative stimulus, S+), and was always punished with saline for licking to the sight of the other stimulus (the negative discriminative stimulus, S−). This task was run in the same apparatus as the recognition task, so that stimuli were presented in the same way when the shutter opened, and the same lick responses were required. Prior to any recording, one monkey was trained with one pair of discriminanda and the other monkey with two pairs of discriminanda. During recording a further S+ was successfully introduced, but was used only approximately once every week, so that responses to a relatively unfamiliar S+ could be tested. The important difference of the visual discrimination task from the recognition task was that in the discrimination task behavioural responses to the S+ were rewarded when it was novel (that is, when it was seen for the first time on a day) and when it was familiar, and responses to the S— were punished both when it was novel and when it was familiar.

Clinical Testing

During this testing the shutter was removed and the screen at the front of the monkey's chair was opened to allow objects to be presented independently of the task, and to allow the experimenter to investigate the effects of a range of visual, auditory, somatosensory, gustatory and olfactory stimuli and movements on the responses of the neuron. For visual stimuli, objects were selected out of sight and presented from behind the screen at an average distance of 50 cm from the monkey. Measurements of the firing rate of the neuron were taken by the computer during the first 1 to 1.5 s of the presentation period. During this testing no warning tones prior to stimulus presentation were given, and lick responses were not reinforced. Often the lick tube was removed.

Recording Methods

The recording methods were similar to those described previously (Rolls *et al.*, 1976) and are described only briefly here. The activity of single neurons was recorded with glass-insulated tungsten microelectrodes advanced by a microdrive supported by a stainless steel ring which had been permanently implanted previously under pentobarbital sodium anaesthesia. The monkey lived in his home cage, and each day was brought to the laboratory where recordings were made from single neurons, with the implant fixed to provide stability, while he performed the visual recognition task for fruit juice reward. Recordings could be made for up to two hours from individual neurons during performance of the tasks. The activity of each neuron was collected and displayed online by a PDP11 computer as a peristimulus dot display, and peristimulus time histograms with cumulative sum statistics (Woodward and Goldsmith, 1964) were computed for every group of 17 trials. Digitized data were stored on disc for subsequent analysis, and examples of raw data were recorded on analogue magnetic tape. The neuronal responses were usually calculated from the number of spikes in a 500 ms period starting 100 ms after the stimuli were presented. This period was used because the responses of the neurons started with latencies longer than 100 ms, because the behavioural responses in the recognition task were made within 600 ms of stimulus presentation, and because fixation of the stimuli (as shown by electro-oculographic recordings) continued for this period. Unless otherwise stated, the neuronal response values given in this paper are expressed as the firing rate in spikes/s during this period.

The sites where particular neurons were recorded were located using microlesions made through the recording microelectrode. X-radiographs were taken on every track to establish the position of the microelectrode relative to nearby permanently implanted reference electrodes. The recording

sites of all other neurons were subsequently reconstructed from the histologically verified positions of the reference electrodes and the microlesions, using 50 μm coronal sections taken in the stereotaxic vertical plane and stained with cresyl violet as described fully elsewhere (Rolls *et al.*, 1976; Rolls, Sanghera and Roper-Hall, 1979).

RESULTS

Recordings were made from both hemispheres in the two monkeys during 290 electrode tracks through many structures which included the hippocampus, mammillary bodies, inferior temporal visual cortex, thalamus and basal ganglia. Typically the responses of more than 12 neurons could be investigated during the performance of the visual recognition task on each track. The responses obtained from a number of neurons recorded in the vicinity of the anterior boundary of the thalamus, which responded to the presentation of familiar but not to novel stimuli, are described here. The cells are treated as a distinct population because of the similarity of their response characteristics and because of their restricted anatomical distribution. At least 1704 neurons were recorded during these tracks aimed through the rostral thalamus (equivalent to 11 to 14 mm anterior in Olszewski's (1952) atlas). Our procedure proved sensitive enough to distinguish the recognition related responses described here from responses which were movement related (e.g. globus pallidus), reward related (e.g. hypothalamus), visual habituating (e.g. tail of caudate nucleus) or visually selective (e.g. inferior temporal cortex) (Rolls *et al.*, 1976, 1977; Rolls, Thorpe *et al.*, 1979, 1981; Rolls, 1981).

Responses to Novel and Familiar Stimuli

Fig. 1. illustrates the activity of one cell to a stimulus on two successive trials. On the first trial when the stimulus was novel the neuron remained inactive, but when the shutter opened on the following trial to reveal the same but now familiar stimulus, there was a large and sustained increase in the firing rate. This response started with a latency of 120 ms and continued throughout the trial while the monkey looked at the stimulus. The figure also shows the correct behavioural (lick) response which occurred at 420 ms on the familiar trial. Twenty-seven cells responded with a large increase of firing rate to the sight of familiar stimuli. These cells were spontaneously active with rates between 10 and 30 spikes/s (mean 18 spikes/s) and generally decreased their firing rates to the sight of novel stimuli. This decrease occurred both for stimuli which had never been seen by the monkey and for stimuli which had been presented on preceding days but were novel on the day of testing. Six further cells with high spontaneous activity (30 to 65 spikes/s) responded by decreasing their firing rate to familiar stimuli and increasing to novel. Thus it was a general characteristic of these 33 neurons that responses to novel and familiar stimuli were opposite in direction. A further 10 cells consistently increased their firing rates differently to novel and familiar stimuli, and had low

spontaneous activity, but their responses were smaller and they are not considered further here. The spontaneous activity was measured in the intertrial interval or when the monkey was not performing the task (differences were not found). The neurons usually showed no or only a minor change in activity to the signal tone which preceded each trial. The responses were usually clear on the rastergrams displayed online for each trial individually, as well as in the cumulative sum distributions computed. (Examples of the responses on single trials are shown in figs. 1, 5 and 9.)

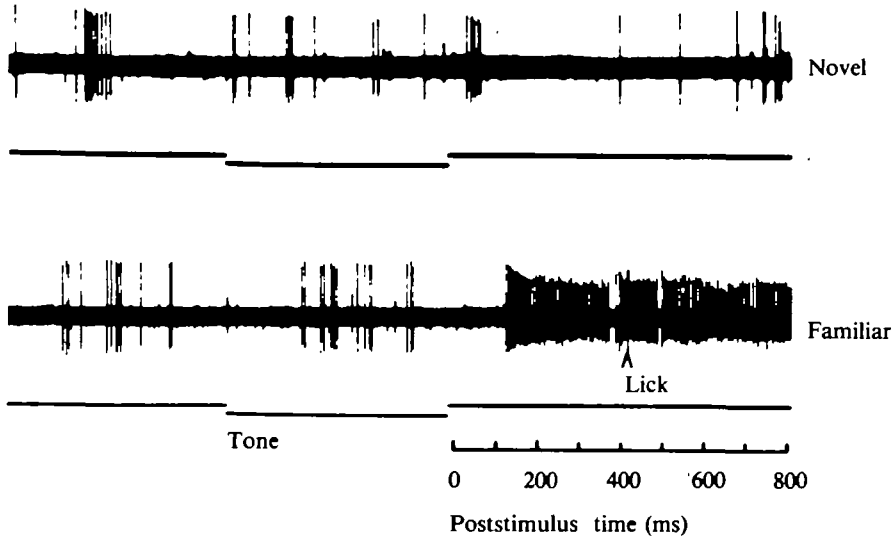


FIG. 1. Electrical recording of single cell activity during presentation of novel and familiar visual stimuli. The horizontal axis represents time in ms relative to the onset of stimulus presentation which occurs after a 0.5 s signal tone (tone duration indicated by downward deflection of the lower of the trace pairs). The *upper* of the trace pairs displays the electrical activity of the neuron recorded (HO22) with action potentials indicated as up and downward deflections from the trace baseline. For the first trace pair, the stimulus is novel and for the second, it is familiar. The occurrence of the monkey's behavioural response (a lick) made during the familiar trial is recorded on the *lower* trace.

Response Magnitude Distribution

The extent to which cells responded differentially to novel and familiar stimuli was analysed by plotting histograms of the responses of individual cells for all trials with novel stimuli and for all trials where stimuli were familiar and had been shown on the preceding trial.

Fig. 2 gives the distribution of responses of one cell calculated from the number of spikes occurring on each trial in the half second period starting 100 ms after the shutter opened. For this cell there is almost no overlap between the low firing rate on trials where the stimuli are novel and the high firing rate on trials where

stimuli are familiar (from the preceding trial). Thus the responses of this neuron differentiated between novel and familiar stimuli in these conditions on almost every trial.

Fig. 3 is a similarly constructed histogram for the responses of a different cell which generally responded to novel stimuli with an increase of firing rate and to familiar stimuli with a decrease of firing rate. This cell had the most overlap between novel and familiar stimuli of the 33 cells studied but even for this cell there was a highly significant difference in response to novel and familiar stimuli ($t = 7.89$, $df = 104$, $P < 0.001$).

This type of analysis indicated that these cells responded to visual stimuli on the basis of their familiarity. That is, the cells responded to practically all visual stimuli irrespective of stimulus shape, size or colour but only when the stimuli were familiar.

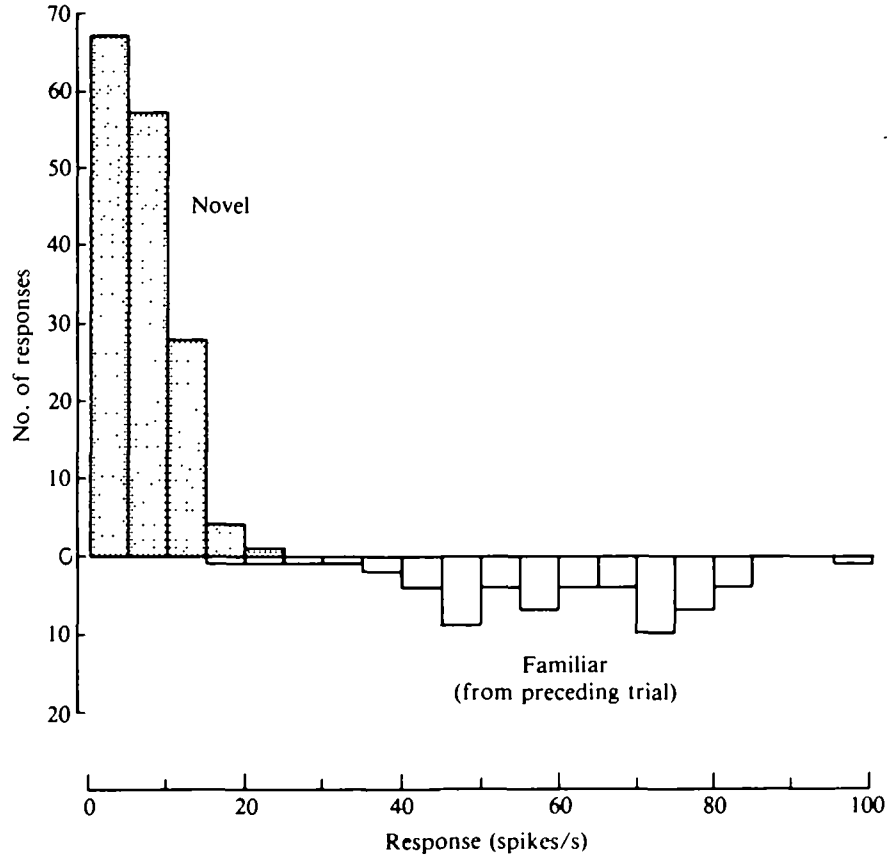


FIG. 2. Distribution of responses on novel and familiar trials for one cell (HO22). Ordinate: number of trials on which a response of particular magnitude occurred. Abscissa: magnitude of responses (spikes/s). For clarity, responses on novel trials (stippled histogram bars) are plotted in the upward direction and responses on familiar trials when stimuli have been seen on the preceding trial are plotted in the downward direction (clear histogram bars). For this cell, familiar stimuli produce a higher discharge rate than novel stimuli.

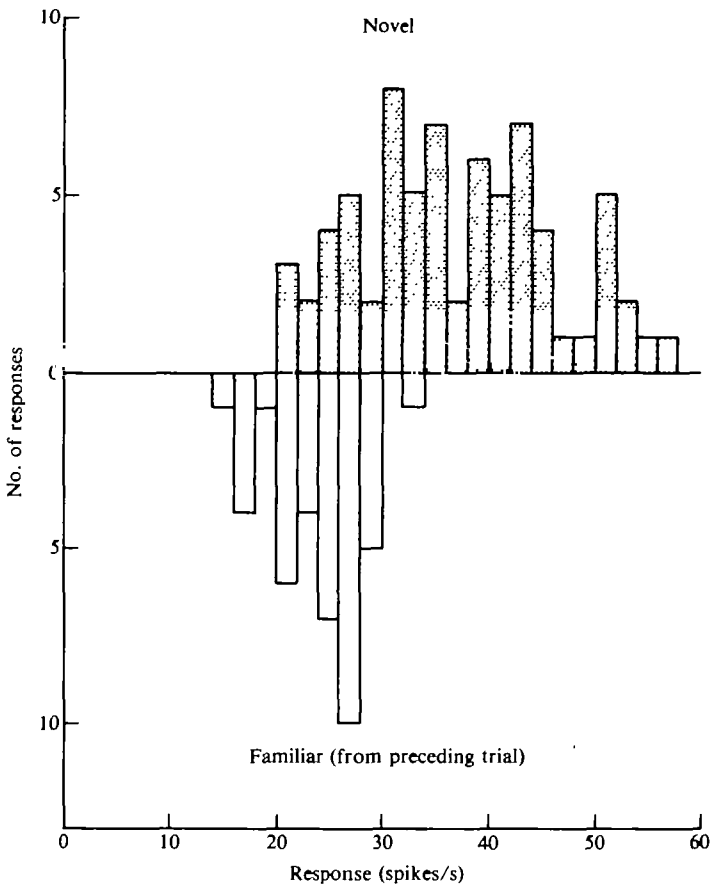


FIG. 3. Distribution of responses on novel and familiar trials for cell GO36. Ordinate/abscissa as in fig. 2. This cell discharged at a relatively low rate during familiar trials (clear histogram bars) and a relatively high rate during novel trials.

Response Latency

The earliest consistent response latency to familiar stimuli for different cells ranged between 100 and 220 ms (see fig. 4). There was often some variability in the response latency of the cells from trial to trial, but the reason for this has not yet been established. Correct behavioural responses (contact of the tongue with the lick tube) were made by the monkey in the recognition task to familiar stimuli at latencies of between 400 and 500 ms. Electromyographic (EMG) recordings have revealed that muscle activity associated with such lick responses begins 100 to 150 ms before the lick contact (Rolls, Sanghera and Roper-Hall, 1979). Thus the discharges of these neurons to familiar stimuli occurred at least 100 ms before the onset of the motor response to these stimuli. Most cells exhibited an early

latency (50 to 100 ms) indiscriminate response to both novel and familiar stimuli. The direction of the early response was usually the same as the response to novel stimuli. Thus most cells showed a decrease in their firing rate about 70 ms after the shutter opened, and this decrease continued if a novel stimulus was presented, but was replaced by an increase of firing rate if a familiar stimulus was presented.

Activity during Correct and Incorrect Performance of Recognition Task

The responses to familiar stimuli could occur both when the monkey was performing the recognition task correctly and when the monkey was making mistakes. This is illustrated in fig. 5. Here data from novel and familiar trials originally run in pseudorandom order have been grouped together. In the first 3 trials with novel stimuli the neuron decreased its firing rate and the monkey correctly did not lick. In the following 3 trials the neuron increased its firing rate to familiar stimuli and the monkey correctly responded with a lick about 400 ms after the shutter opened (the lick responses are denoted by L). In the lower novel and familiar trials the pattern of neural activity was similar to that above but the behavioural performance was incorrect. This dissociation of the neuronal from the behavioural responses shows that the neuronal responses cannot be interpreted as the presence of premotor activity. This dissociation of the unit activity from lick response was typical for all 33 cells studied.

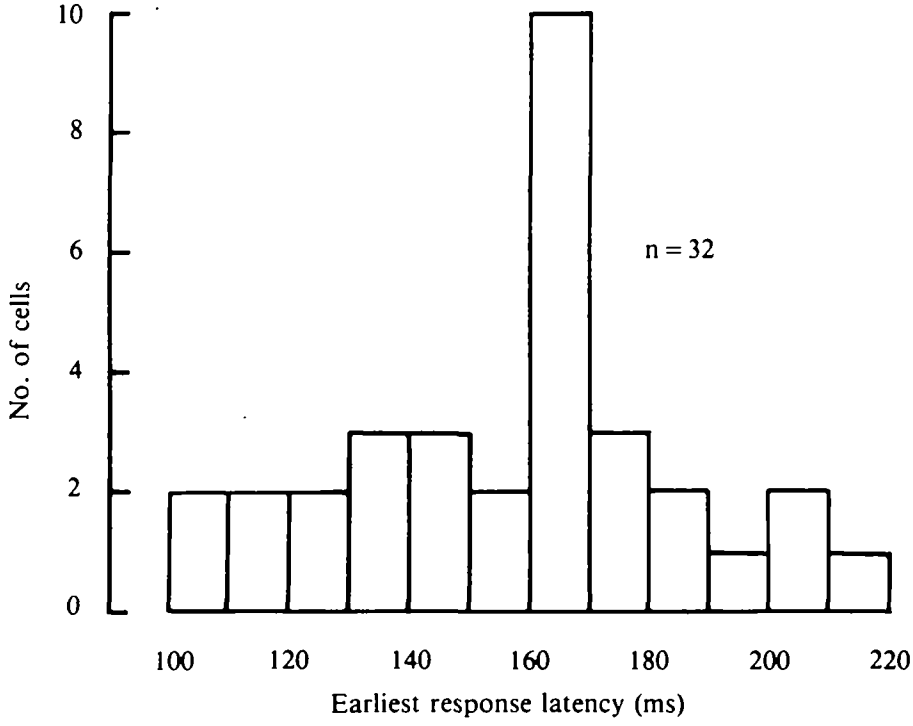


FIG. 4. Histogram of earliest response latencies to familiar stimuli for 32 different cells with recognition related responses.

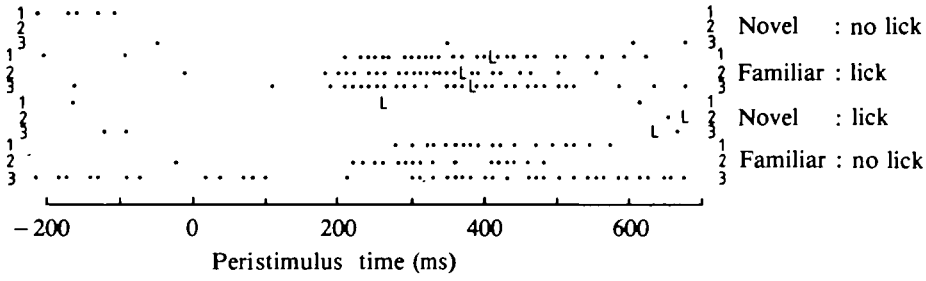


FIG. 5. Activity of one cell during correct and incorrect recognition task performance. Peristimulus time (ms) is calibrated along the horizontal axis with stimuli presented at time zero. Dots represent the occurrence of one or more action potentials in a 10 ms time bin. Each dot row gives the neuronal activity on separate trials. First 3 trials: novel stimuli were shown and the monkey correctly gave no lick response. Second 3 trials: the monkey correctly gave a lick response (L) at the sight of familiar stimuli. The lower 6 trials illustrate activity on novel and familiar trials when the monkey gave incorrect responses.

Responses to Familiar Stimuli after Intervening Trials

The responses of these neurons to familiar stimuli could still occur strongly even when 17 intervening interfering trials occurred between the novel and familiar presentations of a given stimulus. This is illustrated in fig. 6, which shows the response of one neuron to familiar stimuli as a function of the number of trials between the novel and familiar presentations of stimuli. The magnitude of the response was calculated from the number of spikes in the 500 ms period of stimulus

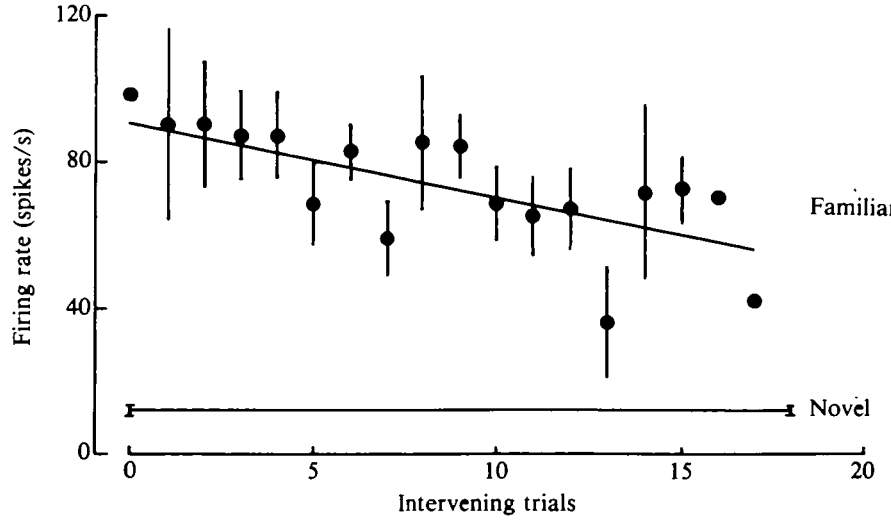


FIG. 6. Effect of the retention interval upon the magnitude of the neuronal responses to familiar stimuli for cell HO22. Ordinate: response magnitude (spikes/s); abscissa: number of trials intervening between novel and familiar presentations of the same stimulus. The mean response magnitude is given for each retention interval with standard errors for means of 3 or more trials. The mean and standard error of the firing rate on novel trials are given for comparison. The line is the linear regression.

presentation starting 100 ms after the shutter opened. For comparison, the response of the neuron to novel stimuli is also shown, and was low (even below the spontaneous activity). It is also shown in fig. 6 that the response of the neuron to familiar stimuli became somewhat smaller as the number of intervening stimuli became greater. Regression analysis for some of these cells which showed that the decay, and thus the effective memory span, differed for different cells is presented below. It should be noted here that for cells with short memories, the monkey might with a large number of intervening stimuli perform correctly, yet the neuron might not respond to the relatively old familiar stimuli shown on these trials, providing further evidence that the responses of these neurons can be dissociated from behavioural responses made by the monkey.

Clinical Testing

During open laboratory testing in which objects were simply presented without a warning tone and with the shutter removed, the monkeys typically fixated each stimulus presented and did not give the lick responses that were made in the recognition task. For 9 cells tested in this situation, however, all continued to respond differentially to novel and familiar stimuli. Fig. 7 gives the mean and standard error for the responses to novel and familiar stimuli from several clinical

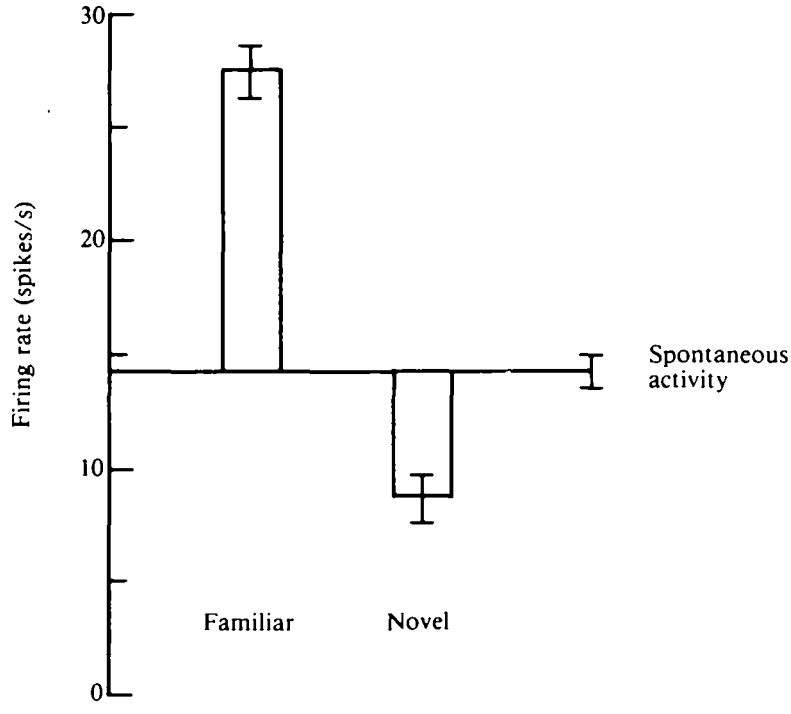


FIG. 7. Responses of a neuron (GO41) to novel and familiar stimuli during clinical testing. Ordinate: firing rate in spikes/s. The mean and standard error of the response magnitude (spikes/s) relative to the baseline are given for trials on which familiar and novel stimuli were presented.

trials for one cell. Relative to the spontaneous firing rate measured during the intertrial interval, the cell decreased its firing rate to novel stimuli and increased its firing rate to familiar stimuli.

These results indicate that these cells discriminated familiarity even when the monkey was not required to do so in a behavioural task. It also provides evidence that the cells belong to a memory system that operates in different environmental contexts. Indeed it was shown that the responses generalized from one viewing condition to the other, so that if a stimulus was shown as novel in the recognition task there was a familiarity response when the same stimulus was shown later in the clinical viewing condition in the open laboratory, and *vice versa* (*see below*).

Neuronal Responses during an Association Memory Task

To investigate whether the responses of these neurons were specific for the memory required in the recognition task, recordings were made from the same

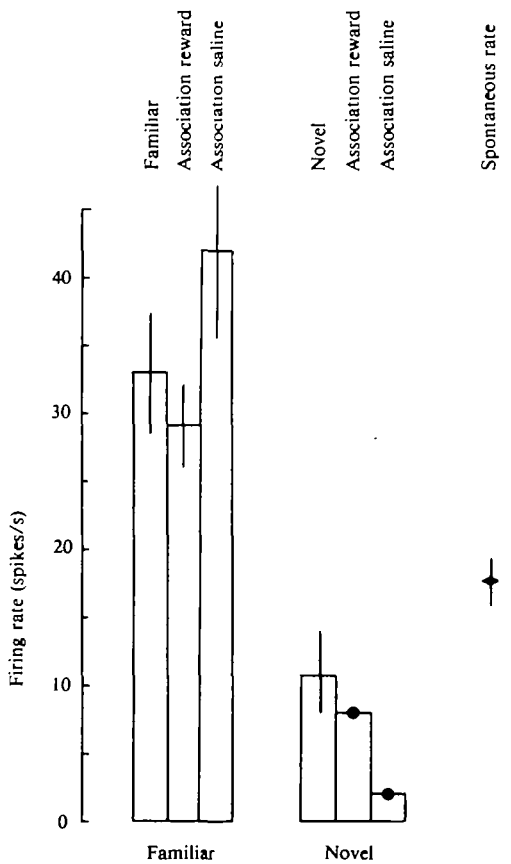


FIG. 8. Neuronal activity during performance of the visual recognition and visual association tasks. The means and standard errors of the responses (spikes/s) of one neuron during performance of the two tasks, and the spontaneous firing rate of the neuron, are illustrated. Responses during trials from both tasks when stimuli presented are familiar are given on the left and during trials when stimuli are novel on the right.

neurons tested in the recognition task while the monkey performed a different, visual discrimination task, in which memory for the association of a stimulus with reinforcement was required.

Examples of the responses of one of these neurons in both the recognition and the association tasks are shown in fig. 8. In the recognition task, the neuronal response (which was measured in a 0.5 s period starting 100 ms after the shutter opened) was a large increase in firing rate to the familiar stimulus, and a decrease in firing rate to the novel stimulus. In the association task (which the monkey performed correctly), the firing rate increased on both S+ (rewarded) trials and on S− trials, if the S+ and S− had been seen previously on that day (*see* fig. 8, Familiar). Thus the neuron responded in the association task both to the stimulus which was associated with reward and to the stimulus which was associated with punishment, provided that they were familiar. If the S+ and S− had not been seen previously on that day, then the neuron did not respond to either (*see* fig. 8, Novel), even though the monkey correctly made a lick to obtain fruit juice to the S+, and withheld a lick to the S− in order to avoid saline. This indicated that even while the monkey performed the association task, the neuron responded independently of the association of the stimuli with reinforcement, and independently of whether the monkey licked to obtain fruit juice reward, but on the basis of the familiarity of the stimuli.

Of the 14 cells with responses related to familiarity in the recognition task which were also studied in the association task, 12 responded similarly to the cell illustrated in fig. 8. The two other cells became inactive in the association task. Thus for all of these cells tested in both tasks, no evidence that their responses were related to the association of stimuli with reinforcement or to lick responses was found, and the majority of the neurons responded on the basis of recognition even in an association memory task.

Analysis of the Effect of Retention Interval on Recognition Responses

For all of the 33 cells studied there was a marked tendency for the responses to familiar stimuli to decline with an increase in the number of trials between the first and second presentations. This was illustrated in fig. 6. Here, the data from particular cells on which prolonged testing was accomplished is considered in order to provide a quantitative description of the nature of the decay of responses as a function of the number of intervening stimuli. From this analysis a 'calculated memory length' of a cell could be obtained in terms of the number of intervening trials which it took to reduce the response to the familiar stimuli to the level of the response to novel stimuli. This provided a useful measure for investigating the effects of alteration of parameters such as the number of times a stimulus was seen on the responsiveness of the neurons.

Linear regression analysis showed for a number of cells a significant decline in the magnitude of the response as a function of the retention interval. However, as in several models of long-term memory the strength of memory traces are

described as decaying exponentially rather than linearly (Wickelgren, 1972; Gaffan, 1978), linear and exponential fits to the decay of the neuronal responses were compared. This was performed by comparing regression analyses performed on both the response magnitude and the log of the response magnitude as a function of retention interval, to determine whether a greater proportion of the variance in the data was accounted for after a log transform. For 5 cells the F ratio was calculated from the linear and logarithmic regression analysis, to provide a measure of the proportion of the variance accounted for by the regression line (*see* Bailey, 1959). Sufficient data were not available for this particular analysis to be performed for other cells in the population studied. The F ratios are given in Table 1. For 4 out of 5 cells the F ratio was larger for the log transform. For one neuron the F ratio was larger without the log transform. Thus for the majority of these cells an exponential decay was a more accurate description of the data than a linear decay.

TABLE 1. ANALYSIS OF THE DECAY OF RECOGNITION RELATED RESPONSES

	F ratio		*n*
Cell	*Linear decay*	*Exponential decay*	*Sample*
HO22	15.34	23.86	98
HO40	2.93	3.52	40
GO36	1.83	2.10	38
GO39	5.27	4.98	23
GO41	1.88	3.72	79

Linear and exponential descriptions of the decay in the response to familiar stimuli with retention interval are compared for 5 neurons. The proportion of variance (F ratio) accounted for by the regression line is tabulated for the regression analysis of response magnitude *versus* retention interval (linear decay) and for the natural log (ln) of response magnitude *versus* retention (exponential decay). The number of data points for which the regression analysis has been performed is given for each cell at the right.

Length of Memory

The decrease in the magnitude of the response as a function of retention interval was found to vary from cell to cell. Table 2 gives the log regression line slope (with the standard deviation of the slope; Bailey, 1959) for 5 cells. In each case the slope was more than 1.96 standard deviations from zero and was thus significant at the $P < 0.05$ level. The negative slope of the regression line shown by 4 cells reflects a decline in the excitatory response to familiar stimuli. The positive slope for cell GO36 reflects a decline in the inhibitory response to familiar stimuli.

For each cell the 'calculated memory length' is given in Table 2 in the right-hand column. It is defined as the average number of intervening trials required to bring the response to familiar stimuli to the level of the response to novel stimuli. It

TABLE 2. THE 'MEMORY' FOR FAMILIAR STIMULI OF THALAMIC CELLS

Cell	*Regression slope* (+/−*SE*)	'*Memory length*'
HO22	−0.035+/−0.015	57
HO40	−0.051+/−0.015	15
GO36	+0.011+/−0.002	36
GO39	−0.078+/−0.034	17
GO41	−0.233+/−0.050	7

For 5 cells the slope and standard error (SE) of the slope of the regression line are given for the regression analysis of ln response magnitude (spikes/s) *versus* retention interval (number of intervening trials). The memory span for each cell is calculated from the regression analysis and defined as the average number of trials necessary to reduce the response to familiar stimuli to the novel level.

was calculated, assuming exponential decay of the response as this was shown above to be the best fit to the decay, by determining the number of intervening trials at which the regression line intercepted the level of the response to novel stimuli. Cell HO22 had a fairly durable memory, with a calculated memory length of 57 intervening items, whereas cell GO41 had a calculated memory length of only 7 items. Thus there was a considerable difference in the length of the memory of the different cells. This difference occurred despite equivalent levels of performance of the monkeys in the recognition task when the different cells were recorded. It should be noted that these decay functions, and thus the 'calculated memory length', depend on the amount of exposure to the stimulus on a given day, as shown below. The particular values obtained in this experiment were with a single short (1 to 1.5 s) exposure of the to-be-remembered stimulus.

Effects of Stimulus Duration on Recognition Related Responses

A. *Brief presentations.* The duration of responses evoked by brief visual stimulation can give some indication as to whether neurons are more sensory or more motor in nature. Exact time locking of responses to stimulus exposure would indicate strong connections of the neurons under study to the sensory input side. To investigate the degree of sensory control over responses the recognition task was used as described earlier except that the shutter duration was shortened to 100 ms for particular trials. Reward contingencies remained as before, that is, lick responses were rewarded only on the second presentation despite changes in the duration of particular presentations. Behavioural performance was not drastically affected by exposure reduction. Monkeys were able to discriminate correctly novel from familiar stimuli presented for only 100 ms, and this correct performance occurred when either the novel presentation or the familiar presentation or both were only 100 ms long.

The responses of one cell on trials with normal and brief exposures are illustrated in fig. 9. The data are taken from testing in which novel and familiar stimuli and trials of long and short duration were interspersed. For the illustration, trials using the same type of stimuli and same duration of exposure are grouped together. On all trials there is evidence of neuronal inhibition starting 70 to 100 ms after the shutter opened. (For brevity, inhibition and excitation are used to refer to a decrease and increase of firing rate.) For trials with novel stimuli presented for 1 s the inhibition continued until 350 to 400 ms after the shutter opened. For trials with novel stimuli presented for 100 ms the inhibition terminated earlier, 250 to 300 ms after the shutter opened. Familiar stimuli presented for 1 s produced prolonged excitatory discharges which started at latencies of 140 to 170 ms and continued at least until the correct lick responses were made at around 500 ms after the shutter opened (lick responses are denoted by L in the dot display). When familiar stimuli were presented for 100 ms, excitatory responses began at similar latencies to 1 s presentations but the neuronal responses terminated much earlier, up to 250 ms before the lick responses.

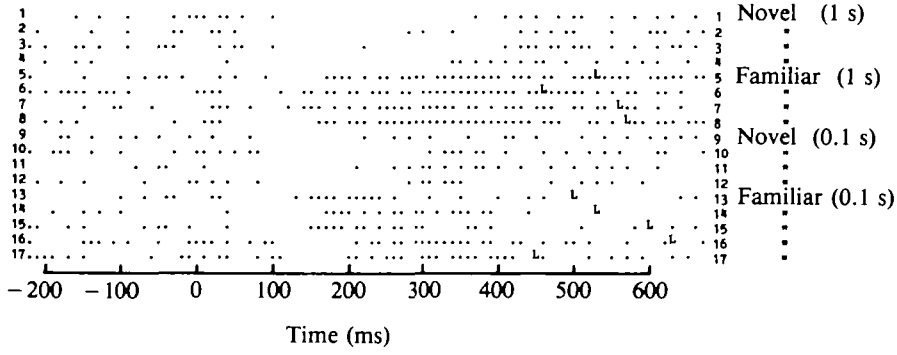


FIG. 9. Effects of brief stimulus exposure on neuronal activity during recognition trials. Activity of one neuron (HO59) on different trials is represented by horizontal rows of dots, a dot denoting the occurrence of one or more action potentials in successive 10 ms time bins, each row containing data from one trial. The horizontal axis at the bottom of the figure represents time. 0 ms = visual stimulus presentation onset. Trials (originally in random order) are grouped according to stimulus familiarity and duration of stimulus exposure.

For all 4 cells tested with brief presentations it was found that the change in the duration of the stimulus presentation did not affect the occurrence of neuronal responses but did affect the duration of the neuronal responses. With 100 ms stimulus presentations the responses typically lasted for 100 to 250 ms, whereas with normal presentations the neuronal responses were more sustained. Thus both the inhibition on novel trials and the excitation on familiar trials were substantially reduced in duration when the stimuli were only briefly exposed. This indicates a sensory control over neuronal responses.

B. *Prolonged exposures.* Exposures of several seconds were used to determine whether excitatory discharges (characteristic of responses to familiar stimuli) could develop during a single continuous presentation of a novel stimulus. The earliest appearance of excitatory recognition related responses provides an estimate of the time which is required for stimuli to be encoded into the recognition memory system. During experiments with standard exposures of 1.0 s the inhibitory responses to novel stimuli normally continued for the greater part of this period. However, when the shutter was left open for several seconds large excitatory discharges were observed to build up. For 6 neurons this excitation began more than 1 s after the stimulus was presented, and for 2 neurons this excitation occurred in less than 1 s after the novel stimulus was presented.

Fig. 10 illustrates the response of one cell to several novel stimuli presented to the monkey for several seconds in the clinical situation where no behavioural response was required. The mean discharge rate during the first 0.5 to 1.0 s of presentation was depressed as was normally found for cells tested in this manner, but in the subsequent period 1.5 to 3.0 s after presentation the discharge rate was elevated, which was characteristic of this and other cells' responses to familiar stimuli.

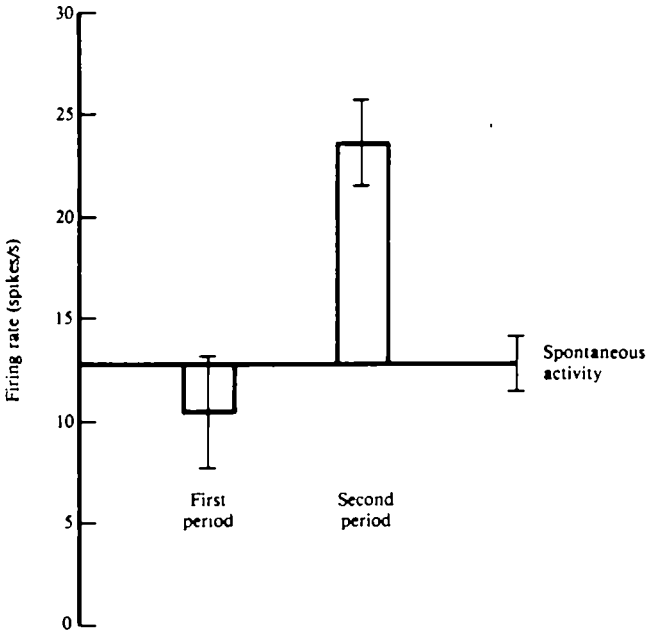


FIG. 10. Effects of prolonged exposure to novel stimuli. The firing rate (spikes/s) for cell (GO37) is illustrated for the first part (0.5 to 1.0 s) and the second part (1.5 to 3.0 s) of continuous exposure to novel stimuli. The mean and standard error of the response rates relative to the spontaneous firing rate are illustrated for 5 trials.

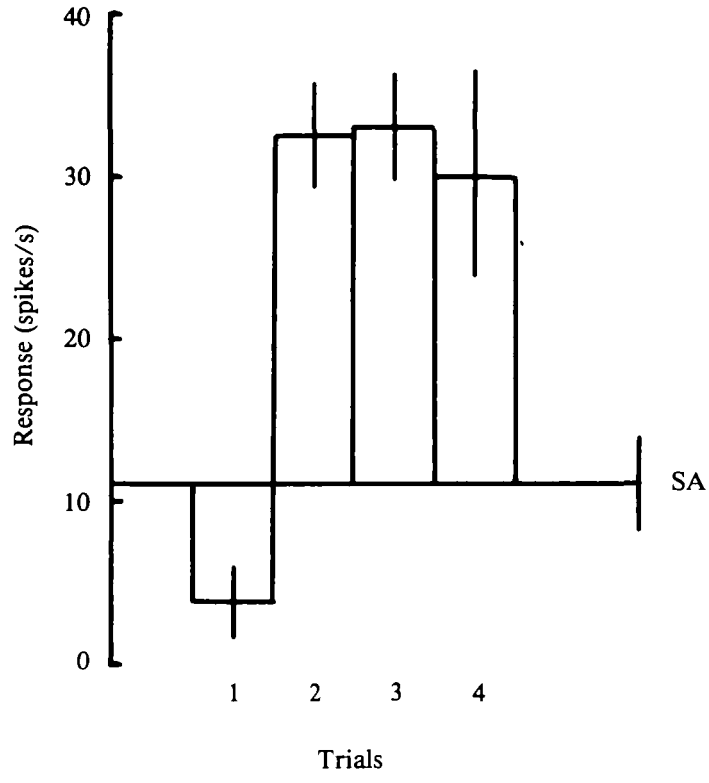


FIG. 11. Responses of one neuron (GO41) to stimuli presented repeatedly with no intervening trials. The mean and standard error of the responses to different stimuli presented on 4 successive trials are illustrated relative to baseline spontaneous activity (SA). On the first trial the stimuli were novel and for subsequent trials they were familiar.

Effects of Repeated Exposure to Stimuli

Gaffan (1978) found in an experiment on human picture recognition memory that repeated exposure to pictures increased the probability that they were recognized as 'seen before' (that is, familiar) when they were tested at long retention intervals of three days. This section investigates whether repeated exposure to stimuli affects the responses of these neurons at the rostral border of the thalamus.

A. *Effects of stimulus repetition without intervening stimuli.* When novel stimuli were presented on several successive trials without intervening trials with other stimuli, there was a change in responsiveness from the novel to the first familiar presentation, but no consistent change in responsiveness for subsequent presentations. Fig. 11 illustrates typical results for one cell. Thus the recognition related responses were maximal on the first familiar presentation and did not increase with further exposures.

B. *Effects of stimulus repetition with intervening stimuli.* For this experiment the basic recognition task (as previously described) was used except that several objects that had been presented as novel and later as familiar for a first familiar trial (F1) were presented again as familiar stimuli (Fn) on subsequent trials on the same day. The total number of presentations for repeatedly exposed (Fn) stimuli ranged from 3 to 10 (including the novel presentation). Trials on which other stimuli were shown intervened between the novel, the first familiar (F1), and the subsequent familiar presentations (Fn) of a given stimulus. Normally the number of such intervening trials was between 1 and 25, but this was extended in some cases to over 100 intervening trials. Novel and familiar trials were pseudorandomly ordered.

TABLE 3. EFFECT OF REPEATED EXPOSURE UPON NEURONAL RESPONSES TO FAMILIAR STIMULI

Cell slope (+/−*SE*)	*Memory length*	*Statistic d*	*Probability*
HO22 −0.024 (+/−0.002)	88	0.63	n.s.
HO40 −0.001 (+/−0.002)	751	3.37	$P < 0.002$
GO36 +0.001 (+/−0.003)	667	2.74	$P < 0.01$
GO39 −0.059 (+/−0.013)	27	0.55	n.s.
GO41 −0.020 (+/−0.008)	96	4.18	$P < 0.001$

For 5 cells the slope and standard error of the slope are tabulated (column 1, left) for the regression analysis of ln response (spikes/s) to repeatedly exposed familiar stimuli *versus* retention interval (number of intervening trials). Column 2 gives the memory length for each cell, calculated from the regression analysis and defined as the average number of trials necessary to reduce the response to familiar stimuli to the novel level. The value of the statistic d calculated for the difference in the regression slopes for stimuli that have been seen once before (Table 2) or 2 to 4 times (this Table) is given together with the probability (columns 3 and 4).

It was found that repeated exposure of a stimulus led to a greater neuronal response when that stimulus was shown later. This was analysed statistically by performing regression analysis for the log of the neuronal response magnitude against the retention interval (that is, the number of intervening trials since that stimulus was last shown) for F1 and Fn stimuli. The slope and standard deviation of the regression line are given for each of 5 different cells in the F1 condition in Table 2 and in the Fn condition in Table 3. When the stimuli had been seen several times before (the Fn condition, Table 3), for all cells the rate of decline in the magnitude of the neuronal response with increasing retention interval was less steep than when the stimuli had been seen only once (the F1 condition, Table 2).

For 3 cells, the difference in the slope of the regression lines under the F1 and Fn conditions was statistically significant, as shown in Table 3 by the values of the statistic d for the comparison between the slopes of the regression lines and their associated levels of significance. (Corrections were made for differences in the variance between conditions according to methods described by Bailey, 1959.)

The 'calculated memory length' for each cell after repeated exposures to the stimuli is also given in Table 3. It was calculated from the regression coefficients as described above, and gives an indication of the extreme durability of the memory of some cells after repeated exposure to stimuli. For 2 cells, a few exposures to stimuli produced an effect lasting on average over hundreds of intervening items. Although this 'calculated memory length' is an extrapolation made from responses to familiar stimuli mainly measured experimentally at retention intervals shorter than 50 intervening trials, it was possible to confirm with direct measurements for particular cells the presence of differential responses to familiar as compared to novel stimuli. This was so even after more than 150 trials with other stimuli had intervened between the two presentations of a particular stimulus. The retention times with these large numbers of intervening trials were more than 1 h.

Responses to Objects Previously Highly Familiar to the Monkey

From the preceding experiment one might expect to find recognition related responses to occur at longest retention intervals for objects with which the monkeys had had considerable experience such as particular types of food. Therefore to investigate further the length of memory of these cells' responses to familiar stimuli, responses were measured to different types of food when they were seen for the first time on a particular day (for example, when they were in the novel condition of the running recognition task).

For 11 cells, there was no evidence for a difference in the responses to foods seen for the first time on a particular day from the responses to other objects seen on novel trials. For one cell (GO36, known to have a relatively durable memory after repeated exposures to stimuli) foods were generally treated as familiar on the first presentation of the day, both in the clinical and shutter situations. For this cell, the mean and standard error of the responses from shutter trials to novel and familiar objects and from trials with five different foods presented as novel and as familiar are presented in fig. 12. The responses on the first presentation of the day with food were significantly different from the responses to novel objects ($t = 3.06$, $df = 72$, $P < 0.005$). Similarly, for a second cell, which gave excitatory responses to familiar stimuli and inhibitory responses to novel stimuli, the only trial on which food was used as a novel stimulus produced a response 4.15 standard deviations larger than the mean response for novel objects. These data thus suggest that some, but not the majority of the cells tested, had memories which extended for more than one day.

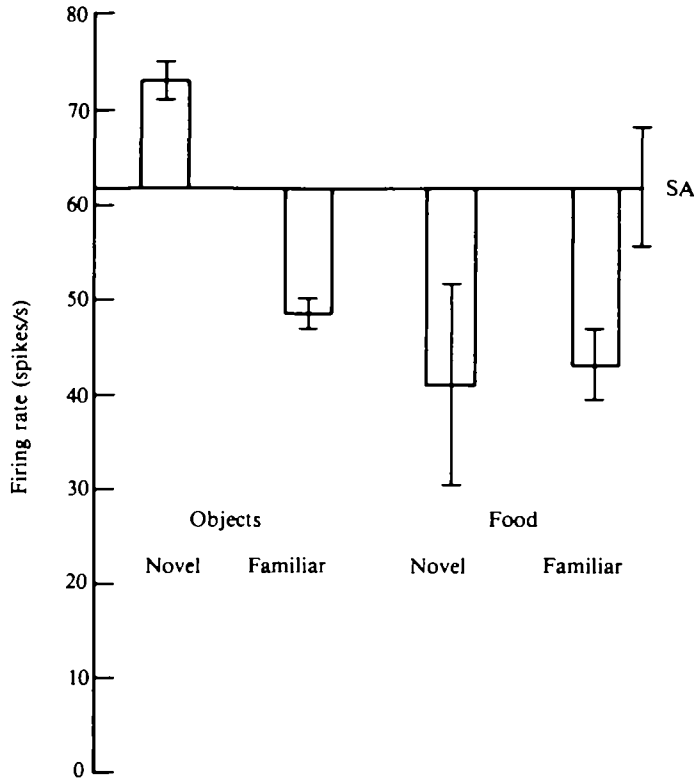


FIG 12. A comparison of responses to food and other objects. The mean and standard error of the responses (spikes/s) of one cell (GO36) to foods and other objects during novel and familiar trials (first and subsequent presentations of the day) are given relative to the cell's spontaneous activity (SA).

Relation of Neuronal Responses to Perceptual Constancy and Recognition

A system involved in the recognition of objects might be expected to be capable of responding to objects despite changes in the conditions under which the objects are seen. It is important to be able to recognize objects even when they are seen from a somewhat different angle and in different lighting conditions. To investigate the extent to which the neurons described here exhibited such perceptual invariance the view of objects was systematically transformed between the initial (novel) and subsequent (familiar) presentations.

The effect of isomorphic rotation of stimuli through 45 to 90 deg was investigated in both the clinical and shutter testing situations. If probe trials to investigate neuronal responses to transformed objects were included in the recognition task, the reinforcement contingency was set to neutral (neither reward nor punishment). Fig. 13 gives the mean and standard error of the responses of one cell, tested clinically, to junk objects. The cell gave an excitatory response both when the objects were seen on the second presentation in the same orientation as on the first presentation, and when they were seen in a different orientation (45 to 90 deg

rotated). Fig. 14 is a similar figure, constructed from the responses during shutter testing of a different cell. Here, too, the cell was found to respond to familiar objects presented at a new orientation, 90 deg rotated from the preceding presentation. (Elongated stimuli were used to obtain this data with isomorphic rotation.) Five cells were studied in this manner and all were found to generalize significantly over orientation. Further tests showed that these cells could generalize

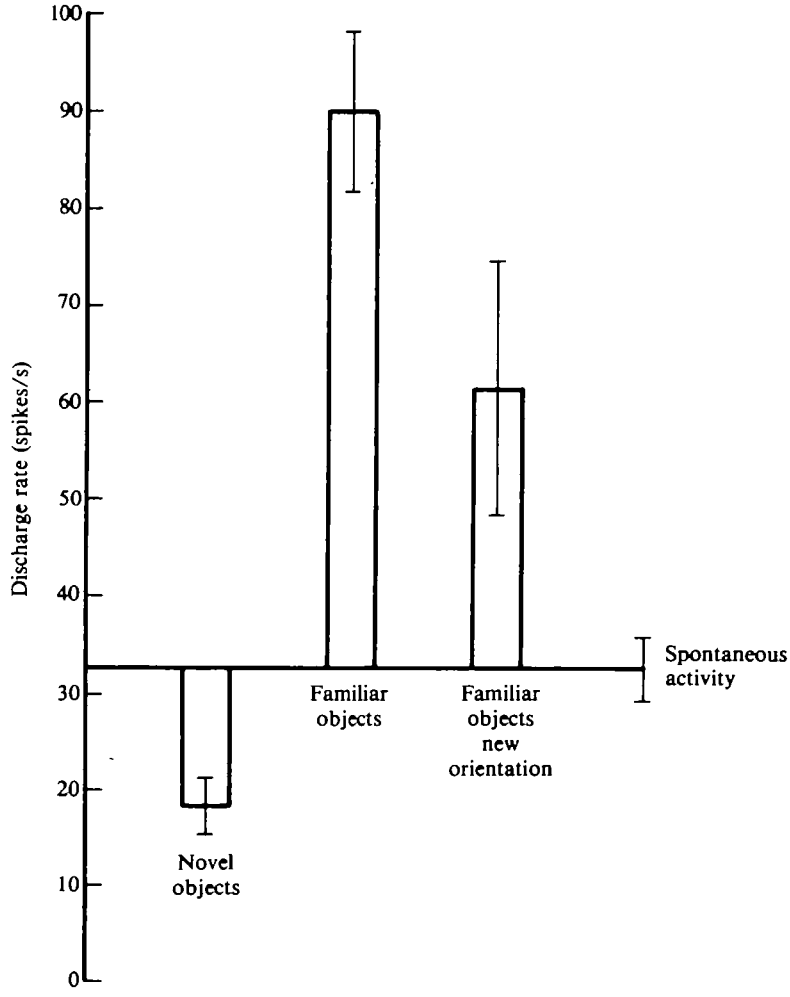


FIG. 13. Effect of stimulus rotation upon the responses of a neuron to familiar stimuli, clinical testing. The mean and standard error of the responses (spikes/s) of one cell (HO22a) are illustrated relative to the baseline spontaneous activity. Histogram bars from left to right give responses to novel and familiar stimuli presented in the same orientation and to familiar stimuli rotated 45 to 90 deg to a new orientation before presentation.

in other ways. For example, 2 cells tested showed some generalization over an approximately fourfold change in viewing distance.

The responses of these neurons were also found to generalize across different background environments and behavioural situations. Thus if a stimulus was first shown in the recognition task, neuronal responses of the type which occurred to familiar stimuli were obtained when the stimulus was shown later in the open laboratory (clinical) viewing condition where behavioural responses were not required, and *vice versa*. Thus the neuronal responses generalized over this change in context.

Recording Sites

Fig. 15 gives the outlines of the brain structures drawn from the brain sections of 2 monkeys, and has the reconstructed recording sites of the 33 cells with recognition related responses marked. It is evident that the cells were recorded at

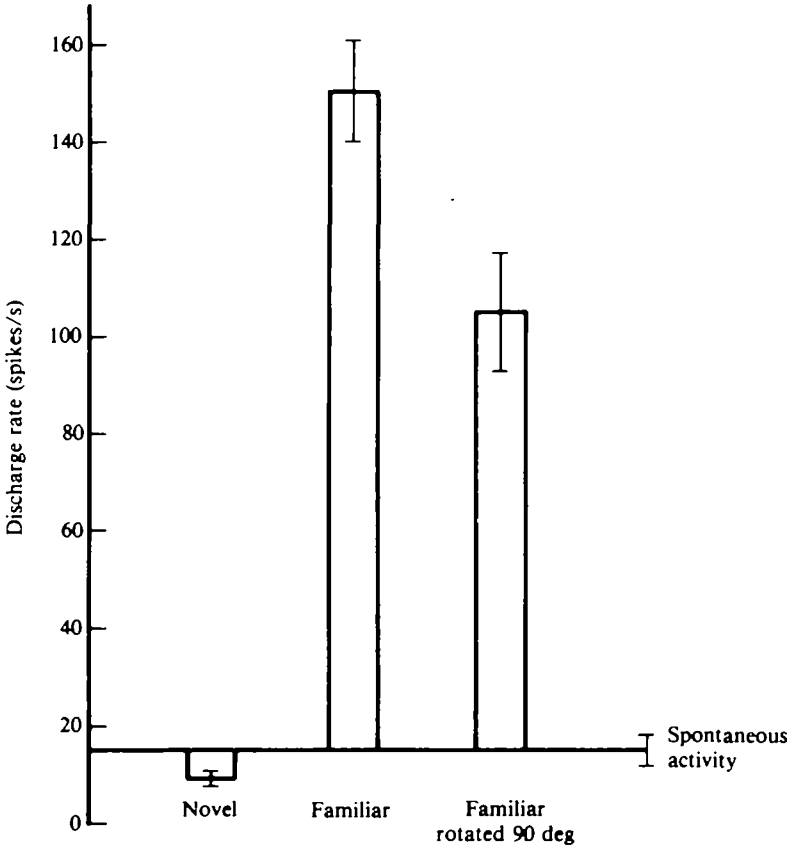
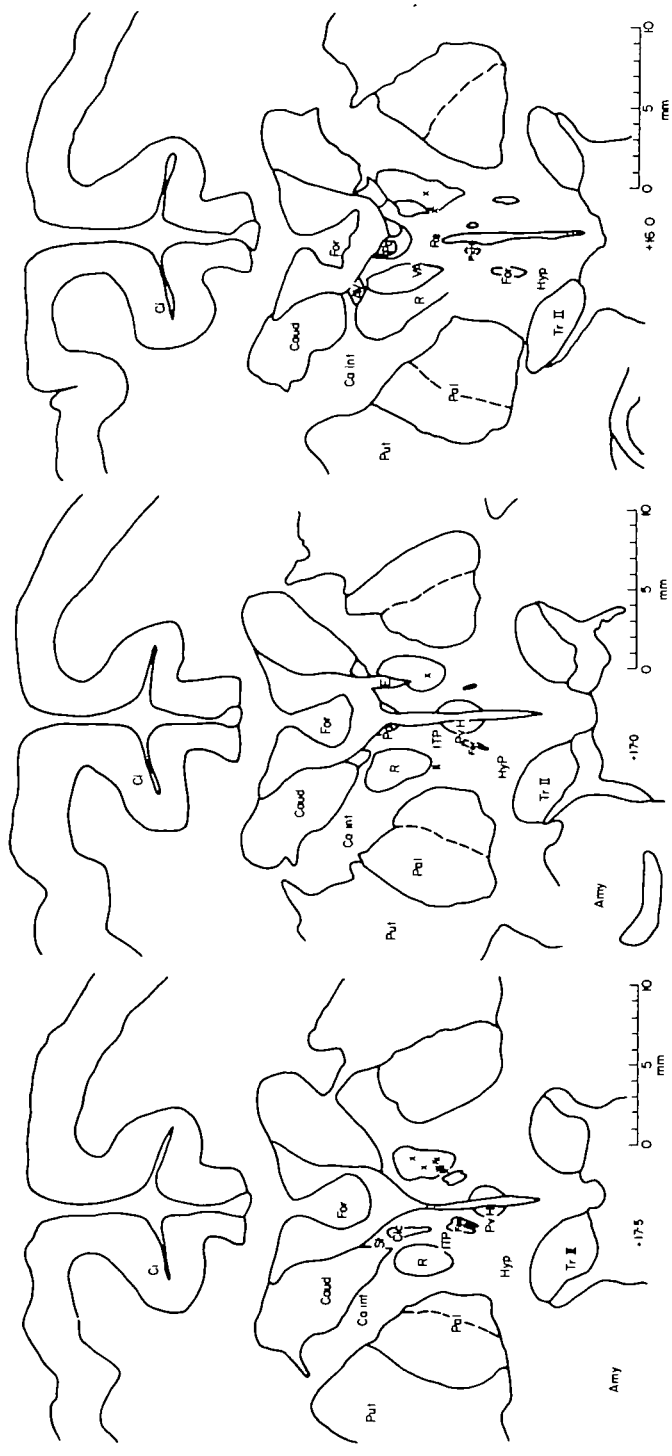


FIG. 14. Effect of stimulus rotation on a neuron's responses during the performance of the recognition task. The mean and standard error of the responses (spikes/s) of one cell (HO22b) to novel and familiar stimuli, and to familiar stimuli rotated by 90 deg, are given relative to the spontaneous firing rate.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the anterior border of the thalamus and were grouped (in both hemispheres) 1.5 to 2.5 mm lateral to the midline and 2 to 4 mm below the floor of the lateral ventricle at the same distance anterior to the interaural plane as the hypothalamic paraventricular nucleus. These cells were clearly not in the anterior thalamic nuclei complex (AV, AD, AM) but were situated 1 to 2 mm in front and 2 mm below these nuclei. From the histology, the neurons were in the vicinity of the rostral midline thalamic nuclei, at the level of the inferior thalamic peduncle and descending fornix, but it is possible that the specific cell type involved belongs to one of the closely neighbouring systems, such as the rostral pole of the reticular nuclei of the thalamus, hypothalamus, magnocellular basal forebrain nuclei, or nuclei of the anterior commissure, all of which adjoin this area.

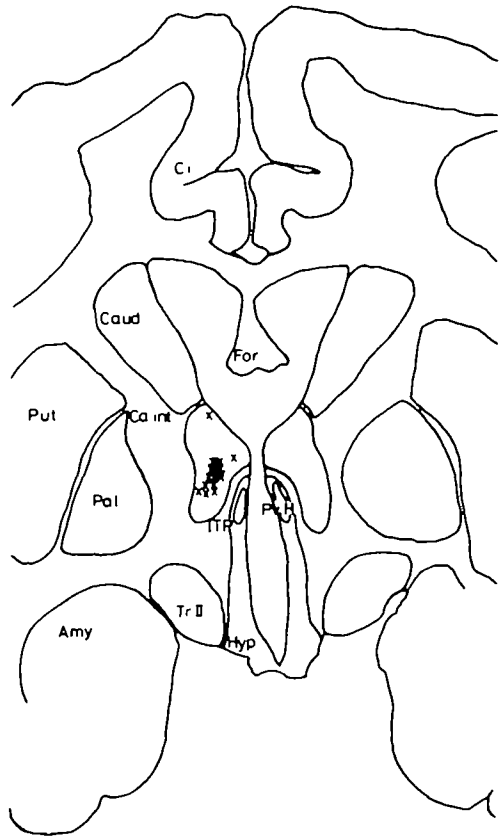

FIG. 15A (*left*), B. Examples from two monkeys of the sites (marked by x) in the region of the anterior and medial thalamus in which neurons with recognition related responses were recorded. Amy = amygdala; AV = nucleus anterior ventralis; Ca. int = internal capsule; Caud = nucleus caudatus; C1 = sulcus cinguli; Clc = nucleus centralis latocellularis; For = fornix; Hyp = hypothalamus; ITP = inferior thalamic peduncle; Pa = nucleus paraventricularis thalami; Pal = nucleus pallidus; Put = putamen; Pv.H = nucleus paraventricularis hypothalami; R = nucleus reticularis thalami; Re = nucleus reuniens; St = stria terminalis; Tr.II = optic tract; VA = nucleus ventralis anterior; E = reference electrode.

DISCUSSION

These results indicate that there is a population of neurons in a region at the anterior border of the thalamus with activity related to recognition, in that their responses occurred to the presentation of familiar but not novel stimuli. The possible reasons for and functions of their responses are the subject of the following discussion. The neurons did not respond when a stimulus was shown for the first time in the day, but did respond when the same stimulus was shown later as familiar. With the use of a visual serial recognition task it was possible to show that the neurons responded to a familiar stimulus even when many items intervened between the novel and familiar presentations of a stimulus. This property is characteristic of human recognition memory, and this is perhaps the first demonstration of neurons with responses which can be directly compared to human long-term memory in terms of resistance to interference.

The following findings indicated that the responses of these neurons were related to the recognized visual stimuli, and not to the lick responses made by the monkey on familiar trials. (1) It was found that the neurons did not respond in relation to licks made outside the recognition task to obtain fruit juice. (2) The neurons did not respond if the monkey licked incorrectly when a novel stimulus was shown (*see*, for example, the third group of three trials in fig. 3), and could respond to a familiar visual stimulus even if the monkey made an error and did not lick (*see*, for example, the fourth group of trials in fig. 3). (During experiments it was possible to induce response errors by the monkey by giving reward or saline in the intertrial interval, which altered response bias, making the monkey more or less likely to lick on the next trial.). (3) The neuronal responses did not occur to novel stimuli, and did occur to the same stimulus presented later, when the stimuli were shown in the laboratory outside the recognition task to the monkey (*see*, for example, fig. 4). (4) The latencies of the responses in the different neurons were 100 to 220 ms, and were thus too short to be associated with the lick movements made by the monkey, which resulted in licks at 400 to 500 ms—the electromyographic (EMG) activity associated with these lick movements would start at approximately 250 to 400 ms on the basis of EMG recordings made in relation to this type of lick response by Rolls, Sanghera and Roper-Hall (1979). (5) The responses of the neurons were found to be unrelated to the lick responses made by the monkey in the association task. In this task, the neuronal responses were independent of the licks the monkey made to the rewarded stimulus and of the absence of licks to the stimulus associated with saline, and in most cases responses occurred to these stimuli equally when they were familiar.

The finding that these neurons responded on the basis of the familiarity of a visual stimulus, and not on the basis of whether it was associated with reinforcement (in, for example, a visual discrimination task) provides neurophysiological evidence for a dissociation of recognition memory from stimulus reinforcement association memory. Further evidence for the dissociation is that neurons in the lateral

hypothalamus and substantia innominata respond in a visual discrimination to the stimulus associated with food, and not to the stimulus associated with saline, even though both stimuli are very familiar (Rolls *et al.*, 1976; Mora *et al.*, 1976; Rolls, Sanghera, and Roper-Hall, 1979; Rolls, 1981). Thus these hypothalamic neurons respond on the basis of association with reinforcement, and not on the basis of familiarity. Evidence consistent with this neurophysiological evidence for dissociation is that section of the fornix in monkeys impaired the performance of a serial visual recognition task but had much less effect on an association memory task (Gaffan, 1971). Also amnesic humans (a group with Korsakoff's psychosis), who had of course a recognition memory deficit, showed eye blink conditioning (Weiskrantz and Warrington, 1979), which is an example of stimulus reinforcement association formation. In fact, these patients showed retention of the conditioned eye blink response even although they denied having ever seen the apparatus used for the conditioning. It is also interesting that when the amnesic patient H.M. was tested on a visual discrimination paradigm he showed an ability to register and retain the simple association between one visual stimulus and reward (Sidman *et al.*, 1968). The neurophysiological evidence presented here for a dissociation is of particular interest because in the behavioural testing of the lesioned monkeys it is difficult to find a task which tests selectively for recognition as opposed to association memory (Gaffan, 1976), and in the human eye blink conditioning the stimulus used, a tone, is much less complex than that normally used for recognition testing.

Temporal Factors and Recognition Related Neuronal Responses

The experiment with brief exposure to stimuli indicated that not only were the responses of these neurons time locked to the onset of familiar stimuli, but also that the neurons stopped responding promptly when the familiar stimuli were no longer visible (*see*, for example, fig. 9). This shows that these neurons are not part of motor systems controlling operations such as the lick responses used in the recognition task (which continued to occur correctly with brief exposures), though of course these neurons may have output connections to such systems. Also, these neurons did not respond in the intertrial interval, so that their activity was not part of a memory process of the type postulated by Hebb (1958) in which reverberatory neural activity maintains information about stimuli in memory for some time after they have been seen. Rather, the experimental findings revealed a dependence of the responses of these neurons (and hence of the stages of recognition encoding prior to the activation of these neurons) upon the sensory input to the brain.

Experiments with brief and prolonged presentations also revealed several aspects of the time course of stimulus encoding and retrieval during recognition. (1) The visual input need not last longer than 100 ms for stimuli to be encoded into memory (as shown by the observation that a 100 ms exposure of a novel stimulus was sufficient for a later correct behavioural and neuronal familiarity response).

(2) The visual input need not last longer than 100 ms for the familiarity of stimuli to be discriminated both at the behavioural level and at the level of the responses of the neurons described here. (3) The response latencies of these neurons to familiar stimuli were between 100 and 220 ms (with the majority between 130 and 190 ms, *see* fig. 4), indicating that matching to encoded memories and readout had occurred within 100 to 220 ms of the presentation of the visual stimuli. This is remarkable, when it is considered that the response latency of neurons in the inferior temporal visual cortex is 100 ms or more (Rolls *et al.*, 1977). The inferior temporal cortex is chosen for this comparison because it has projections to many limbic and related areas implicated in memory (Rolls, 1981), and it appears to be on a pathway for memory in that lesions of it disrupt memory tasks such as delayed matching to sample (*see* Mishkin, 1982). (4) The observation that differential responses to familiar stimuli could occur when novel and familiar trials were separated by only 1 to 2 s, and the experiment with prolonged exposures in which on the first presentation of an object the neurons could start to respond after one or two seconds of continuous viewing, showed that at least some part of the recognition system is able to register new objects as familiar within one or two seconds of initial exposure. These temporal factors place important constraints on the types of change which underlie this form of long-term memory.

Perceptual Constancy and Recognition Related Neuronal Responses

Since the conditions of viewing an object are almost bound to change when the object is out of sight for any length of time, it is a useful property of a recognition system, or of any long-term memory for objects, that it tolerates these changes, otherwise all learning about objects would have to start afresh. In this light, perceptual tolerance of the responses related to recognition of the neurons described here is of interest. However, not all accounts of pattern recognition would predict such immediate generalization to isomorphically rotated stimuli. Sutherland (1973) suggests that 'our ability to recognize a rectangle as a rectangle in any orientation is almost certainly mediated by learning and possibly by the use of language'. The present experiment reveals that objects (including a simple black bar) are treated as equivalent, when isomorphically rotated, by part of the nervous system presumably involved in one type of recognition memory, after only one exposure. (This was found with completely novel stimuli, as well as with stimuli which had been seen on a previous day.) Thus the neural processing antecedent to the activation of these neurons is both able to differentiate the pattern of many hundreds of objects, and for each object is also able to encode high level pattern attributes that allow recognition responses to occur over certain changed conditions of viewing.

Cumulative Experience

The results of experiments with repeated exposure to stimuli indicate that at very short retention intervals stimuli seen several times before do not produce

larger neuronal responses than stimuli seen only once previously. The slope relating the decline in response with increase in retention interval, however, is less steep for stimuli that have been seen several times before than for stimuli seen only once before (compare Tables 2 and 3), indicating that multiple exposures do improve recognition related responses at long retention intervals. In this light, the multiple exposures to stimuli can be seen to decrease significantly the rate of 'forgetting' of at least some of the neurons described here. In certain cases, a few exposures to stimuli produced long-lasting memories that resisted interference from more than 100 trials with other stimuli. That cumulative experience with stimuli can improve the responses of these neurons to familiar stimuli further relates their responses to memory, for human recognition memory for pictures is improved by using, for example, multiple exposures of the stimuli or increasing the duration of each exposure (Huppert and Piercy, 1977; Gaffan, 1978).

Length of Memory

Despite the monkeys' considerable previous experience with particular types of food, most of the neurons described here did not respond to such stimuli as familiar on the first trial of the day on which they were shown. Although many of these neurons thus cannot be considered to show very long-term recognition memory, the length of memory did vary from neuron to neuron, and some neurons had very substantial memories lasting over more than 100 intervening items, and indeed over days. (Two neurons had familiarity responses to stimuli which had not been seen for more than one day, and responses over more than 100 intervening stimuli were found experimentally and indicated by extrapolation for other neurons.) Therefore, an accurate account of all the present data would be that these neurons with recognition related responses differ in the periods over which they respond to stimuli as familiar, and that some neurons at least may have responses related to very long memories.

There are several possible reasons for the predominance of neurons in this study with memories which are not very long term, even if as a whole the neural system of which these neurons are a part is involved in recognition related processing. (1) The recognition task employed was usually a discrimination of relative recency since many objects used as novel on a particular day were used in testing on preceding days. The present study may have been biased to studying neurons without very long-term memories, since such neurons would produce only small differential responses on novel and familiar trials (as the stimuli shown on novel trials would be recognized from preceding days). (2) It may be that the length of memory found in these neurons reflects the strategy being used by the monkey to solve the running recognition task, for which relative recency judgements were required as most of the items were to some extent familiar from testing on preceding days. If in other tasks, such as the discrimination of completely novel from familiar objects, the monkey employed different strategies for problem solving, then more of these neurons might have responses related to longer memories. Only 2 neurons

in the whole study showed any indication of an effect of the decision strategy being employed, and these cells were effectively turned off during the performance of the association memory task (*see above*). The possibility that the memory length of the neurons reflects some type of decision strategy being employed is thus not strongly supported but cannot entirely be dismissed. (3) Another possibility is that monkeys simply do not have a good long-term recognition memory. Although it has been difficult to obtain evidence on whether monkeys can discriminate the familiarity of stimuli in recognition tasks in retention intervals of 24 hours (M. Mishkin, personal communication, 1979), Overman and Doty (1980) have been able to train monkeys in a 96 h delayed matching to sample task. It would be of interest to record from the neurons described here during the performance of such a 96 h memory task. Another approach to the measurement of long-term recognition effects is simply to record the length of fixation of visual stimuli, which is usually shorter for stimuli when a monkey has seen the stimulus before (Humphrey, 1972, 1974).

Recording Sites

The sites in which these neurons with responses related to recognition were found were in a medial perifornical region at the anterior border of the thalamus. This region receives inputs from the fornix as it descends through the perifornical nucleus (Poletti and Creswell, 1977), which is situated in this location, and from the amygdala, which sends fibres into the bed nucleus of the stria terminalis, part of which is also in this region (Price and Amaral, 1981). This region is also at the rostral border of the reticular nucleus of the thalamus, and this part of the reticular nucleus receives inputs from the anterior, midline and mediodorsal nuclei of the thalamus (Jones, 1975). The anterior nuclei of the thalamus themselves receive inputs from the fornix, and the midline nuclei have connections with the amygdala and hippocampus (Mehler, 1980; Amaral and Cowan, 1980; Herkenham, 1978). These connections to this region are of interest in view of the amnesia which follows temporal lobe surgery in which the hippocampus and amygdala are damaged in man (Scoville and Milner, 1957). Mishkin (1978) has argued that damage to both the hippocampus and amygdala is required to account for this human amnesia, on the basis of the severe disruption of a delayed nonmatching to sample memory task produced by combined but not separate lesions of the hippocampus and amygdala in the monkey. It is also of interest that in humans with amnesia associated with Korsakoff's psychosis arising, for example, from chronic alcoholism, abnormalities are described most frequently in two structures, the mammillary bodies and the medial thalamus (Victor *et al.*, 1977; Mair *et al.*, 1979). Also, it has been reported that electrical stimulation of the thalamus can influence recognition memory performance in man (Ojemann, 1977). The recent finding that lesions of the medial thalamus can impair the relearning of a recognition memory task, delayed nonmatching to sample (Aggleton and Mishkin, 1981), is clearly consistent with the neurophysiological findings described here, and provides

independent evidence that neurons in this region are important for recognition memory. Although the sites at which neurons with recognition related responses were recorded in the monkey may be somewhat anterior to these thalamic regions with damage in man and the monkey, the precise localization of the system damage to which produces amnesia is difficult to define. It may be hoped that further recording studies in the monkey will allow the exact localization of this system to be defined, and will allow other parts of a system involved in long-term memory to be identified by analysing the afferent and efferent connections of these neurons. It may also be hoped that the neurotransmitter used by the memory related neurons can be identified, and at least three distinct populations of cells with different types of transmitter have already been found in the region near the rostral pole of the thalamus: vasopressinergic (Rhodes *et al.*, 1981), cholinergic (Divac, 1975) and GABAergic (Massari *et al.*, 1976).

Possible Functions of these Neurons with Recognition Related Responses

When we have described these neurons as having recognition related responses, we have used this as an operational description of the finding that in a continuous recognition task, these neurons responded differently to the stimuli which had to be recognized as having been seen before as compared to the stimuli which had not been seen before on that day. In that the responses occurred to the to-be-recognized stimuli (and were shown not to be due to movements or to reward associations of the stimuli), the responses were described as recognition related. The question then arises as to the type of processing which these responses reflect, and there are a number of possibilities. First, it can be noted that whatever the processing, it appears to be of a type which is impaired in anterograde amnesia in man and by fornix lesions in monkeys, and indeed the running recognition task was used in this study to ensure that memory which could resist interference by intervening stimuli could be studied. In anterograde amnesia in man, performance of picture recognition tasks in which a series of pictures must be remembered is impaired (Warrington, 1974), and in monkeys with fornix lesions a memory deficit is evident when several stimuli intervene between the novel and familiar presentations of a given stimulus (Gaffan, 1974, 1977).

Secondly, it appears that the responses of the majority of the neurons described here are not related to recognition of whether a stimulus has ever been seen before, in that the majority of neurons responded as novel to stimuli when they were shown for the first time on a day, even when the stimuli had been seen on preceding days. As noted above, neurons which did differentiate between absolute novelty and familiarity might not have been observed in this study even if they had been present in this region. Of the neurons which were found, some did have very long memory spans (of more than 150 intervening items), and two responded over 24 h periods. Thus in general, neurons with a range of memory durations were found in this region, and these could be very useful in the discrimination of recency, as well as for those with the longer memories, of whether a stimulus had ever been

seen before. One problem here is that there has been rather little investigation of pure recognition memory over delays of longer than 24 h in nonhuman primates, although where memory function in monkey and man has been compared directly (Sands and Wright, 1980; Overman and Doty, 1980) it has proved very similar. It would be helpful to know how these neurons responded if the monkeys became accustomed to using memories for items presented one or several days previously. The point that the responses of some of these neurons could be useful for recency judgements further links them to amnesic disorders, for recency judgements ('Did you see this picture today?') are more severely impaired in Korsakoff's syndrome than is absolute recognition ('Have you seen this picture before?') for pictures which had been seen either the day before or a few minutes earlier (Huppert and Piercy, 1976, 1978*a*). Perhaps correspondingly, monkeys with fornix lesions were much more impaired in a delayed matching to sample task if the stimuli had been seen on previous days, than if the stimuli had never been seen before so that absolute familiarity could be useful (Owen and Butler, 1981).

Thirdly, it is possible that the responses of these neurons are related to contextual aspects of memory. Thus the majority of these neurons which did not respond to such stimuli as foods, the first time these were seen on a particular day, even though both were highly familiar to the monkeys, might not have responded to them because of the context, in that they were treated as part of the running recognition task which required stimuli to be treated as novel the first time they were seen on a day, or were not in the context of the home cage. One way to obtain information on this would be to train monkeys in a 24 h recognition task, and to determine whether these neurons responded over these long periods in the context of the 24 h task. Some evidence already available suggests though that one type of context is not a major factor in determining whether these cells respond to familiar stimuli, in that these neurons responded if objects which had been seen in the open laboratory testing condition were used as stimuli in the recognition task, and *vice versa*. Also, the majority of these neurons responded to the discriminanda in the visual discrimination (association) task on the basis of whether the stimuli had been seen before that day, even though the monkey was using the stimuli to perform the association task, and not a recognition task. Thus the available evidence suggests that while the effect of this type of context on the responses of these neurons should be investigated further, this type of context, and the strategy being used by the animal when he sees the stimuli, are not all important factors in determining whether these neurons will respond. It will also be of interest to determine whether the responses of these neurons which occur mainly in the context of the familiarity of a stimulus on a given day, respond in this way because of context or because of a limit on the duration of the memory of elements in this part of the system.

If these neurons do respond in relation to recency, or in some cases to longer term recognition related processes, it may be considered what functions these neurons perform. In that they respond to almost any visual stimulus provided

that it is familiar as described above, they would appear to reflect processing at a stage at which the incoming visual information has been compared (matched) to existing, perhaps recent, memory traces. If no match is found, no neuronal response occurs, whereas if a match is found, the neurons fire vigorously (and remarkably rapidly, after 130 to 190 ms). This firing could then be used in a number of ways. It could represent information available to the monkey on whether he has seen the stimulus before, and could be used for judgements of familiarity or recency. It could also be used to alter subsequent processing of that stimulus, indicating for example that new memory traces need not be laid down, but that the existing (and appropriate) traces should be strengthened. Now at least the first, and perhaps the second, of these processes is impaired in anterograde amnesia in man (Warrington, 1974; Warrington and Taylor, 1973; Huppert and Piercy, 1976, 1977, 1978*a*, *b*, 1979). Such firing could also alter the priorities with which that and other stimuli are subsequently processed. It may be hoped that further study of the neural system described here will clarify the neurophysiological basis of long-term memory and its pathology in amnesia.

The possible functions of these neurons are also of interest in relation to memory disorder in a variety of other neuropathologies, including the *déjà vu* and *jamais vu* of temporal lobe epilepsy and the 'absences' of *petit mal* epilepsy. Electrical stimulation of the anterior pole of the thalamus can mimic, in animals (Jasper, 1954) and man (Bancaud, 1971), the cortical synchronization typical of a *petit mal* seizure. Further, both the fornix and stria terminalis project to this region from the temporal lobe. Before considering in detail the relation of these neurons to the function of any one of the different neural systems known to be present at the anterior border of the thalamus, such as the reticular nuclei with their possible functions in attention and orienting to novel stimuli (*see* Scheibel and Scheibel, 1970), it will be helpful to obtain anatomical identification of these neurons, by, for example, testing for antidromic activation from the different sites to which neurons in this region are known to project, and by testing for transsynaptic activation of these neurons from the different sites which send projections into this region.

In conclusion, the experiments described here provide some of the first electrophysiological evidence on neuronal systems related to long-term recognition memory, and provide a basis for further studies of long-term memory mechanisms.

ACKNOWLEDGEMENTS

This research was supported in part by the Medical Research Council. We thank Drs D. Gaffan and T. P. S. Powell for helpful discussions, and Tim Perrett and Paul Attenborough for technical support.

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(Received December 15, 1981. Revised April 15, 1982)