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Neuronal responses related to the novelty and familiarity of visual stimuli in the substantia innominata, diagonal band of Broca and periventricular region of the primate basal forebrain

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Summary. This study examined correlates of memory processes in neuronal activity recorded from the substantia innominata, the diagonal band of Broca and the periventricular region or the basal forebrain of monkays performing recognition and/or visual discrimination tasks. Two types of neurons were found that responded differentially to stimuli on the basis of their novelty or their familiarity. Neurons (5/572) in the periventricular region rostral to the thalamus and caudal to the anterior commissure responded to familar stimuli with increases in firing rate. Neurons in the substantia innominata (16/1058) and in the diagonal band (14/489) responded maximally to novel stimuli, with smaller responses to repeared presentations of these stimuli. The properties of these two types of neurons were similar in three respects: (1) the magnitude of the differential response to novel and familiar presentations of stimuli were largest for stimuli presented on successive trials, and were attenuated for stimuli that had not been seen for some intervening trials; (2) both types of neurons responded to highly familiar stimuli as if they were novel if they had not been recently seen; (3) both types responded to two- and three-dimensional stimuli; and were recorded in rhesus monkeys trained on the recognition tasks and in untrained cynomolgus monkeys. An injection of HRP into the periventricular region of one monkey resulted in retrograde labeling of ventromedial regions of the prefrontal, cingulate and temporal cortices, of the amygdala, medial thalamus, supramammillary region of the midbrain. These data indicate that information about the novelty, familiarity or recency of presentation of visual stimuli is reflected in the responses of some basal forebrain neurons. Neurons in the substantia innominata and diagonal band of Broca could not be distinguished using the battery of applied tests, suggesting functional mechanisms common to both regions. The results of the anatomical experiment suggest that ventromedial limbic cortical and subcortical regions projecting to or through the periventricular region may be important for the transmission of information about visual stimuli and for memory function.

Key words: Alzheimer's disease – Basal forebrain – Basal nucleus of Meynert – Memory – Neurophysiology – Monkey

Introduction

Amnesia is commonly associated with damage to the region of the walls of the third ventricle, and lesions of the anterior hypothalamus, the medial thalamus, and the mammillary bodies produce memory impairments in man (Mair et al. 1979; Squire and Moore 1979; Nichelli et al. 1982). However, it is not clear exactly which functions these diencephalic structures contribute to memory.

In a previous study, the functions of structures adjacent to the third ventricle were examined by recording neuronal activity in this region in monkeys performing recognition memory tasks (Rolls et al. 1982). Populations of neurons were recorded which showed memory-related activity; these neurons responded differentially to visual stimuli on basis of their novelty or familiarity. One neuronal population responded to familiar visual stimuli; the other population responded maximally to novel visual stimuli. The magnitude of the differential responses to novel and familiar stimuli decayed when the monkey had not seen a given stimulus for some trials. These neurons were located in a periventricular region close to the walls of the third ventricle, near the anterior border of the thalamus, the descending columns of the fornix, the inferior thalamic peduncle and hypothalamus.

The familiarity-related responses of these periventricular neurons suggest that they are part of, or receive information from a neural representation of the stimuli

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stored in memory. There are a number of brain structures implicated in memory function, notably the medial temporal lobes, the medial thalamus and mammillary bodies. Impairments of memory follow damage to these regions in man (Scoville and Milner 1957; Van Buren and Borke 1972; Mair et al. 1979; Squire and Moore 1979; Winocur et al. 1984). Furthermore, damage to these regions in monkeys produces impairments in the performance of object recognition tasks (Mishkin 1978; Mahut et al. 1982; Aggleton and Mishkin 1983; Zola-Morgan and Squire 1985), providing further evidence that these structures are important for memory function. One purpose of the present study was to identify the structures afferent to the periventricular region and to compare them with those structures implicated in memory function. Thus an injection of the retrograde tracer horseradish peroxidase was made into the periventricular region in which neurons with memory-related responses were found.

A second aim of the present experiments was to determine if neurons with memory-related responses are found lateral and anterior to the periventricular region, in the substantia innominata and the diagonal band of Broca. There are several reasons to suspect this possibility. Firstly, these regions are believed to contribute to memory function, in that damage to the basal forebrain and afferent structures produces severe memory deficits in man (Friedman and Allen 1969; Gascon and Gilles 1973; Damasio et al. 1985), and impairs the performance of recognition memory tasks in monkeys (Aigner et al. 1984; Bachevalier and Mishkin 1986). Further, degeneration has been found in the basal nucleus of Meynert, a structure within the substantia innominata, in the brains of patients with Alzheimer's disease (Whitehouse et al. 1982), in which impairments of memory are an early symptom (Flicker et al. 1985). Secondly, the substantia innominata and diagonal band of Broca are known to be anatomically connected with regions implicated in memory function. Pathways originating in the temporal and prefrontal cortices, and the amygdala are known to course to and through the periventricular region, the substantia innominata and the diagonal band of Broca (Whitlock and Nauta 1956; Jurgens and Muller-Preuss 1977; Leichnetz and Astruc 1977; Price and Amaral 1981; Mesulam and Mufson 1984; Russchen et al. 1985). It is possible, therefore, that these pathways might be responsible for the memory-related neuronal activity observed in the periventricular region. Thirdly, as the substantia innominata and diagonal band of Broca are adjacent to the periventricular region, it is possible that the familiarity-responsive neurons form a medial component of the basal forebrain. This is consistent with recent observations on the anatomy of the basal forebrain, which have shown that cell bodies with axons projecting to the cortex are distributed throughout the substantia innominata, the diagonal band of Broca, and also in the region of the dorsal lateral hypothalamus (Kievit and Kuypers 1975; Jones et al. 1976; Mesulam et al. 1983).

This paper describes further examples of neurons recorded in the periventricular region that responded on the basis of the familiarity of visual stimuli. Additionally, it is reported that a second population of neurons in the substantia innominata, the diagonal band of Broca and in the periventricular region respond to novel stimuli. Some of the data presented here have been published in abstract form (Wilson et al. 1984).

Methods

Recording techniques

Some of the methods used in this paper have been described previously (Rolls et al. 1982). Neuronal activity was recorded using glass-insulated tungsten microelectrodes, which were advanced with a hydraulic microdrive mounted on an implanted stainless steel chamber. The signal was fed to an FET buffer amplifier, filtered, amplified, and displayed on an oscilloscope. Neuronal activity was discriminated with the trigger circuit of an oscilloscope and converted to digital pulses. A PDP–11 computer sampled and displayed neuronal activity on successive trials in the form of a dot display, relative to the onset of the task stimuli. Silver-silver chloride ball electrodes implanted in bone surrounding the orbit were used to record changes in horizontal eye position. EOG traces were usually sampled at 100 Hz, digitised and stored with neuronal activity on computer disc and magnetic tape. Chronically implanted electrodes were used to deliver single pulse electrical stimulation through constant current stimulus isolation devices.

Subjects, stimulus presentation, behavioural responses and reinforcement

Two rhesus monkeys were trained to perform both recognition memory and visual discrimination tasks. Two cynomolgus monkeys were trained only on the visual discrimination tasks. When sitting in the primate chair the monkeys' view of the laboratory was limited to a circular aperture in an enclosure that surrounded the chair. Head fixation and the enclosure ensured that the field of view was restricted to visual stimuli presented in the aperture. The aperture allowed different types of visual stimuli to be presented: (1) three-dimensional objects were presented using a 6.4 cm aperture electromagnetic shutter mounted on the enclosure 20 to 30 cm from the monkey; (2) video images were presented on a monitor screen and viewed through the aperture and (3) objects and foods were presented and delivered to the monkey through the aperture. A tube mounted in front of the mouth delivered saline or juice reinforcement, dependent upon the behavioural responses. During the performance of the tasks, a tone cue of 500 ms duration preceded the visual stimuli, facilitating fixation of the stimuli. Visual stimuli were presented for 1.5 s and the inter-trial interval was generally 6 s, or 8 s for selected experiments. Lick responses in the intertrial interval resulted in the delivery of saline.

The monkeys were fed fruit and nuts throughout the experiment, and drank juice obtained through task performance. Laboratory chow and ad libitum water was available after their return to their home cage. The monkeys weighed between 4–6 kg; their weight increased steadily during the experiments.

The recognition memory tasks

During the performance of the serial visual recognition memory task, lick responses during the presentation of novel stimuli elicited aversive saline, while lick responses to familiar stimuli resulted in the delivery of rewarding fruit juice. Thus the monkeys had to determine the novelty or familiarity of the stimuli in order to obtain juice. The first (novel) presentation of a stimulus was followed by a second (familiar) presentation of the stimulus after 0 to 16 other trials, selected in pseudo-random order. A typical stimulus sequence

was as follows: N1→N2→F2→N3→N4→F1→N5→F4. The novel stimulus (N1) shown on trial 1 was shown again after four intervening trials as familiar (F1) on trial 6, while the novel stimulus (N2) shown on trial 2 was repeated with no intervening trials on trial 3.

In one version of the serial visual recognition memory task, three-dimensional objects were presented using the electromagnetic shutter. Stimuli were hand-held, but only the objects were visible against a white background. A given object, drawn from a population of approximately 2000 objects, was presented twice daily, once as novel and once as familiar. The monkey saw the entire stimulus set once every two to four weeks. Thus a novel stimulus is operationally defined as a stimulus not seen for fourteen or more days. The monkeys responded to stimuli that had not been seen for two weeks as if they were novel. Their performance on the recognition task was on average better than 90% correct.

In a second version of the recognition memory task, two-dimensional coloured visual images were presented on a monitor screen, viewed through the aperture in the primate chair. The video images ($n=607$) were digitised, stored on computer disc and displayed using a Matrox QRGB framestore. The images were seen twice monthly before replacement.

The visual discrimination tasks

All four monkeys were trained to perform visual discrimination tasks. In one version of this task, the electromagnetic shutter was used to present two highly familiar syringes, one on each trial. Lick responses at the presentation of a black syringe (the S−) resulted in the delivery of saline, while responses to the white syringe (the S+) resulted in the delivery of fruit juice. These two stimuli were seen many times daily. In a second version of this task, two visual images equated for size, colour and brightness, but differing in shape were displayed on a video monitor. Lick responses to the yellow circle (S+) produced fruit juice, while responses to the yellow square (S−) produced saline.

Clinical tests

In 'clinical' tests, objects, foods and the S+ and S− syringes used in the visual discrimination task were presented to the monkeys through the aperture in the primate chair using a standard protocol in which counts of mean firing rate were made by computer during the steps in the protocol. The protocol consisted of (1) the presentation of the experimenter's arm viewed through the aperture; (2,3) reaching movements to and from the stimulus to be presented, with the stimulus still out of view; (4,5,6) the sight, approach and finally, delivery of the stimulus (food, the S+ and S−, but not objects) to the monkey. The stimuli were presented without a preceding tone cue. The subsequent delivery of foods to the monkeys was not contingent upon lick responses.

General experimental procedure

Recordings of single neuron activity began when the electrode penetrated the cortex; collection of data began at a depth of 15 mm from the cortical surface. This sampling resulted in a profile of the brain structures through which the electrode passed, which aided localisation of the basal forebrain as traversal of the internal capsule and anterior commissure resulted in cessation of neuronal activity and provided a guide to the proximity of the basal forebrain. Sampling of neuronal activity in the cortex, basal ganglia and amygdala provided control data with which neurons in the basal forebrain could be compared. After recording from a basal forebrain neuron, the electrode was advanced by a minimum of 100 microns before sampling other neurons.

During the recordings the monkeys continuously performed the different tasks. The presentation of novel and familiar objects, the S+ and the S− were interdigitated in pseudorandom order. Each neuron was tested for responsiveness to novel and familiar stimuli, and to the S+ and S−. If the neuron responded to the presentation of any of these stimuli, extensive testing for periods of up to four hours continued in order to identify the properties of the stimuli that elicited the responses. A record of the depth of each neuron was made, as well as its response properties or lack of responsiveness. Every neuron logged during these experiments forms part of the data base of this study.

Data analysis

For each trial of the memory tasks the computer counted the number of spikes emitted over a 500 ms period, starting 100 ms after the stimulus onset. Data for the different trials (novel, familiar, S+, S−) were compared using one way analysis of variance and subsequent Tukey tests (Bruning and Kintz 1977). The comparisons between novel and familiar stimuli were based on data collected from between 6 and 164 novel stimuli for each neuron. All the differential responses cited are significant ($p<0.05$), the majority being significant at $p<0.01$.

Scatter plots are used to represent the responses of differential neurons. This technique is used in order to show how each neuron responded in the various conditions. The data points were calculated by determining the spontaneous firing rate of a neuron, and then subtracting this value from the responses elicited by the stimuli. Thus the data points represent increases or decreases in firing rate from the baseline activity, represented by the axes.

The latencies at which neurons responded differentially to novel and familiar stimuli were determined with the use of cumulative sum techniques (Woodward and Goldsmith 1963) implemented on a computer. Peristimulus time histograms were computed for each type of trial (e.g. to novel and familiar stimuli), and subtracted from each other; the cumulative sum of this difference array was then calculated to allow estimation of the differential response latency.

Localisation of the recording sites

Frontal and sagittal X-radiographs were taken of the skull and the microelectrode in situ at the conclusion of each experiment. This enabled the construction of a three-dimensional map plotting the location of each neuron, relative to implanted stimulation electrodes. Small lesions were made at the site of selected neurons by passing DC current (80–100 microamperes for 80 s) through the recording electrode. These lesions were made in a 3 week period prior to perfusion and were targeted to bracket the brain regions in which the recordings took place. The lesions were also used to determine brain shrinkage due to perfusion by making two lesions per track at a known distance apart. A 1mm tube was inserted through the brain in the horizontal plane after sacrifice and an X-ray was taken, providing a further reference. These techniques allowed an accurate determination of the location of the recorded neurons, as evidenced by the correspondence between the locations of neurons and regions in which action potentials were not recorded, which were found to be the internal capsule, anterior commissure, optic tract and ventricles after the reconstructions were made. The locations of responsive neurons were plotted on large scale drawings of histological sections at 1 mm intervals.

The anatomical experiment

The afferent connections of the periventricular region were studied in a cynomolgus monkey. The region was first mapped with microelectrodes, and then an injection of horseradish peroxidase (0.1 microlitre of 30% HRP) was made into the hemisphere opposite to that in which a microlesion was made, marking the site of a neuron

that responded on the basis of familiarity. The injection site was determined on the basis of neuronal recordings and by comparisons of X-radiographs taken of the electrode tip with those of the lesion site in the opposite hemisphere. After the recordings were completed, the microelectrode was withdrawn and replaced by a Hamilton one microlitre syringe under X-ray control. The HRP was ejected over a 20 min period using an electrically-driven piston. Withdrawal of the syringe took place in stages over 60 min. After a survival time of 48 h the monkey was perfused under deep barbiturate anaesthesia with 2.5% paraformaldehyde and 1.5% glutaraldehyde in 0.1M phosphate buffer, and the brain left in 30% sucrose for two days. The brain was frozen, cut in 50 micron sections with every section collected for microscopic analysis. Every fifth section was reacted for HRP using p-phenylenediamine and catechol (Hanker et al. 1977) as the chromogen. Drawings of the locations of retrogradely labeled cells were made using an X–Y plotter coupled to the stage of a microscope.

Results

The activity of 2119 neurons was recorded in three regions: the periventricular region close to the walls of the third ventricle, the substantia innominata (SI) and the diagonal band of Broca (DBB). This report deals specifically with two types of neurons with memory-related activity: neurons that responded on the basis of novelty and other neurons that responded on the basis of the familiarity of the visual stimuli. Both types of neuron were recorded in the periventricular region, in contrast to the SI and the DBB, where neurons responding on the basis of novelty, but not familiarity, were found. The responses of a third type of neuron that encoded the reinforcement value of visual stimuli, also reflected information stored in memory (Wilson et al. 1984). Table 1 shows the proportions of responsive neurons recorded in the three structures.The term 'differential' will refer to both types of neurons that responded differentially to novel compared to familiar stimuli.

Neuronal activity related to stimulus familiarity: the periventricular region

Basic properties of familiarity-related neuronal activity. The periventricular region is defined here as extending from the wall of the third ventricle to the internal capsule, from the anterior commissure to the frontal pole of the thalamus, and from the ventral margin of the caudate nucleus to the ventromedial hypothalamus. The term 'periventricular' refers to the general region in which the recordings took place, which includes parts of the hypothalamus and adjacent structures.

Neurons (5/572) responsive to stimuli on the basis of their familiarity were located within the periventricular region near the descending columns of the fornix, the internal capsule and the inferior thalamic peduncle. Such neurons were not observed in the SI and the DBB, nor in much of the periventricular region that was sampled. Lesions made at the site of two familiarity-responsive neurons are shown in Fig. 1. The two lesions are located at the medial border of the internal capsule in the region of the dorsal lateral hypothalamus and inferior thalamic peduncle, as were the other neurons. The neuron in Fig. 1b was the most laterally and ventrally located neuron in this and in a previous study (Rolls et al. 1982).

The activity of one neuron responding on the basis of the familiarity of visual stimuli is shown in Fig. 2. Three of these neurons responded to familiar stimuli with increases in firing rate. Presentations of novel stimuli often elicited decreases in firing rate. Two neurons responded to both novel and familiar stimuli with decreases in firing rate, with a larger decrease to novel stimuli. The scatter plot in Fig. 3. (see Methods) shows the responses of the five neurons to presentations of novel and familiar objects and/or video images. The slope of a regression line calculated on these data ($y=1.1x+19$; $r=0.78$; $p<0.05$) indicates that the firing rate to familiar stimuli

Table 1. These data show that approximately half of all neurons in each of the three regions were found to be active during the tests. Some neurons responded differentially to stimuli depending on their novelty/familiarity. The responses of other neurons were related to the reinforcement value of the stimuli, the properties of which also reflect access to information in memory (Wilson et al. 1984). Many task-related neurons were responsive during the tone cue and/or during the presentation of visual stimuli during the shutter period, or were responsive during the presentation of stimuli during the clinical tests

	Periventricular region	Substantia innominata	Diagonal band
Memory-related neurons			
'Familiarity' neurons	5	0	0
'Novelty' neurons	3	16	14
Task-related neurons			
Reinforcement-related neurons	23	73	24
Tone cue/shutter period neurons	117	87	74
Shutter period neurons	171	190	102
Other responsive neurons	51	108	13
Unresponsive neurons	202	584	262
Total	572	1058	489

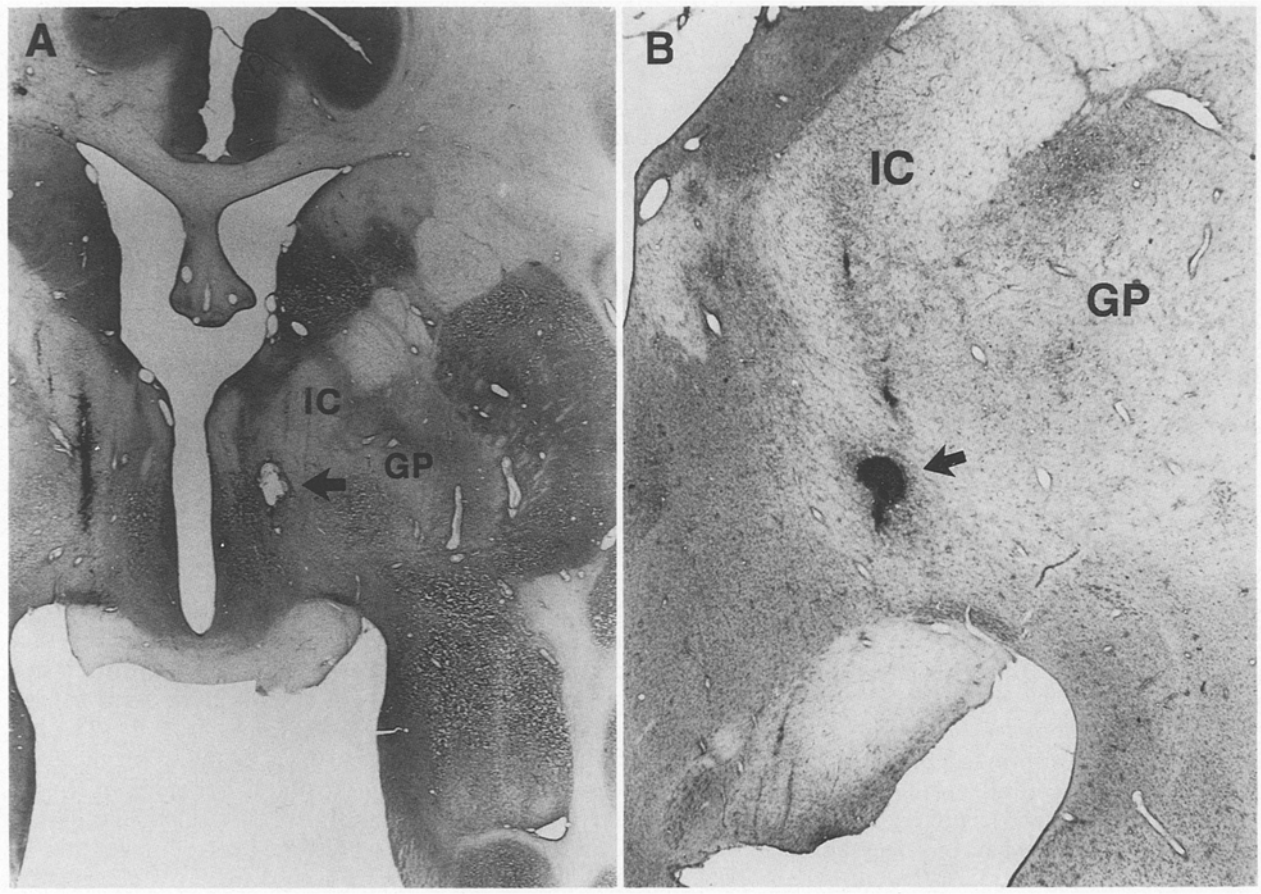


Fig. 1A,B. Marker lesions made at the site of familiarity-responsive neurons. The lesion in (**A**) was made in a rhesus monkey trained in the recognition memory tasks. The lesion in (**B**) was made in an untrained cynomolgus monkey. The lesions are located adjacent to the fibres of the internal capsule

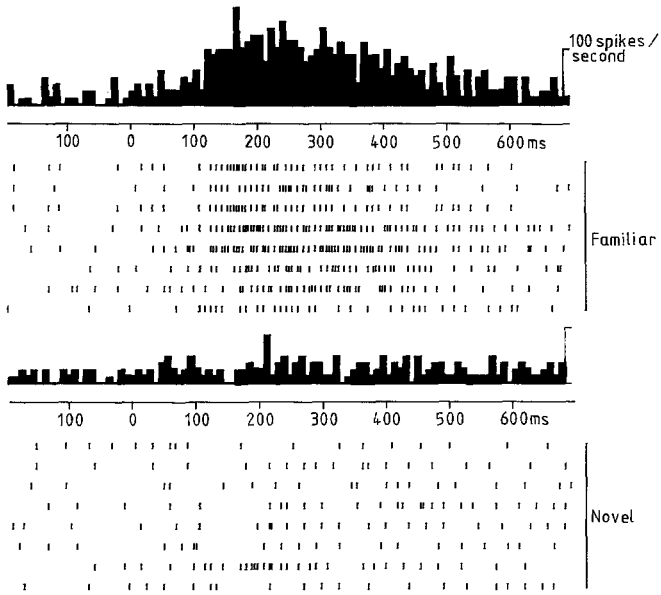
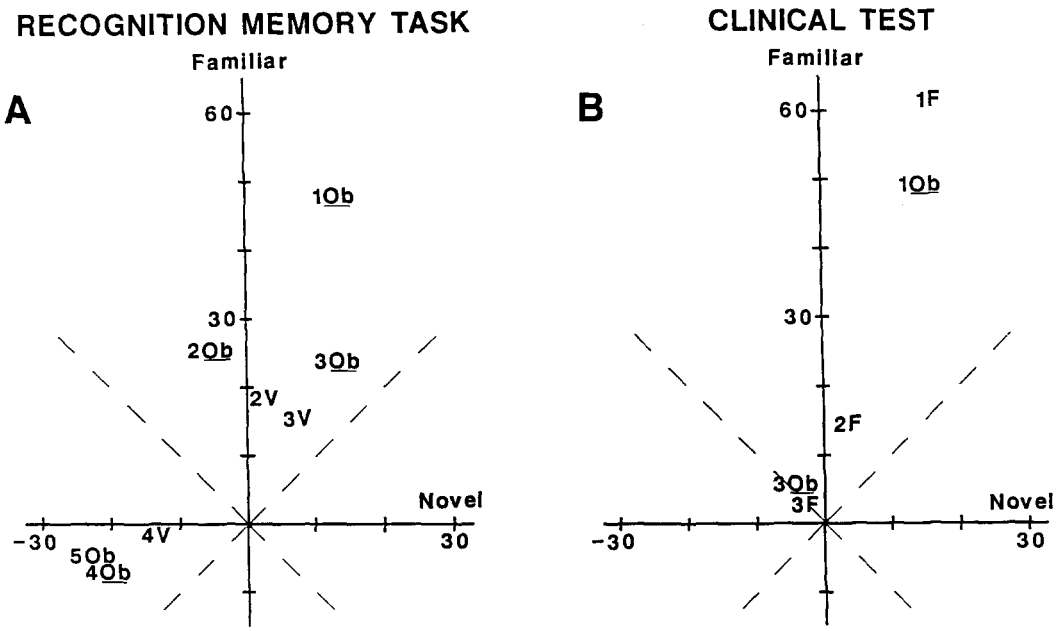


Fig. 2. Neuronal responses related to the familiarity of the stimuli. Each row represents neuronal activity on a single trial, with the onset of the stimuli at time 0. The responses to 8 stimuli (of the 164 stimuli shown in this experiment) are shown here, presented once as novel and again as familiar, originally in pseudorandom order. Trials are grouped for clarity in the order in which they were presented e.g. the stimulus in row 1 of the familiar trials corresponds to the stimulus in row 1 of the novel trials. This neuron (no 1) was recorded in an untrained cynomolgus monkey, who did not make behavioural (lick) responses to the presentation of these stimuli

is larger than to novel stimuli. Responses that were equal to novel and familiar stimuli would be located along the dashed lines. All differential responses that are shown are significantly different (ANOVA). The spontaneous firing rate of these neurons ranged from 9.7 to 42.9 spikes/s, with a mean of 23.7 spikes/s.

Three of the five neurons were recorded in a rhesus monkey trained on the recognition memory tasks. These neurons responded significantly differently to novel and familiar presentations of objects, and to novel and familiar presentations of images displayed on a video monitor. Thus the familiarity of the stimuli, but not the colour, shape and size, were relevant for the neuronal responses.

Two of the five familiarity-responsive neurons were recorded in the two cynomolgus monkeys who were not trained to perform the recognition memory tasks. In these experiments, stimuli varying in their novelty and familiarity were presented in pseudorandom order as for



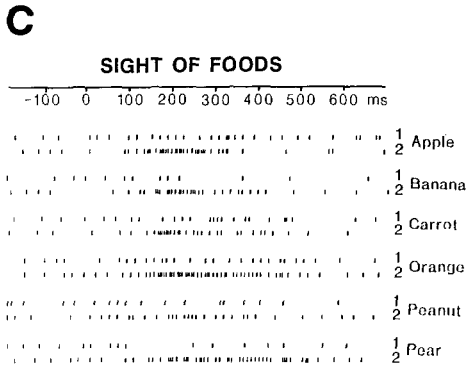


Fig. 3A–C. Scatter plots of the responses to objects and foods during the recognition tasks and clinical tests. In (**A**) the magnitude and direction of the responses of five familiarity-responsive neurons are shown. Each neuron is identified by a number and the type of stimulus presented (*Ob* = object; V = video image). Data points were obtained by subtracting the spontaneous firing rate of each neuron from the responses to novel and familiar stimuli. Each data point represents the response to familiar stimuli (plotted along the ordinate) compared to the response to novel stimuli (plotted along the abscissa) plotted in spikes/s. In (**B**) the responses of three neurons to the first (novel) and second (familiar) presentations of objects and foods in clinical tests are shown. Each neuron is identified by its number and a letter representing the stimulus: the sight of objects (*Ob*) and foods (F). In two cases there is a decrease in firing rate to the first (novel) presentation of the stimuli. In (**C**) the responses to presentations of foods using the electromagnetic shutter are shown. Stimulus presentation occurred at time zero and lasted for 1.5 s. The foods were presented twice, on successive trials, first as novel and subsequently as familiar. The neuron responded maximally to familiar presentations of foods. This neuron (no 1) was recorded in an untrained cynomolgus monkey

the trained monkeys. The untrained monkeys did not make behavioural responses at the presentation of these stimuli and reinforcement was not delivered during these experiments. The responses of the neuron shown in Fig. 2 were recorded in an untrained monkey and Fig. 1b shows a lesion made at the site of this neuron. The responses of the two neurons in the untrained monkeys were similar to those found in the trained monkeys. Thus the training in the recognition memory task, the behavioural responses and the delivery of reinforcement are not responsible for the differential neuronal responses, which reflect the familiarity of the stimuli.

The latencies at which these neurons responded differentially to novel and familiar stimuli were measured using the cumulative sum method. Differential response latencies ranged from 180 ms to 230 ms, with a mean of 204 ms.

The effect of intervening trials on the magnitude of the differential response. The differential neuronal responses to novel and familiar stimuli reflect memory for the familiarity of the stimuli. The duration of the memory for

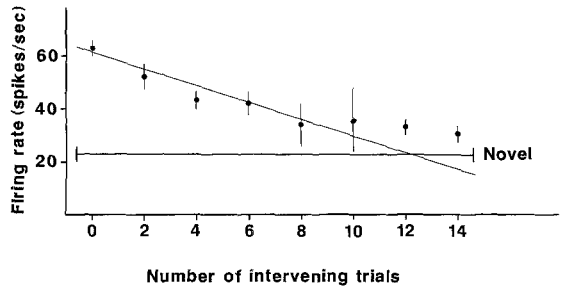


Fig. 4. The effect of intervening trials on the magnitude of the responses to familiar stimuli. The differential responses are maximal when a stimulus is shown as novel and as familiar on successive trials (0 intervening trials). Each data point represents the mean and S.E.M. for stimuli shown as novel or as familiar after various numbers of intervening trials. There is a reduction in the magnitude of the differential response with increasing numbers of intervening trials. The correlation between firing rate and number of intervening trials is significant ($r = -0.37$; $p < 0.01$), obtained by presenting one hundred and sixty four novel stimuli, first as novel and then as familiar, during the recording. This neuron (no 1) was recorded in an untrained cynomolgus monkey

the stimuli was measured by comparing the response to novel stimuli with presentations of the same stimuli seen after a number of other intervening trials. Stimuli were first presented as novel and again as familiar after 0, or between 1 and 16 other intervening trials. Correlations between neuronal firing rate and the number of intervening stimuli were significant in three of the five neurons (e.g. Fig. 4), indicating that the magnitude of the differential neuronal responses decreases with increasing numbers of intervening trials. Linear regressions were used to estimate the point at which the magnitude of the differential neuronal responses decayed to zero. This occurred after 7, 10 and 12 intervening trials for the three neurons, indicating a decay of memory – the memory span – for the stimuli. In two cases, the correlations were not significant. The slopes of these two regression lines were shallow, yielding estimated memory spans of 34 and 37 trials.

Responses in the visual discrimination task. The differential responses to novel and familiar stimuli were not attributable to the reinforcement value of the task stimuli in the case of the cynomolgus monkeys, who were not trained on the response/reinforcement contingencies in the recognition memory tasks. In order to ensure that the differential neuronal responses recorded in the trained rhesus monkeys were not attributable to the fruit juice and saline available on familiar and novel trials respectively, the monkeys performed visual discrimination tasks, in which they responded differentially to the highly familiar S+ by licking and to the S− by not licking. The analysis of variance showed that none of the neurons responded significantly differently to the S+ and S−. The mean responses to the S+ and S− were calculated using the second of two successive presentations of these stimuli. The mean responses of the five neurons to the S+ and S− compared to the responses to familiar stimuli are shown Fig. 5, which shows that the responses to the S+ and S− were very similar, as would be predicted on the basis of their equal familiarity. In general, the neuronal responses to familiar objects presented in the recognition memory tasks were slightly greater than responses to the S+ and S−. In three of five cases, this difference was significant.

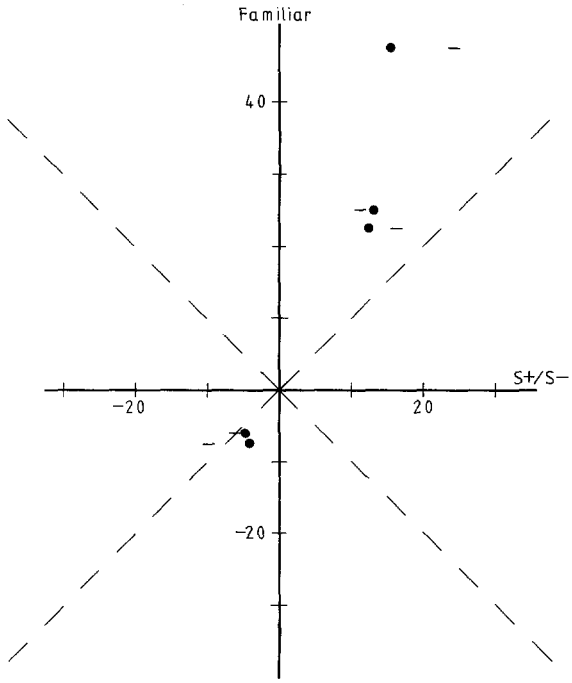


Fig. 5. A comparison of the responses to the S+ and the S− with familiar objects. The spontaneous firing rate of each neuron was subtracted from the mean responses to the S+, S− and familiar stimuli. Each data point represents the mean responses to familiar stimuli plotted along the ordinate compared to the mean responses to the S+ (filled circles) and the S− (minus sign) plotted along the abscissa. Firing rate is plotted in spikes/s along both axes. There is no significant difference between responses to the S+ and S−, indicating that the reinforcement value of the stimuli does not determine the familiarity-related neuronal response

Clinical tests. The firing rates of the familiarity-responsive neurons were measured in the clinical tests in which visual stimuli were presented to the monkey, but behavioural responses were irrelevant for the delivery of food or syringes containing juice to the monkeys. The stimuli were shown first as novel and again as familiar. The first presentation of a food was termed novel when it had not been seen for many trials. Fig. 3B shows the responses of all neurons to novel and familiar presentations of foods and objects. The response to the second, familiar presentations of objects and foods are greater than the first, novel presentations of the same stimuli when they had not been recently seen.

Food stimuli were also presented to the monkeys using the electromagnetic shutter during the performance of the recognition memory task. The responses of neuron no 1 (Fig. 3C) show that these familiarity-responsive neurons respond more to the second (familiar) presentation of different foods. The differential responses to novel and familiar foods indicates that the neuronal responses reflect a form of memory affected by the recency of the stimulus presentation, and not the absolute familiarity of the stimuli per se.

Connections of the periventricular region. Horseradish peroxidase was injected into the periventricular region in one cynomolgus monkey. The injection site was in the hemisphere opposite to the lesion at which a familiarity-responsive neuron (Fig. 1b and 2) was recorded. The distribution of retrogradely labeled cells is shown in Fig. 6. The numbers of labeled cells in the representative regions shown in Fig. 6 are found below in parentheses. The heaviest labeling occurred in layers 5 and 6 of the ventromedial, orbital and cingulate cortices of the frontal lobe (159). The medial thalamus (83) and supramammillary region (55) were also heavily labeled. Lighter label was found in the amygdala (17), substantia innominata (11), nucleus accumbens (4), midbrain reticular formation (19), the ventromedial temporal cortex (4), and temporal pole (16).

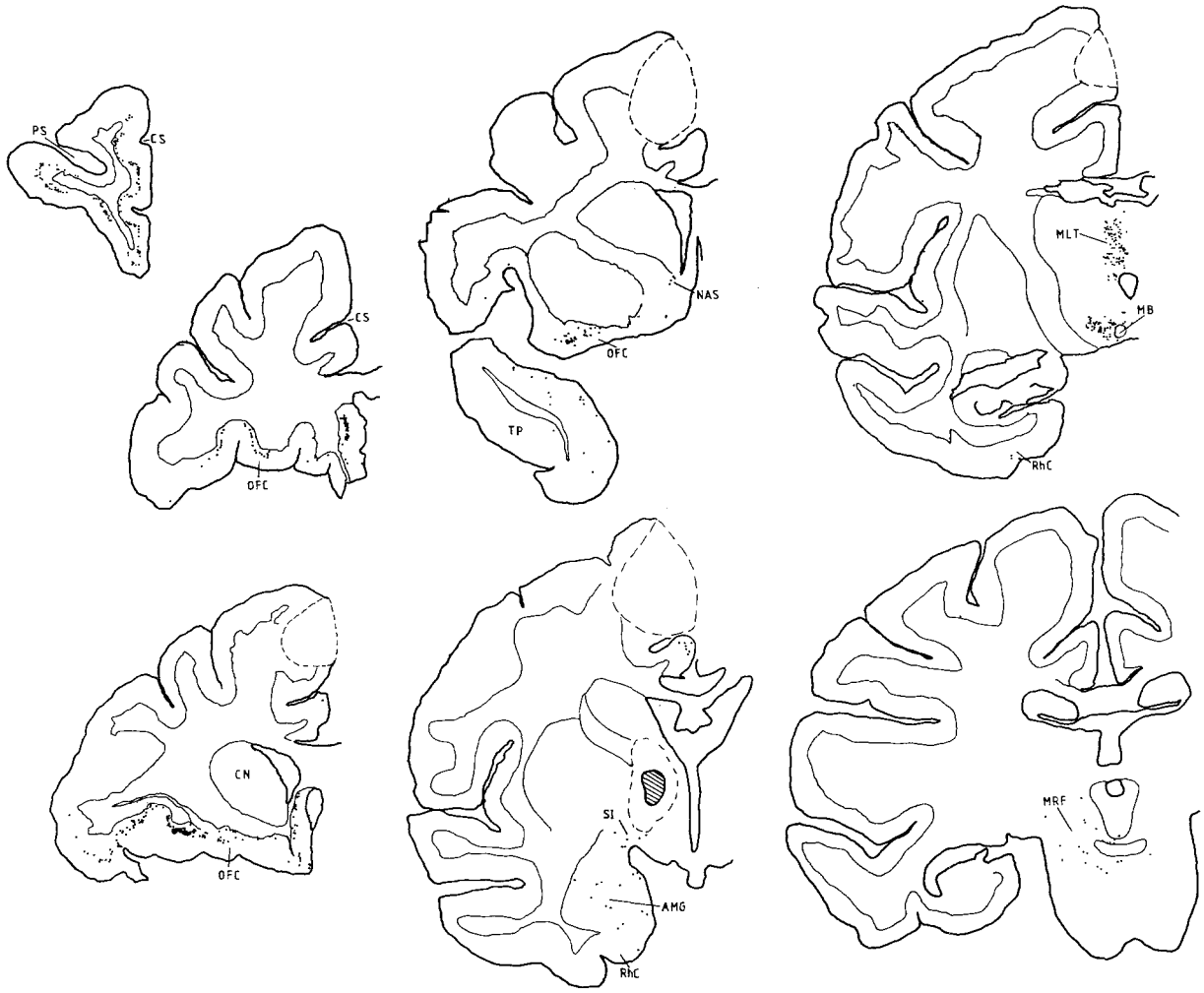


Fig. 6. The pattern of retrogradely labeled cells after an injection of HRP into the periventricular region. Each dot represents a labeled cell. The center of the injection site is shown as a circular region of hatching. AMG: amygdala. CN: caudate nucleus. CS: cingulate sulcus. MB: mammillary bodies. MLT: midline thalamus. MRF: midbrain reticular formation. NAS: nucleus accumbens septi. OFC: orbital frontal cortex. PS: principal sulcus. RhC: rhinal cortex. SI: substantia innominata. TP: temporal pole. The cortical region circumscribed with dashed lines was found to be necrotic on histological analysis

Neuronal activity related to stimulus novelty: the substantia innominata and diagonal band of Broca

Basic properties of novelty-related neuronal activity. Populations of neurons recorded in both the substantia innominata (16/1058) and diagonal band of Broca (14/489) responded maximally to novel visual stimuli. Twenty eight of these neurons were recorded in the two rhesus monkeys trained to perform the recognition memory tasks. Two further differential neurons were recorded in the two cynomolgus monkeys who were not trained to perform the recognition memory tasks. Three further differential neurons were recorded in the periventricular region medial to the SI. In all respects, these periventricular neurons responded similarly to the differential neurons recorded in the SI and DBB, and will not be discussed further. Marker lesions made at the recording sites of differential neurons in the SI and the DBB are shown in Fig. 7. The anatomical distribution of all differential neurons throughout the SI, the DBB and the periventricular region is shown in Fig. 8. The mean spontaneous firing rate of these neurons was 17 spikes/s, ranging from 1 to 51 spikes/s.

The responses of one differential neuron, recorded in the SI, to the presentations of novel and familiar stimuli are shown in Fig. 9. The neuronal responses to novel stimuli were increases in firing rate. Familiar stimuli also elicited increases in firing rate that occurred with the same onset latency as with novel stimuli, but the durations of the responses were more transient. The responses of each differential neuron to novel and familiar stimuli are shown in Fig. 10. In order to compare the two populations of differential neurons in the SI and the DBB, regression lines were calculated representing the responses of the two groups to novel and familiar stimuli (Fig. 10). The slopes of the two regression lines were not significantly different ($F = 0.13$; $df = 1.40$). These data were obtained from 44 tests, as certain neurons were

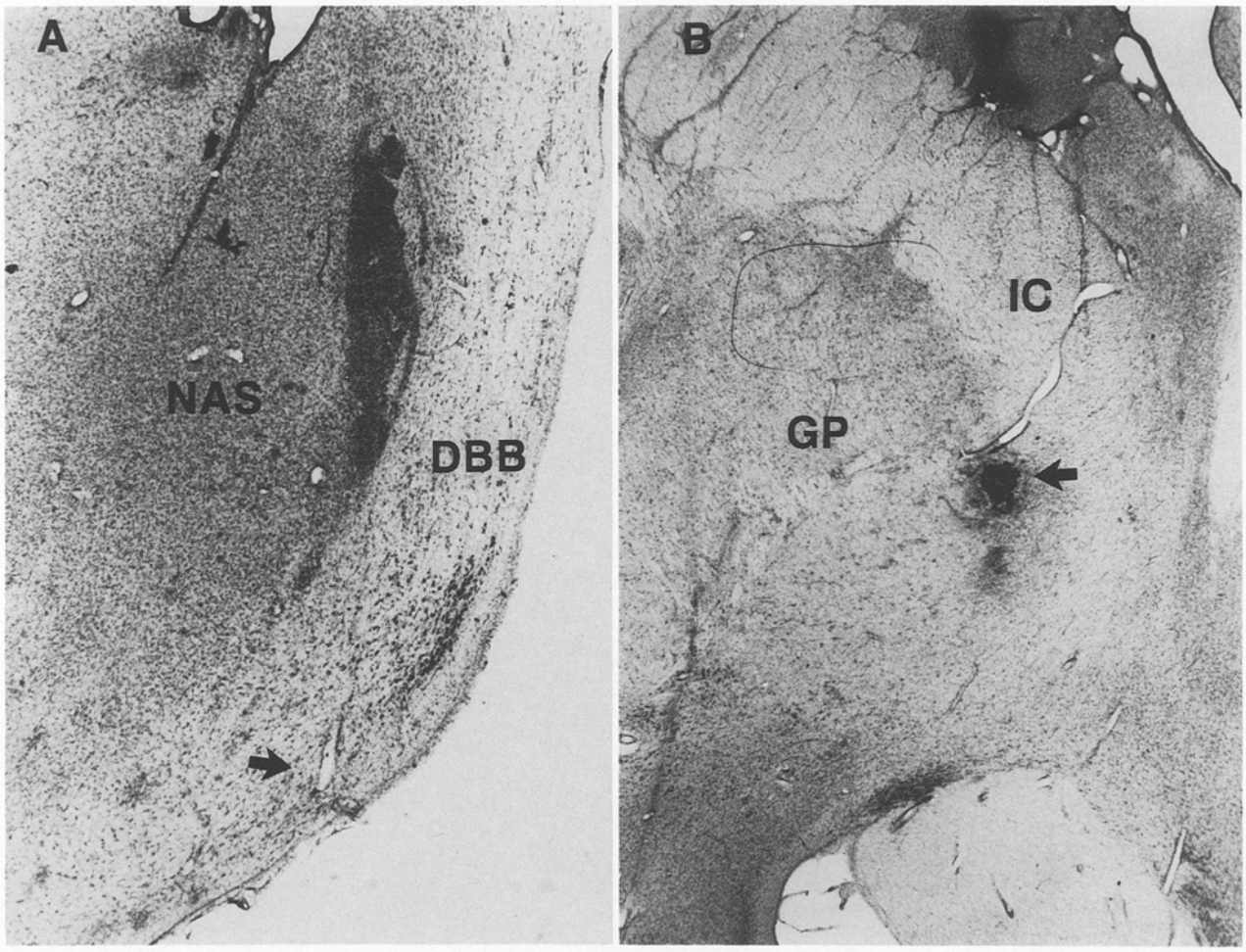


Fig. 7A,B. Lesions made at the site of neurons responding maximally to novel stimuli. The lesion in (**A**) is located close to the base of the brain in the diagonal band of Broca. The lesion in (**B**) is located at the border of the substantia innominata and medial edge of the globus pallidus. Cells forming part of the basal nucleus of Meynert are located in both regions (Jones et al. 1976; Parent and DeBellefeuille 1982; Mesulam et al. 1983; Hedreen et al. 1984)

tested in both versions of the recognition tasks. These results indicate that the two populations of differential neurons in the SI and the DBB responded similarly in the recognition memory tasks.

Differential neurons responded maximally to novel presentions of stimuli, and significantly less so to familiar presentations of the same stimuli. The thirty differential neurons in the SI and DBB were tested in one or both of the two versions of the recognition memory tasks. Significant differences in response to novel compared with familiar stimuli were found for 23/24 differential neurons tested with three-dimensional objects, and 16/20 differential neurons tested with two-dimensional images. Thus differential neurons in the SI and the DBB responded to both two and three-dimensional novel visual stimuli.

The effect of repeatedly presenting a stimulus (between three and five times) was tested during the performance of the tasks. Typically, the decrement in the response to a familiar stimulus was largest on the first familiar presentation, with smaller decrements with repeated presentations occuring every eight seconds (Fig. 11), and this was so for neurons in the SI and the DBB. Correlations between firing rate and number of stimulus repetitions were significant for 15 of the 16 neurons tested. This indicates that the decline in the neuronal responses is maintained as the stimuli become increasingly familiar.

The neuronal responses to familiar presentations of stimuli are more transient than responses to novel stimuli (Fig. 9). The latencies at which these neurons responded differentially to novel and familiar stimuli were calculated using cumulative sum histograms (see Methods). The differential response latencies for the SI (mean = 208 ms; range = 140 to 420 ms) and the DBB (mean = 214 ms; range = 150 to 270 ms) are not significantly different (t test; $p > 0.12$). These data illustrate that after approximately 200 ms of exposure to a visual stimulus, these neurons respond differently to novel and familiar stimuli. This processing occurs similtaneously in the SI and the DBB.

The effect of intervening trials on the magnitude of the differential responses. The decrement of the neuronal response to stimulus repetition appears to reflect increas-

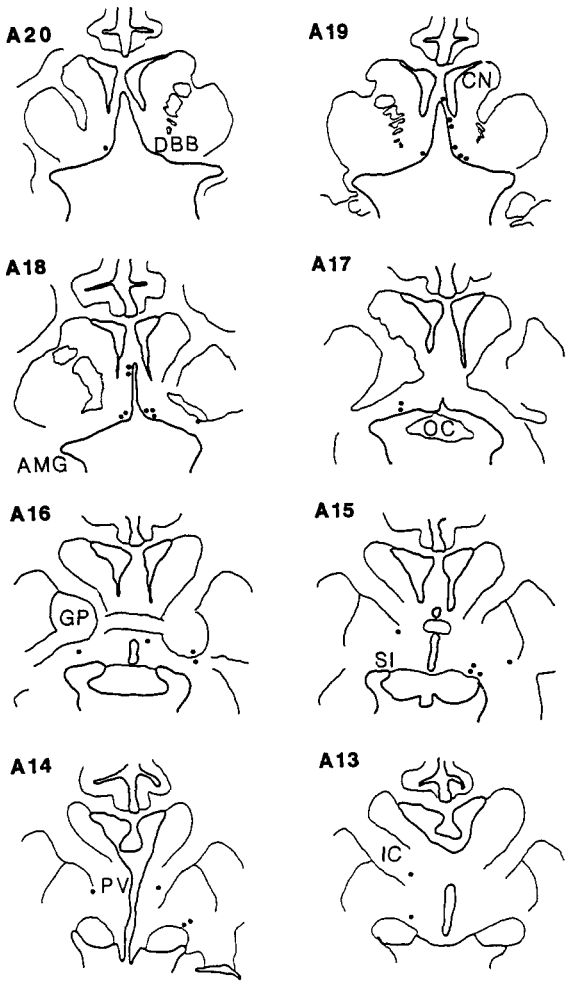


Fig. 8. The distribution of neurons with responses related to stimulus novelty. Drawings are plotted anterior to the interaural line. Each dot represents a single neuron. Rostrally, the neurons were located in the diagonal band of Broca. More caudally, the neurons were located in the substantia innominata ventral to the globus pallidus. Some neurons were found around the base of the internal capsule and medially, in the region of the third ventricle. CN: caudate nucleus. GP: globus pallidus. OC: optic chiasm. Other abbreviations as for Fig. 6

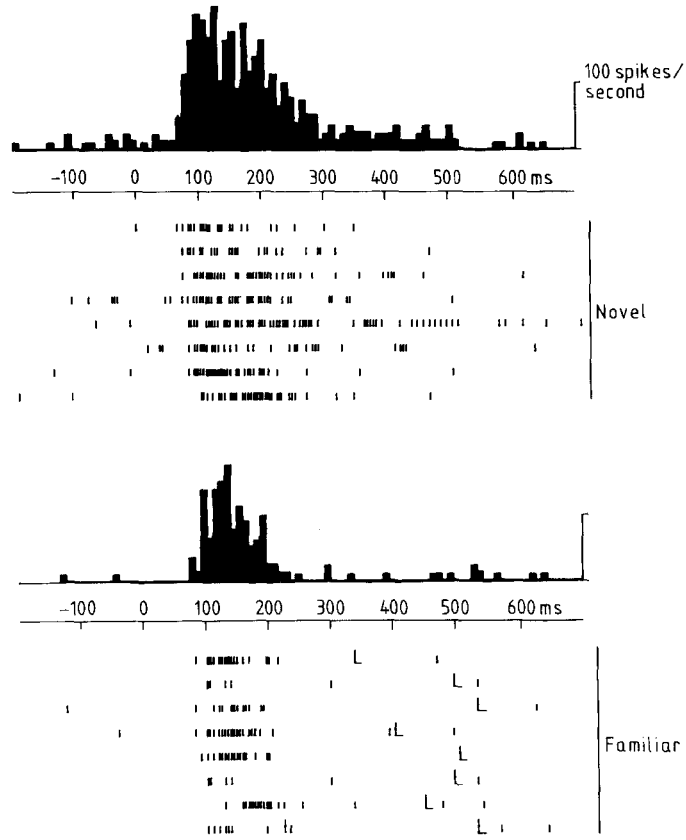


Fig. 9. The responses of a neuron (no 255) with maximal responses to novel stimuli. The rows represent the responses to 8 different stimuli (of 79 shown during the experiment) presented first as novel and then as familiar at time zero. Trials were presented originally in pseudorandom order, but are grouped for clarity in sequential order e.g. the stimulus in row 1 of the novel trials corresponds to the stimulus in row 1 of the familiar trials. The responses are typically transient, particularly when the stimuli are familiar

ing familiarity, and thus reflects a form of memory for the stimuli. The durability of the memory for the stimuli was measured by comparing the neuronal response to stimuli as novel and then as familiar when 0, or between 1 to 16 other trials intervened between the two presentations of any given stimulus. The responses of one neuron are shown in Fig. 12. In call cases, the magnitude of the decrement of the response to familiar stimuli was attenuated by increasing numbers of intervening trials, indicating that the 'memory spans' of the neurons are limited. Correlations between firing rate and the number of intervening stimuli were significant for 16 of 23 neurons tested. For those neurons with significant correlations, the slopes of regression lines intercepted the response to novel stimuli (e.g. Fig. 12) with a median value of 9 intervening stimuli and a range of 1 to 67 intervening stimuli for different neurons. Thus the responses of these neurons appear to reflect the recency of stimulus presentation. Calculated memory spans for neurons in the SI (median span = 8; range = 1 to 67) and the DBB (median span = 10; range = 2 to 60) did not differ significantly (Mann-Whitney test; $p > 0.34$).

For neuron no 255, the effect of the time interval between stimulus presentations on the differential responses was examined. Four novel stimuli were presented and shown several times as familiar at intervals of 5 to 30 s later. After 30 s intervals there was a large difference in the neuronal responses to novel compared to familiar presentations of stimuli. However, the differential response was attenuated by the increasing time interval (Fig. 13). By extrapolation along the regression line, the attenuation of the differential response was estimated to be complete after an interval of approximately 90 s.

Responses in the visual discrimination task. The neuronal responses to novel stimuli are not attributable to the saline reinforcement available on novel stimulus trials. An analysis of variance was used to compare the responses to presentations of novel stimuli with responses to presentations of the S+ and S−. The data for the S+ and S−

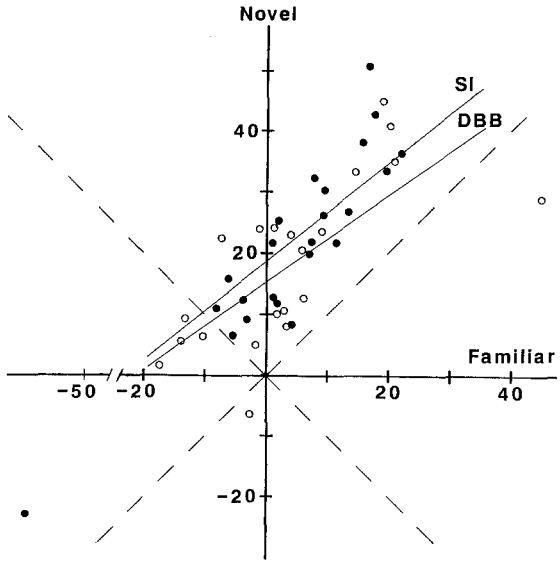


Fig. 10. The responses of all novelty-responsive neurons to novel and familiar stimuli in both recognition tasks. The data points represent the mean response of each neuron to novel and familiar stimuli, plotted on the ordinate and abscissa respectively (spikes/s). The spontaneous activity of each neuron was subtracted from the responses elicited by the stimuli. Filled circles represent neurons in the SI; empty circles represent neurons in the DBB. The neurons responded maximally to novel stimuli, with smaller responses to familiar stimuli, as indicated by the regression lines (SI: $y=0.8x+18.4$, $r=0.86$, $p<0.001$; DBB: $y=0.7x+15.7$, $r=0.71$, $p<0.001$)

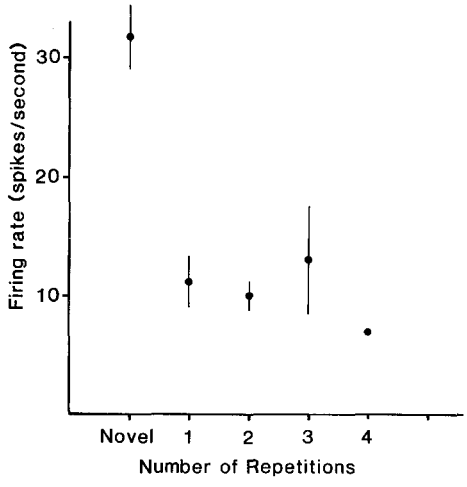


Fig. 11. The effect of repeatedly presenting stimuli (neuron no 255). The main effect of repetition is a large decrease in firing rate between the first (novel) and the second (familiar) presentation of the stimuli. The decrement in the response to familiar stimuli is maintained on subsequent presentations. The final data point represents the neuronal response on a single trial

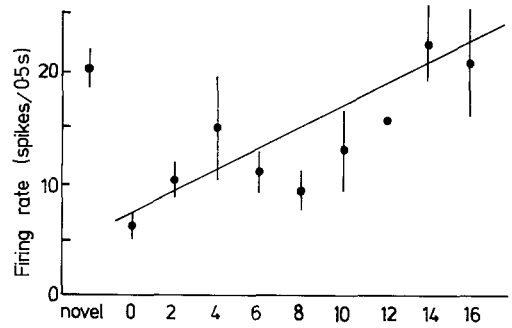


Fig. 12. The estimation of the memory span for a novelty-responsive neuron (no 255). Each data point represents the mean response (and S.E.M.) to novel or to familiar stimuli presented after a number of intervening trials between the first and second presentations of each stimulus. The differential response is largest when the two presentations occur on successive trials (novel and zero intervening trials). The magnitude of the differential responses decreases with increasing numbers of intervening stimuli ($r=0.53$; $p<0.01$); 79 stimuli were presented as novel and then as familiar. Thus the neuron responds to familiar stimuli not seen for 10 trials as if they were novel

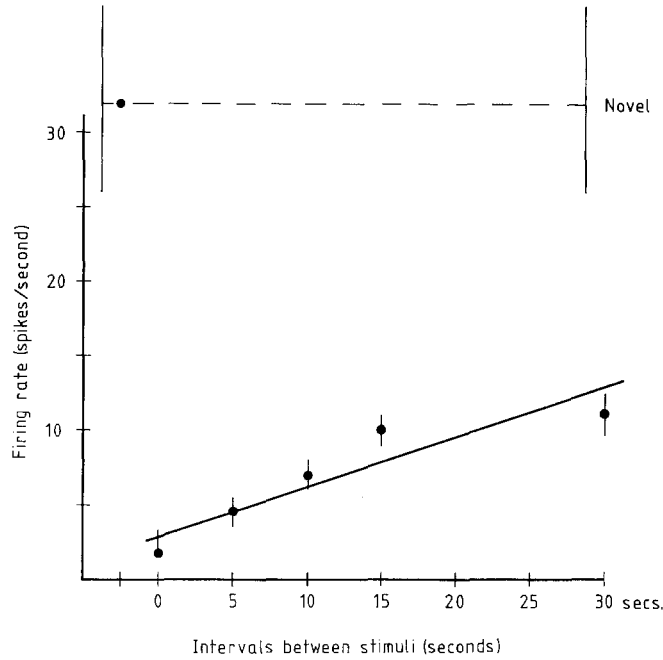


Fig. 13. The effect of time intervals on the differential response (neuron no 255). Stimuli were presented as novel and subsequently as familiar at intervals of up to 30 seconds. The magnitude of the differential response is attenuated after an interval of 30 seconds, but still shows evidence of memory for the stimuli ($y=0.33x+6.5$; $r=0.77$; $p<0.01$)

trials were obtained for presentations of these stimuli that occurred after a minimum of 16 trials between successive presentations of these stimuli. In the visual discrimination task the majority of these differential neurons responded significantly more to novel stimuli than to both the S− (75.9%–22/29 neurons tested) and the S+ (51.7%–15/29 neurons tested). In no case did the differential neurons respond more to the S− than to the S+. Additionally, the two neurons recorded in the untrained cynomolgus monkeys responded maximally to novel stimuli, while the neuronal responses in the visual discrimination task were not significantly different. These animals were untrained in the recognition memory task, and did not make lick responses to novel or familiar stimuli. Figures 9 and 14 illustrate the responses of one

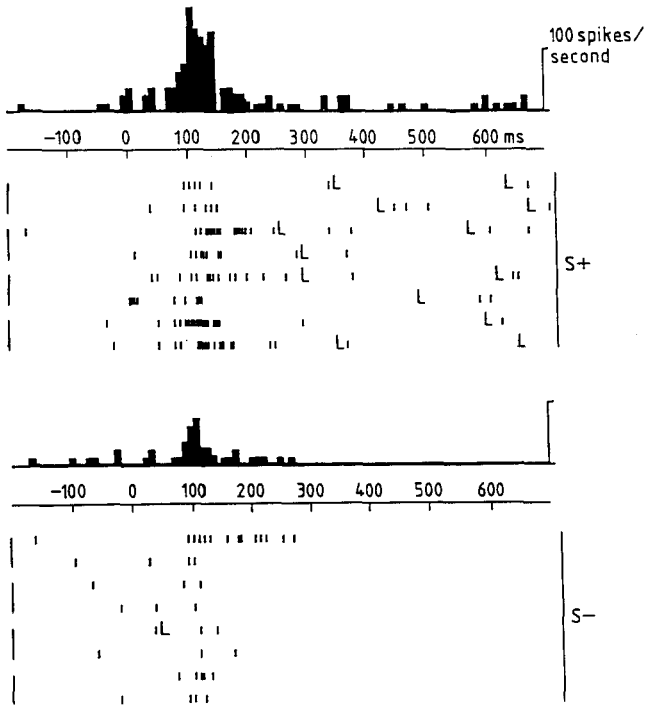


Fig. 14. Responses to the stimuli in the visual discrimination task (neuron no 255). The S+ and S− were originally presented in pseudorandom order, interdigitated with presentations of novel and familiar objects. Trials are grouped for clarity. The stimuli were presented in pairs on adjacent trials as indicated by the vertical bars on the left of the raster display. The second presentation of the S+ on adjacent trials elicits a smaller response than the preceding presentation. The response to the S− is smaller than the S+, suggesting that the reinforcement value of the stimuli may influence the neuronal responses

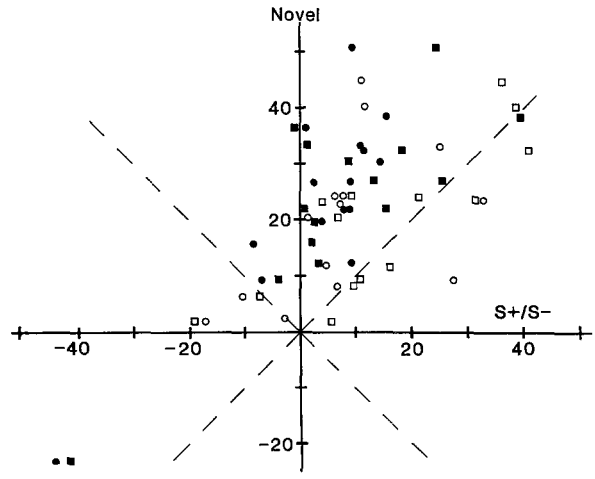


Fig. 15. Responses to the S+ and S− for all novelty-responsive neurons. Each data point represents the mean responses of a neuron to novel stimuli (plotted along ordinate) compared with the responses to the S+ (squares), or to the S− (circles), which are plotted along the abscissa. Neurons in the SI are represented by the filled symbols; neurons in the DBB are represented by the empty symbols. The spontaneous activity of each neuron was subtracted from the mean responses to the stimuli. Linear regressions were calculated for the responses of SI and DBB neurons to novel stimuli and the S+ (SI: $y=0.71x+19.6$; DBB: $y=0.65x+11.1$), and to novel stimuli and the S− (SI: $y=0.8x+21.9$; DBB: $y=0.5x+16.1$, n.s.). The slopes of the regression lines indicate that the responses to novel stimuli are generally greater than to the S+ and the S−

differential neuron in both tasks, the maximal response elicited by novel stimuli, and the smallest response by the S−. Thus novelty, not saline reinforcement, was important for the neuronal response.

Most differential neurons responded transiently to presentations of either the S+ or S− (i.e. when not seen recently), with a decrement in response to presentations of these stimuli on the following trial. However, 9/29 differential neurons responded significantly more to the S+ than to the S−, although generally less than to novel stimuli (see Figs. 9 and 14). Four of these nine neurons were also active in relation to arm movements made to obtain reinforcing stimuli such as foods and objects. This suggests that although the learned reinforcement value of the stimuli could not account for the responses of these neurons to novel stimuli, nevertheless, some neurons did respond more to stimuli that the monkeys would try to obtain. Thus some of these neurons responded to novel stimuli and to positively reinforcing stimuli. Differential neurons with larger responses to the S+ relative to the S− were observed in both the SI and the DBB. Note the erroneous lick response on trial 5 of Fig. 14. This occurred without a neuronal discharge and shows that behavioural and neuronal responses are dissociable.

The mean responses of all neurons to the S+ and S− compared to the responses to novel stimuli are shown in Fig. 15. A comparison was made of the two neuronal populations in the SI and the DBB in their responses in the visual discrimination task. The slopes of the regression lines of the responses to novel stimuli relative to the S+ and S− were compared. No significant differences were found in the responses of the two populations to novel stimuli compared to the S+ ($F=0.12$, $df=1.25$), or for the responses to novel stimuli compared to the S− ($F=1.17$; $df=1.25$). Thus the novelty-responsive neurons in the SI and the DBB responded similarly in the visual discrimination tasks.

Responses in the clinical tests. The responses of differential neurons to objects and foods were examined by presenting these stimuli to the monkeys who observed them through an aperture in the primate chair. The foods, but usually not the objects, were delivered to the monkeys after the visual presentations. The lick responses which the monkeys had learned were relevant in the recognition memory and visual discrimination tasks were not relevant in the clinical tests. The monkeys did not make lick responses during these tests.

Fig. 16 shows the neuronal responses to the first and second presentations of foods and objects. The firing rate of each neuron was greater for the first compared to the second presentation of foods and objects ($r=0.93$; $p<0.001$) which in this situation did not signal availability of reinforcement, unlike the recognition memory task. Thus, the presentation of novel stimuli elicited responses in these differential basal forebrain neurons, irrespective of training or behavioural responses.

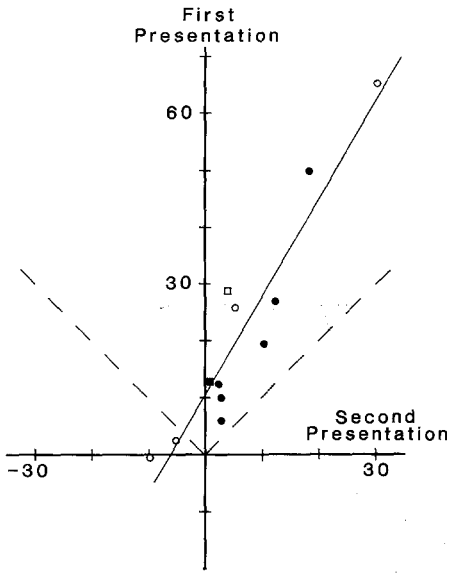


Fig. 16. Responses during clinical tests. The neurons respond maximally to the first presentation of foods and objects ($y = 1.8x + 10.6$; $r = 0.93$; $p < 0.001$), with smaller responses to subsequent presentations of the stimuli, similar to the responses found in the recognition memory task. Unlike the recognition task, the objects do not signal the availability of fruit juice or saline, or require a behavioural response for the delivery of foods. Filled circles represent responses to foods and unfilled circles represent responses to objects recorded from 7 neurons located in the substantia innominata. The filled and unfilled squares represent responses to foods and objects by a neuron in the diagonal band of Broca

Of ten neurons in the SI and the DBB tested for responsiveness to arousing tactile stimuli to the trunk and limbs of the monkeys, nine were unresponsive and one showed a decrease in firing rate opposite to the response to novel stimuli. Thus, non-specific arousal does not account for the neuronal responses to novel stimuli.

Discussion

The responses of two populations of neurons recorded in the periventricular region, the SI and the DBB in this study reflected memory for visual stimuli. The first neuronal population typically responded with increases in firing rate to familiar stimuli, and was located in a periventricular region rostral to the thalamus and caudal to the anterior commissure. These neurons appear to be more closely associated with the fibre tracts coursing through this region than with a specific nuclear structure. The second population responded maximally to novel stimuli and these neurons were found throughout the SI, the DBB and the periventricular region. The periventricular region differed from the other structures in that neurons with familiarity-related responses were observed only in this region. Further recordings will be necessary to examine the possibility that neurons of this type may be found caudally in the medial thalamus.

The two neuronal populations responded to both two- and three-dimensional visual stimuli in the two versions of the recognition memory tasks, and thus the novelty or familiarity of the stimuli, rather than physical appearance, was the basis of the neuronal responses. The neurons were recorded in both trained and untrained monkeys, indicating that neuronal responses of these types are not a necessary product of training.

The responses of these two populations are not attributable to the reinforcement value of the stimuli for several reasons. Firstly, the novelty and familiarity-responsive neurons often responded equally to the S+ and S− even though these stimuli differentially signalled the availability of juice or saline, and the monkeys responded differentially to these stimuli. Secondly, these neurons also responded differentially to novel and familiar stimuli when they were simply observed by the monkeys, and were not being used to obtain reinforcement, as in the clinical tests. Thirdly, neurons that responded differentially to novel and familiar stimuli were also found in monkeys that were not trained on the recognition memory task, and for these monkeys the novelty and familiarity of the stimuli was not important in obtaining reinforcement. These observations also eliminate movements as a cause of the neuronal responses, as the untrained monkeys did not respond to either novel or familiar stimuli, but only to the S+ and S−, for which they had been trained. However, four neurons did respond more to stimuli (novel objects and foods) that the monkeys tried to obtain with an arm movement, indicating that the interest value of the stimulus (Humphrey 1972) plays a role in the elicitation of the neuronal response. Eye movements did not account for the differential activity, which were similar on novel and familiar trials over the time period in which neuronal data were collected (Wilson 1985). Similarly, non-specific arousal is not responsible for the differential neuronal responses, as both manipulation of the torso and limbs, and ingestion of aversive saline on error trials did not elicit a response from these neurons.

Although the proportions of neurons with differential responses found in the present study are small, there are several lines of evidence indicative of the functional importance of these neurons. Firstly, damage to the basal forebrain is found in patients with Alzheimer's disease (Whitehouse et al. 1982), and such patients are impaired in recognition memory and other tasks (Albert and Moss 1984). Lesions of the basal forebrain in the monkey also produce deficits in object recognition tasks (Aigner et al. 1984), indicating that these regions, and presumably differential neurons with memory-related responses, contribute to memory function. Secondly, recordings in other brain structures using identical techniques have not revealed neurons with familiarity-related activity (Rolls et al. 1982; Wilson et al. 1988). Thirdly, another group of basal forebrain neurons (Table 1) with responses related to reinforcement show substantial memory-related properties (Wilson et al. 1984). Thus approximately 15% of all responsive neurons in the basal forebrain show memory-related activity. Furthermore, the familiarity-responsive neurons appear to be located in a restricted

subarea of the periventricular region, adjacent to the fibers of the inferior thalamic peduncle and internal capsule. As the periventricular region in which the recordings took place surrounds and is much larger than the area in which these neurons were found, the proportions of these neurons may be under-represented.

The basal forebrain and memory

The present experiments were undertaken to examine possible neuronal correlates of memory function in the periventricular region, the substantia innominata and diagonal band of Broca. There is evidence that these subcortical structures play a role in memory function. Firstly, damage to the hypothalamus and distension of the walls of the third ventricle has been reported to produce memory deficits in man (Williams and Penneybacker 1954; Geffen et al. 1980; Nichelli et al. 1982). Damage to the fornix does not consistently produce memory deficits, and it has been observed that those patients with amnesia and fornix lesions also have damage to the walls of the third ventricle around the columns of the fornix (Horel 1978). Secondly, it has been shown that neuronal degeneration of the basal forebrain occurs in Alzheimer's disease (Whitehouse et al. 1982), in which impairments of memory occur early in the course of the disease (Flicker et al. 1985). Thirdly, memory deficits often occur following aneurysms of the anterior communicating artery, damaging the region of the diagonal band of Broca (Taren 1965; Talland et al. 1967; Volpe and Hirst 1983; Alexander and Freedman 1984; Damasio et al. 1985). In addition, pathways originating in cortical regions implicated in memory function project to and through the periventricular and basal forebrain regions (Whitlock and Nauta 1956; Leichnetz and Astruc 1977; Jurgens and Muller-Preuss 1977; Mesulam and Mufson 1984; Russchen et al. 1985), and therefore damage to the basal forebrain would disconnect memory systems from their functional outputs, which appears to include the neurons in the SI, the DBB and the periventricular region.

The two populations of neurons recorded in the present study showed a reduction in the magnitude of the differential response with increasing numbers of intervening stimuli. Thus the majority of neurons in both populations demonstrated a form of memory of limited duration for visual stimuli presented in the recognition memory tasks. This conclusion is supported by the neuronal responses to foods, and to the S+ and S−. Both populations typically responded to these highly familiar stimuli as if they were novel, provided that they had not been recently seen. In the experiment in which the time interval between stimulus presentations was varied, the neuronal responses demonstrated the retention of information over an interval of 30 s, with an extrapolated value of 90 s for complete attenuation of the differential response. Thus although the memory for the stimuli is relatively durable, and does not decay within a few seconds of the presentation of the stimuli, it is limited to recent events and appears to be sensitive to interference generated by presentations of other stimuli.

These data indicate that the two neuronal populations do not encode the absolute novelty or familiarity of visual stimuli, but appear to reflect the recency of the presentation of the stimuli. There is evidence for the existence of a mechanism that makes information about the recency of stimulus presentation available to normal subjects, and the ability to use information about recency and frequency is impaired in certain disorders of human memory. Korsakoff patients are impaired in making overt judgements of recency and frequency (Huppert and Piercy 1978), and deficits in memory for recent events occur in elderly humans, in patients with senile dementia, and in aged monkeys (Flicker et al. 1985; Dean and Bartus 1985). It is possible that the memory-related neuronal responses reported here reflect the types of processes that are disrupted in patients with impairments of memory for recently ocurring events.

The differential neuronal responses could conceivably be part of a substrate for memory mechanisms, or could reflect the output of such mechanisms, as suggested by the existence of afferent anatomical pathways from structures implicated in memory function, described below. There are several possible uses of information about the recency of events or short term changes in the visual environment, for example, in the facilitiation of orientation, attention and learning. Behavioural studies have shown that rhesus monkeys prefer to look at novel stimuli or stimuli that have not recently been seen (Humphrey 1972). The focusing of attention to a stimulus may facilitate learning, and there is evidence that the basal forebrain has a role in certain forms of learning and memory. Electrical stimulation of the hypothalamus facilitates conditioned eye blink responses, and such stimulation has been shown to facilitate the rate of conditioning of neurons in the pericruciate cortex (Woody et al. 1983). Furthermore, ibotenic acid lesions of the SI and the DBB impair the performance of object recognition tasks in monkeys (Aigner et al. 1984), indicating that the basal forebrain does play a role in the performance of recognition memory tasks. Thus although the properties of neurons that respond differentially to novel and familar stimuli resemble the processes of habituation and sensitisation, these neurons may play a role in object recognition, unlike for example, neurons in the spinal cord in which habituation and sensitisation is also observed.

The anatomical distribution of the novelty-responsive neurons

The novelty-responsive neurons are distributed throughout the SI, the DBB and the periventricular region. The differential neurons in the SI and the DBB did not differ from each other in their responses in the recognition memory and visual discrimination tasks, suggesting that certain populations of neurons in these two structures are functionally homogeneous. In fact, other classes of neurons are also distributed in approximately equal propor-

tions throughout the basal forebrain (Table 1). These data suggest that the SI and the DBB are functionally equivalent in terms of their responses in the tasks.

Anatomical and neurochemical studies of the SI and the DBB have also revealed similiarities in these two regions (Jones et al. 1976; Mesulam et al. 1983; Hedreen et al. 1984). The cell bodies of the basal nucleus of Meynert are distributed throughout the SI and the DBB, and some of them are cholinergic. These cells project to cortical regions and it is possible that the neurons described here form part of the basal nucleus of Meynert. A test of this hypothesis will be the demonstration of antidromic activation elicited by electrical stimulation of the cortex. One class of neuron activated by the learned reinforcement value of visual stimuli, and projecting to the neocortex has been reported (Wilson et al. 1984), and such neurons are located in the SI and the DBB.

The afferents of the basal forebrain and memory function

The familiarity-responsive neurons described here, and those of a previous study (Rolls et al. 1982) are located in the region of the inferior thalamic peduncle and the ventral amygdalofugal pathway. Anatomical studies employing anterograde tracing techniques have described pathways from the temporal and prefrontal cortices, the medial thalamus, the amygdala, supramammillary region and midbrain that travel to and through the periventricular region (Whitlock and Nauta 1956; Jürgens and Müller-Preuss 1977; Leichnetz and Astruc 1977; Price and Amaral 1981; Veazey et al. 1982; Aggleton and Mishkin 1984; Mesulam and Mufson 1984; Russchen et al. 1985). The present anatomical experiment is consistent with these studies.

The cortical regions projecting to the SI and the DBB are limited to the ventromedial parts of the temporal and prefrontal cortices (Mesulam and Mufson 1984). These regions were labeled after the injection of HRP into the periventricular region in the present experiment. This suggests that these cortical regions are functionally important for both the periventricular region and the basal forebrain.

The cortical and subcortical structures projecting to the periventricular region, the SI and the DBB have all been implicated in memory function as damage to these regions produces memory deficits. Patients with damage to the ventromedial temporal lobes suffer from amnesia (Scoville and Milner 1957; Van Buren and Borke 1972). Similar lesions in monkeys impair the performance of recognition memory tasks (Mishkin 1978; Zola-Morgan and Squire 1985). Damage to the amygdala specifically impairs the judgement of whether a recognised object was presented recently (Murray and Mishkin 1984), and neurons that respond maximally to novel stimuli have been recorded in the amygdala (Wilson and Rolls 1987). Furthermore, cooling of the inferior temporal gyrus impairs the performance of a delayed match to sample task (Horel et al. 1987), a task requiring recent memory, and combined damage to the ventromedial temporal cortex and the amygdala produces a severe impairment in the performance of object recognition tasks (Murray and Mishkin 1986). In neurophysiological studies of the ventromedial temporal cortex in monkeys, single neurons have been found that are maximally responsive to novel stimuli, similar to the neurons described in this paper (Brown et al. 1987; Wilson et al. 1988). These neurons are located in the region of the ventromedial temporal cortex known to project to the basal forebrain, and thus may influence the responses of basal forebrain neurons directly, or through the amygdala. Neurons with familiarity-related activity were not observed in the hippocampus, indicating the specificity of the periventricular region and the apparant lack of involvement of the hippocampus in the behavioural tasks, which is consistent with the absence of retrograde label in the hippocampus following the HRP injection.

Damage to the ventromedial prefrontal cortex, like the ventromedial temporal cortex, has been reported to produce impairments of memory and attention in man (Luria et al. 1967; Wallesch et al. 1983). Ventromedial prefrontal damage impairs the performance of recognition memory tasks in monkeys (Bachevalier and Mishkin 1986). Angelergues (1969) has characterised prefrontal amnesia as deficits in memory for recent events, which appears to be the type of memory reflected in the activity of the differential neurons described in this paper. Furthermore, combined lesions of the ventromedial temporal and prefrontal cortices and the basal forebrain produce a devastating amnesia or even dementia in man (Friedman and Allen 1969; Gascon and Gilles 1973; Damasio et al. 1985).

Damage to the medial thalamus and mammillary bodies is also associated with impairments of memory in man (Mair et al. 1979; Squire and Moore 1979; Winocur et al. 1984) and is known to impair the performance of recognition memory tasks in monkeys (Aggleton and Mishkin 1983). Aggleton and Mishkin (1984) have suggested the importance of fibres coursing in the inferior thalamic peduncle for memory function, the region in which the familiarity-responsive neurons are located. Collectively, these diverse studies, in conjunction with the present results, suggest the existence of a system of anatomically connected cortical and subcortical structures (Mishkin 1982) that are important as a substrate for visual recognition or in the utilisation of this information.

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