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# Neuronal responses related to reinforcement in the primate basal forebrain

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In the present study neurones recorded in the substantia innominata, the diagonal band of Broca and a periventricular region of the basal forebrain responded differentially to stimuli signalling the availability of fruit juice or saline obtained by making lick responses in two different visual discrimination tasks. The activity of certain neurones reflected the rewarding nature of stimuli used to signal the availability of juice in the tasks, responding to the sight and delivery of both foods and syringes used to deliver juice in tests in which behavioural responses were irrelevant. The activity of other neurones reflected aversion, responding to task stimuli signalling availability of saline and to syringes used to deliver saline to the mouth. In another task an auditory cue that signalled the availability of juice elicited neuronal responses. These neurones also responded to a tone cue used to signal the onset of the trial, and during certain mouth and arm movements which the monkey used to obtain reinforcement. The responses of these differential neurones were similar in most respects in all 3 regions of the basal forebrain. Thus these neurones respond to a range of visual and auditory stimuli that monkeys have learned can be used to obtain reinforcement, but not on the basis of sensory properties such as shape or colour of the stimuli. We conclude that the reinforcement-related nature of the neuronal signal from the basal forebrain could be used to facilitate processing in cortical regions, optimising the functioning of sensory, motor and association cortices, thus increasing the probability of responding appropriately to learned environmental contingencies. We suggest that the properties of these neurones are due to afferent inputs from ventromedial regions of the prefrontal and temporal cortices and amygdala.

## INTRODUCTION

The basal forebrain — the hypothalamus, the substantia innominata and the diagonal band of Broca — has often been implicated in the regulation of vegetative functions and in the control of motivated behaviours such as feeding and drinking. It has been repeatedly shown that lesions and stimulation of the basal forebrain elicit changes in feeding and drinking behaviour, and in the levels of hormones known to play a role in these behaviours. One mechanism through which the basal forebrain may influence motivated behaviour is that of reinforcement, a process ensuring that biologically successful behavioural acts are learned and repeated. There are two major findings that suggest that the basal forebrain is involved in the substrate of reinforcement. First, monkeys will work to obtain electrical stimulation of the basal forebrain[4,5,57,59]. Second, electrophysiological studies of the basal forebrain have found neurones that respond to reinforcing stimuli such as the sight and delivery of foods and fruit juice[11,40,48,54,55,66,68].

Changes in motivated behaviour also occur in human patients with damage to the basal forebrain. Such patients exhibit abnormal levels of hormones and autonomic responses, demonstrate marked changes in feeding behaviour, with striking changes in emotional states, such as extreme violence and lethargy[47]. Electrical stimulation of the septal region and nucleus basalis in man produces emotional responses, including pleasure and aversion[20,62], encouraging the view that structures within the basal forebrain provide a substrate for reinforcement.

In recent years there have been two major advances in our knowledge of the basal forebrain. Anatomical studies have shown that cells in the basal nucleus of Meynert within the basal forebrain project to, and provide the cholinergic innervation of the cerebral cortex[12,27,33]. A second major discovery has been the finding of degeneration of the basal nucleus of Meynert in patients with Alzheimer's disease[70], indicating that damage to the basal forebrain may be responsible for the neuropsychological changes afflicting patients with Alzheimer's disease[10]. In view of these new findings, we examined a number of issues in the physiology of basal forebrain neurones in order to understand more clearly the

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relationship between the motivational and cognitive processes occurring in the basal forebrain, and thus how damage to this subcortical region might influence cognitive behaviour. Several issues were addressed in the present study. Firstly, we examined the importance of the sensory properties of visual stimuli on reinforcement-related neuronal activity, testing this by recording from neurones while monkeys responded to several sets of visual stimuli that were physically dissimilar but were identical in their reinforcement value. Secondly, as the basal forebrain plays a role in both feeding and drinking behaviours, we examined the possibility that individual neurones would respond to foods and stimuli signalling availability of fluids. Thirdly, we tested the possibility that reinforcement-related neurones would respond to stimuli in different sensory modalities that signalled the availability of reinforcement. Fourthly, the distribution of reinforcement-related neurons within the basal forebrain was determined by recordings made in the substantia innominata, the diagonal band of Broca and a periventricular region that includes the anterior hypothalamus and adjacent structures. Some of the data described here have been published in abstract form[72].

## MATERIALS AND METHODS

*Recording techniques*

Neuronal activity was recorded using glass-insulated tungsten microelectrodes (approximately 5 $\mu$m wide, 10–15 $\mu$m long, with a blunt tip), 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. EOG data were usually sampled at 100 Hz, digitized and stored with neuronal activity on computer disc and magnetic tape. Electrodes implanted in cortical and subcortical structures were used to deliver single pulse electrical stimulation through constant current stimulus isolation devices in order to identify connections between the basal forebrain and other structures.

*Subjects, stimulus presentation, behavioural responses and reinforcement*

Two rhesus and two cynomolgus monkeys were trained to perform 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 20–30 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, which facilitated fixation of the stimuli. Visual stimuli were presented for 1.5 s and the intertrial 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 gained weight steadily during the course of the experiments.

*The go/no go visual discrimination tasks*

In the visual discrimination shutter-based task (VDS), the electromagnetic shutter was used to present two highly familiar syringes mounted in square plaques of different colours, one per 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. In the visual discrimination computer-based task (VDC), 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 for a 2 s period 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 and 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 neurone 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 neurones in the basal forebrain could be compared. After recording from a basal forebrain neurone, the electrode was advanced by a minimum of 100 $\mu$m before sampling other neurones.

During the recordings the monkeys continuously performed the discrimination tasks. The presentation of the S+ and the S–, novel and familiar objects, foods and faces were interdigitated in pseudorandom order. If the neurone responded to the presentation of any of these stimuli, extensive testing for periods of up to 4 h continued in order to identify the properties of the stimuli that elicited the responses. A record of the depth of each neurone was made, as well as its response properties or lack of responsiveness. Every neurone 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 (the S+, S–, novel and familiar objects) were compared using one way analysis of variance and subsequent Tukey tests[7]. Statistical analyses were based on data collected from 8 to 20 trials for each stimulus. 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 neurones. This technique is used in order to show how each neurone

responded in the various conditions. The data points were calculated by determining the spontaneous firing rate of a neurone, 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 neurones responded differentially to the S+ and S– were determined with the use of cumulative sum techniques[78] implemented on a computer. Peristimulus time histograms were computed for each type of trial (e.g. the S+ and S–), 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 neurone, relative to implanted stimulation electrodes. Small lesions were made at the site of selected neurones by passing DC current (80–100 $\mu$A 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 hollow rod 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 neurones, as evidenced by the correspondence between the locations of neurones 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 neurones were plotted on large scale drawings of histological sections at 1 mm intervals.

## RESULTS

A total of 2119 neurones in 325 electrode penetrations were recorded in 3 regions of the basal forebrain: (1) the substantia innominata (SI); (2) the diagonal band of Broca (DBB) and (3) a periventricular (PV) region

TABLE I

*Summary of functional categories of basal forebrain neurones*

Two groups of neurones responded differentially in the tasks, either on the basis of the reinforcement value of the stimuli, or to the novelty and familiarity of the stimuli[58,76]. Many neurones were responsive to the tone cue or during the presentation of visual stimuli (shutter period neurones), but these responses were not differential.

| | *Substantia innominata* | *Diagonal band of Broca* | *Periventricular region* |
|---|---|---|---|
| Differential neurones | | | |
| Reinforcement-related neurones | 73 | 24 | 23 |
| Novelty/familiarity neurones | 16 | 14 | 8 |
| Task-related neurones | | | |
| Tone-cue/shutter period neurones | 87 | 74 | 117 |
| Shutter period neurones | 190 | 102 | 171 |
| Other responsive neurones | 108 | 13 | 51 |
| Unresponsive neurones | 584 | 262 | 202 |
| Total | 1058 | 489 | 572 |

TABLE II

*Characteristics of reinforcement-related neuronal populations*

The table provides information about the number of neurones recorded in the 3 regions of the basal forebrain; the incidence of *S+* and *S– neurones*; their average spontaneous furing rate (spikes/s); and the average size of action potentials (300–400 $\mu$V) recorded from these neurones.

| | *Substantia innominata* | *Diagonal band of Broca* | *Periventricular region* |
|---|---|---|---|
| Reinforcement-related neurones | 73 | 24 | 23 |
| S+/S– ratio | 54:19 | 18:6 | 12:11 |
| Mean spontaneous firing rate | 25.3 | 21.3 | 18.5 |
| Mean action potential size | 3:1 | 4:1 | 4:1 |

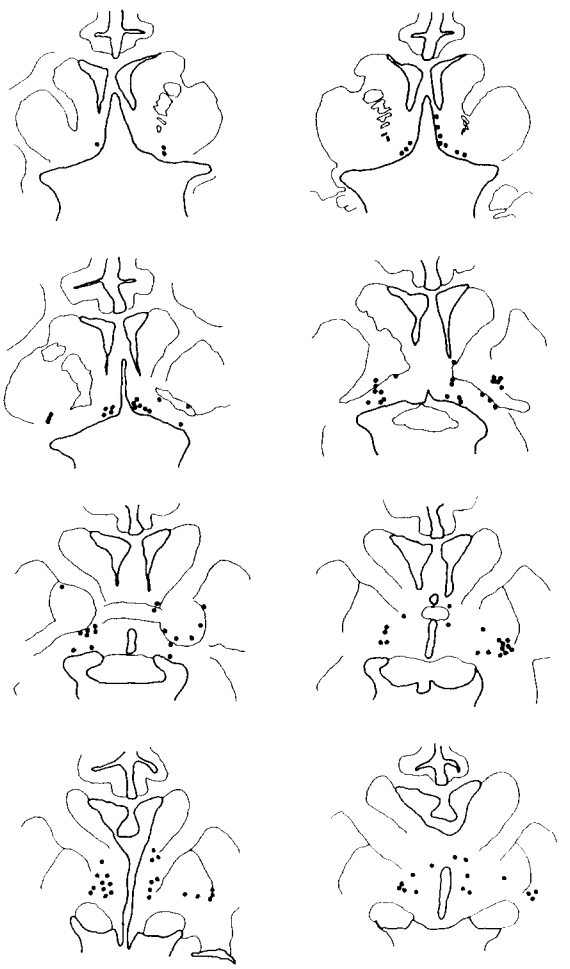

Fig. 1. The distribution of reinforcement-related neurones. Each drawing represents a section of brain 1 mm in extent. Rostrally, the neurones are located in the diagonal band of Broca. More caudally, the neurones were located in the substantia innominata ventral to the globus pallidus. Medially, neurones were located around the internal capsule and inferior thalamic peduncle. There is a tendency for the neurones to be located around fibre tracts such as the anterior commissure, internal capsule and ansa peduncularis.

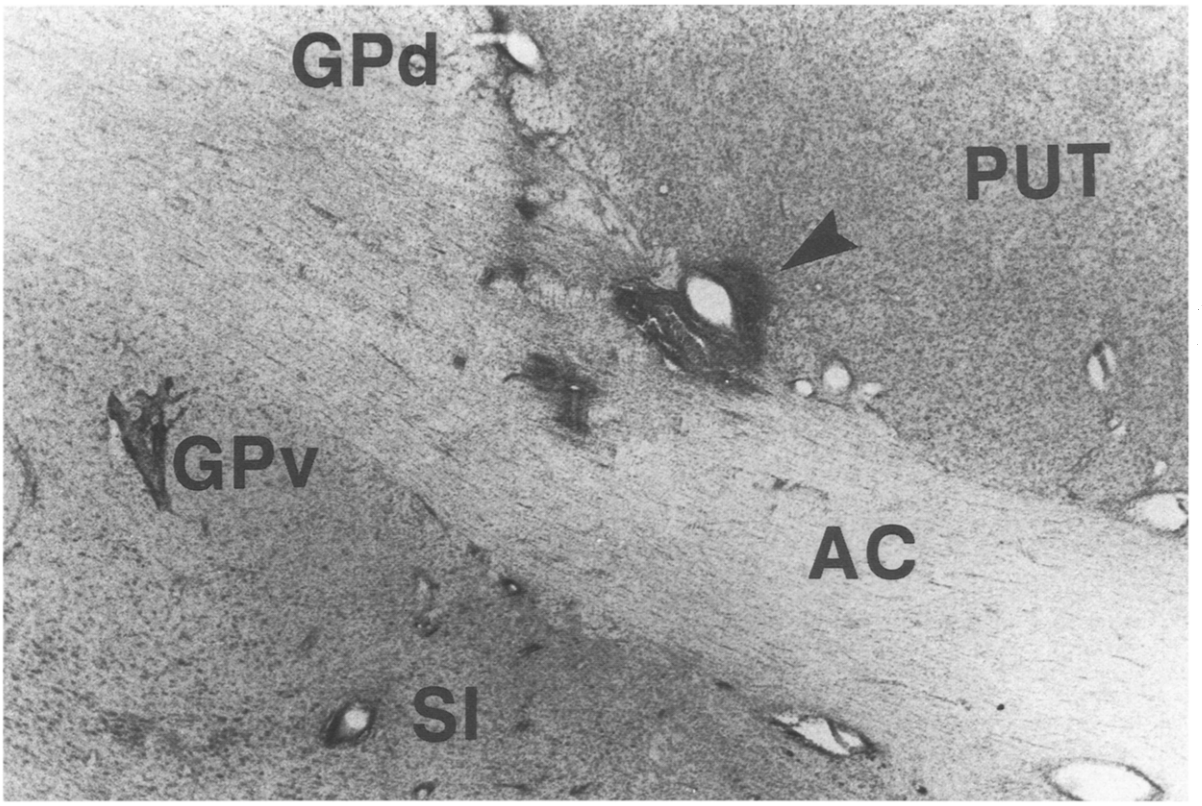


Fig. 2. A marker lesion made at the site of a reinforcement-related neurone. The lesion (see arrow) is located at the border of the anterior commissure (AC), globus pallidus (GP dorsal, ventral) and putamen (PUT). Interstitial cells of the basal nucleus of Meynert are found in such locations[22,33,42].

bordered by the wall of the third ventricle and the internal capsule, by the anterior commissure and the rostral pole of the thalamus, and by the ventral margin of the caudate nucleus and the ventromedial hypothalamus. Table I summarises the different types of neurones recorded in the basal forebrain. The subject of this paper is specifically those neurones ($n$ = 120) whose responses were related to the reinforcement value of the stimuli used in the tasks. These neurones responded differentially to positively or negatively reinforcing stimuli and thus are termed differential neurones in this paper. Differential neurones with reinforcement-related activity were recorded in the 3 regions of the basal forebrain in which the experiments took place; the proportions of differential neurones in these regions were broadly similar (Table II) and there were few differences in the response properties of the differential neurones in the 3 regions. These differences will be noted in the text.

Reinforcement-related neurones were found in the vertical and horizontal limbs of the diagonal band of Broca, the substantia innominata, and the periventricular region (Fig. 1). Differential neurones were often located adjacent to the fibres of the anterior commissure and the internal capsule. A lesion made at the site of a differential neurone was situated at the border of the anterior commissure, the globus pallidus and putamen (Fig. 2). These neurones may be interstitial cells of the basal nucleus of Meynert which are found at the borders of the substantia innominata, the anterior commissure and internal capsule[22,33,42].

*(1) General properties of reinforcement-related neurones*

Reinforcement-related neurones were generally spontaneously active and demonstrated easily discriminable action potentials (Table II). The action potentials of these neurones could often be recorded over movements of up to 200 $\mu$m of the recording electrode. Fig. 3 shows the action potentials of a typical neurone recorded in the substantia innominata. The mean spontaneous firing rate and action potential size did not differ substantially across the 3 regions of the basal forebrain (Table II).

*(2) The go/no go visual discrimination tasks*

In most cases, reinforcement-related neurones were initially defined during the experimental tests by their differential responses to the stimuli presented in one of the visual discrimination tasks. However, we found that the responses in one task predicted the way in which

these neurones responded in the other discrimination task, in reversal and recognition memory tasks[74,77], and in the clinical tests.

All reinforcement-related neurones showed statistically significant differential responses in the visual discrimination tasks (Table III). The stimuli in the two tasks were generated either by computer (VDC task) and displayed on a video monitor, or using an electromagnetic shutter (VDS task) to display three-dimensional objects. Approximately half of all differential neurones were tested on the VDS task, while the other neurones were tested on the VDC version of the task. Some neurones (Table III) were tested on both versions of the visual discrimination task and in some of these cases did not attain (but frequently approached) significance in one of the tasks. In those cases in which one test did not attain significance, the neurones responded differentially as they did in the other tasks, although the magnitude of the response was smaller and more variable. Some differential neurones were tested on the recognition memory task alone: 11 in the PV region and 6 in the SI. The neuronal responses in this task also reflected the reinforcement value of the stimuli, even though the reinforcement contingency differed completely from that of the discrimination tasks[77].

Reinforcement-related neurones were of two different types, based on their responses to the type of reinforcement signalled by the different visual stimuli: *S+ neurones* responded with phasic increases in firing rate to stimuli signalling the availability of fruit juice (e.g. No. 253, Fig. 4), and *S– neurones* responded with phasic increases in firing rate to stimuli signalling the availability

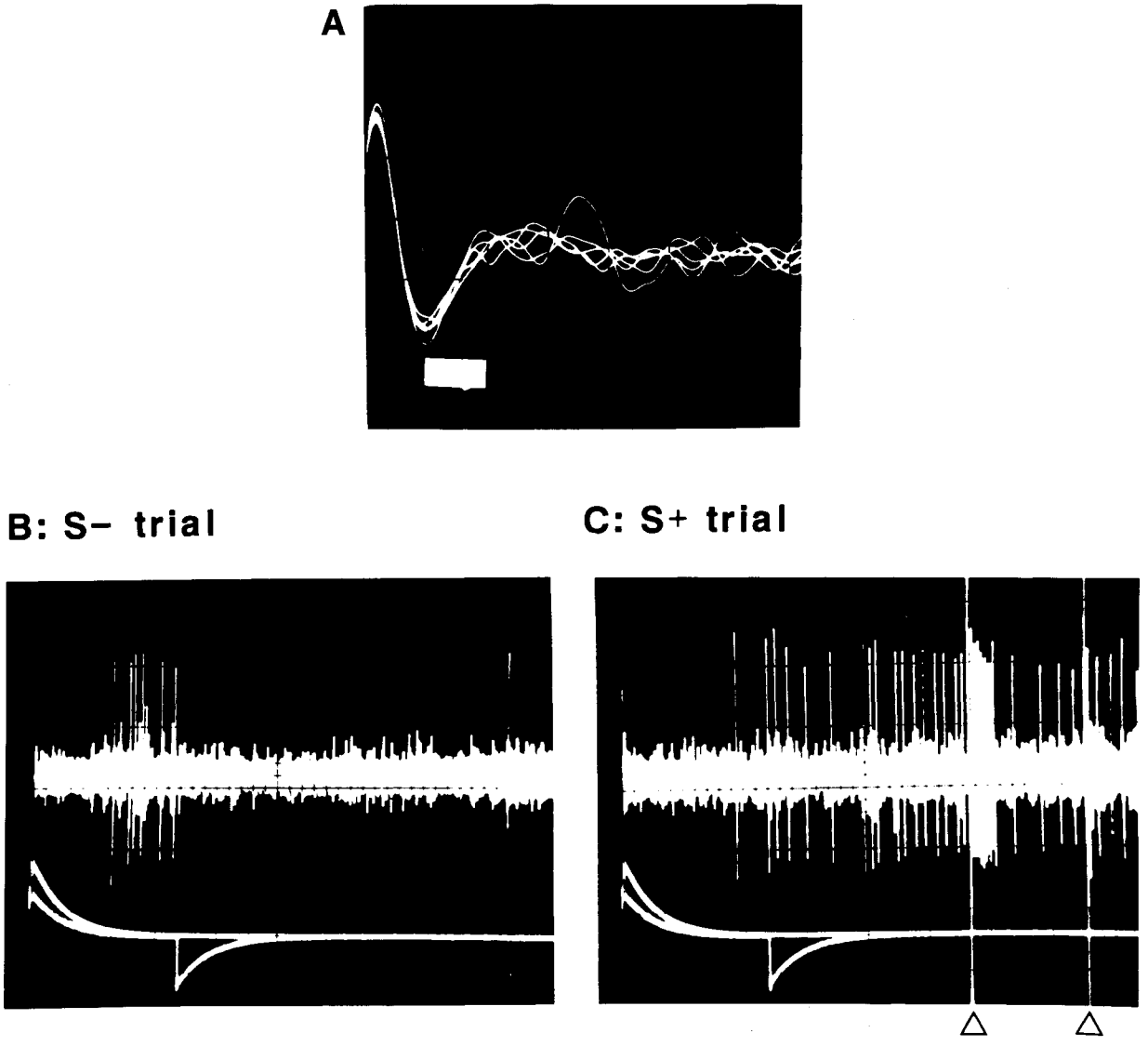


Fig. 3. Action potentials recorded from a reinforcement-related neurone in the substantia innominata. In (A) the time base is 1 ms and in (B,C) is 500 ms. The neurone responds differentially to the presentation of the S+ and S–. The occurrence of lick responses is indicated by the arrows.

TABLE III

*The results of the analysis of variance: the number of significant differences in the visual discrimination tasks*

The data are separated into tasks in which the stimuli are presented by computer (VDC) on a video monitor, or using the electromagnetic shutter (VDS). Some differential units were tested on the recognition memory (RM) tasks only, and are reported elsewhere[77].

| | *Substantia innominata* | *Diagonal band of Broca* | *Periventricular region* |
|---|---|---|---|
| No. of differential units | 73 | 24 | 23 |
| Neurones tested: | | | |
| VD tasks | 67 | 24 | 12 |
| RM only | 6 | 0 | 11 |
| *Discrimination task* | *Number of significant tests/neurones tested:* | | |
| VDC task (Computer) | 34/41 (82%) | 14/18 (78%) | 8/8 (100%) |
| VDS task (Shutter) | 40/42 (95%) | 15/15 (100%) | 4/4 (100%) |

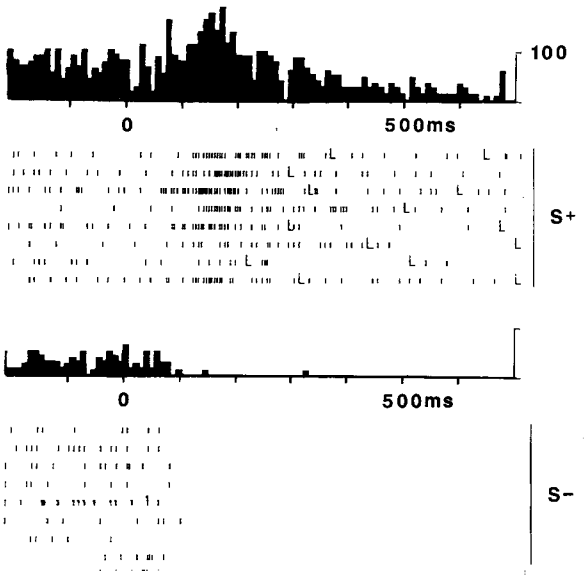


Fig. 4. Responses of a reinforcement-related neurone (No. 253) in the visual discrimination task. Each row represents the responses to the presentation of the S+ or S– (presented at time 0). There is a biphasic response to the presentation of these stimuli: an increase in firing rate for the S+ and a decrease for the S–. The presentation of the stimuli was done in pseudorandom order but is grouped for clarity. The L indicates the occurrence of the lick response. The scale at the right of the histogram represents a firing rate of 100 spikes/s. Bin width = 10 ms. See also Figs. 6 and 11.

of saline. *S+ neurones* were in the majority for the SI and DBB, while *S+* and *S– neurones* were found in approximately the same proportions in the PV region (Table II).

The responses of a given neurone to a stimulus were of two basic patterns: (1) increases in firing rate to both positively and negatively reinforcing stimuli, with one of the stimuli eliciting a significantly larger response; or (2) responses to these stimuli that were opposite in direction, e.g. increases in firing rate for rewarding stimuli and decreases in firing rate for aversive stimuli. Scatter plots of the responses of these differential neurones are shown in Fig. 5. This figure compares the responses of each neurone to the S+ and S– in the VDC discrimination task. From Fig. 5 it is clear that in all 3 regions of the basal forebrain, the firing rate of *S+ neurones* is greater to the S+ than to the S–, as indicated by the clustering

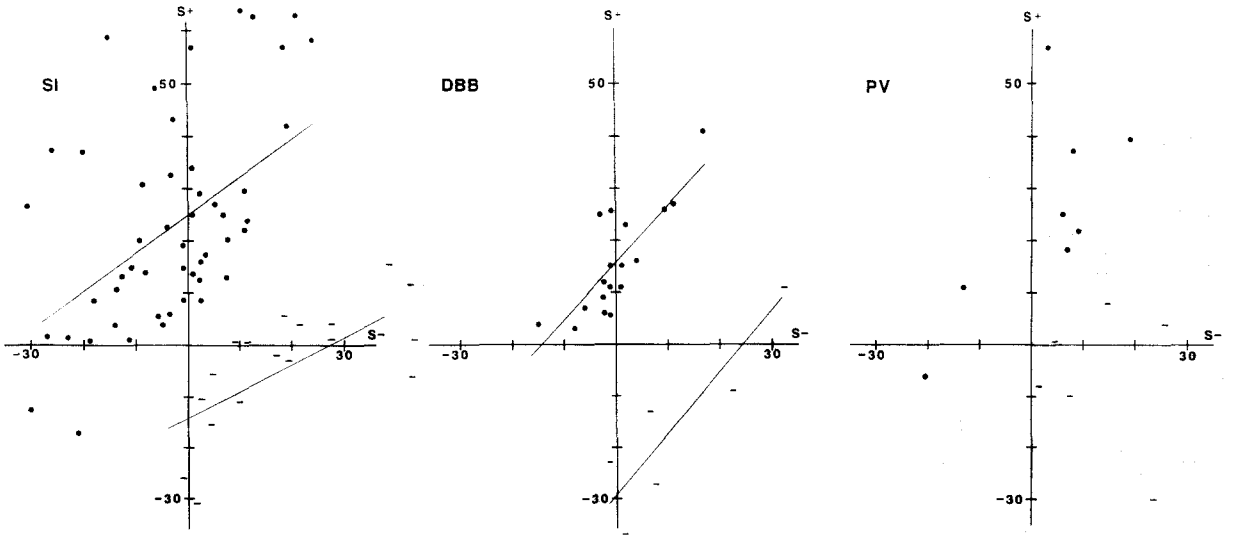


Fig. 5. Responses to the S+ and S– in the SI, DBB and PV. Each data point represents the mean responses (spikes/s) of one neurone to the S+ (ordinate) and the S– (abscissa) from which the spontaneous firing rate of that neurone was subtracted. This transformation demonstrates the magnitude and direction of the neuronal responses. Neurons are grouped into *S+ neurones* (filled circles) and *S– neurones* (–). Many neurones show a biphasic response to the stimuli: an increase in firing rate to the S+ (or S–) and a decrease in firing rate to the S– (or S+). Regression lines represent different groups of neurones for which significant correlations between the responses to the S+ and S– were obtained: SI (*S+ neurones*: $y = 0.7x + 25.3$, $r = 0.5$, $P < 0.01$, $n = 49$); *S– neurones*: $y = 0.5x + -13.9$, $r = 0.68$, $P < 0.01$, $n = 18$); DBB (*S+ neurones*: $y = 1.1x + 15.6$, $r = 0.82$, $P < 0.01$, $n = 18$); *S– neurones*: $y = 1.2x + -29.2$, $r = 0.89$, $P < 0.02$, $n = 6$).

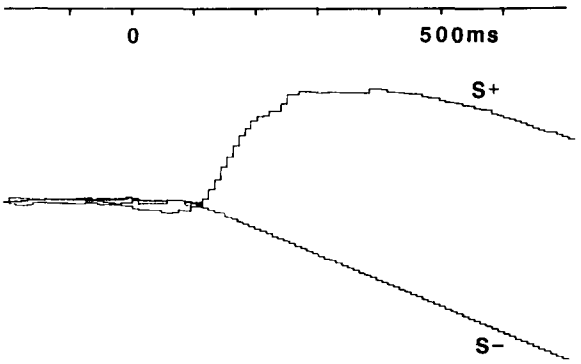


Fig. 6. Analysis of differential response latencies using cumulative sum histograms (neurone No. 253). Each histogram represents the neuronal activity on one of the two different types of trial. The data were derived from trials used to illustrate the raster display shown in Fig. 4. Responses to the S+ are increases in firing rate; responses to the S- are decreases in firing rate.

around the ordinate. The firing rate of *S- neurones* is greater to the S- than to the S+ and the responses of these neurones are clustered around the abscissa. Many neurones show a biphasic response pattern, with an increase in firing rate to one stimulus and a decrease in firing rate to the other stimulus. Note that the neuronal responses are represented as changes in firing rate from the spontaneous activity of each neurone. This allows the response magnitude and direction to be compared independently of spontaneous firing rate. The regression lines are fitted to data points representing *S+* or *S- neurones* in the SI and DBB. The slopes of the regression lines are similar (Fig. 5), indicating that the responses of the populations of *S+* and *S- neurones* in the SI and DBB are similar.

*(3) Differential response latencies*

The time taken for a neurone to respond differentially to the S+ and the S- is termed the differential response latency. This was determined by constructing cumulative sum histograms[78] and measuring the latency of the inflection point indicating changes in response to the stimuli. The change in the slope of the histogram represents the change in firing rate for a particular type of trial. The cumulative sum histograms of neuron No. 253 (Fig. 6) show that the responses to the S+ and S- are different (latency = 140 ms) in their direction, with increases in firing to the S+, compared to decreases in firing to the S-. The mean differential response latencies for the visual discrimination task for the three basal forebrain regions are shown in Table IV. Fig. 7 shows the distribution of differential response latencies for the discrimination tasks in the three regions, which are similar. It is notable that the latencies for *S+* and *S- neurones* are also similar.

TABLE IV

*The analysis of differential response latencies obtained in the visual discrimination task*

The data are separated into tasks in which the stimuli were presented by computer (VDC) on a video monitor, or using the electromagnetic shutter (VDS). Mean values are in milliseconds after the onset of the stimulus presentation.

| | | *Substantia innominata* | *Diagonal band of Broca* | *Periventricular region* |
|---|---|---|---|---|
| VDC task: | *S+ neurones* | 175 | 153 | 168 |
| | *S- neurones* | 160 | 200 | 170 |
| VDS task: | *S+ neurones* | 175 | 203 | 105 |
| | *S- neurones* | 171 | 176 | 280 |
| Tone cue | | 275 | 273 | 308 |

*(4) Clinical tests*

As the evidence suggests that the availability of fruit juice signalled by the visual stimuli was important for the

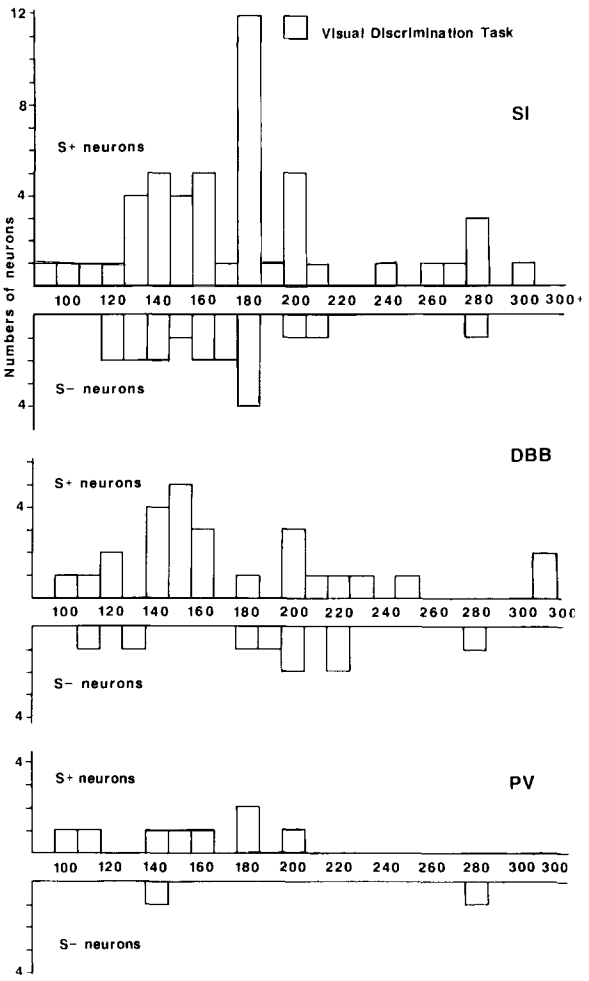


Fig. 7. The distribution of differential response latencies for reinforcement-related neurones in the 3 regions of the basal forebrain. Latencies for *S+* and *S- neurones* in the visual discrimination task are separated and are essentially identical.

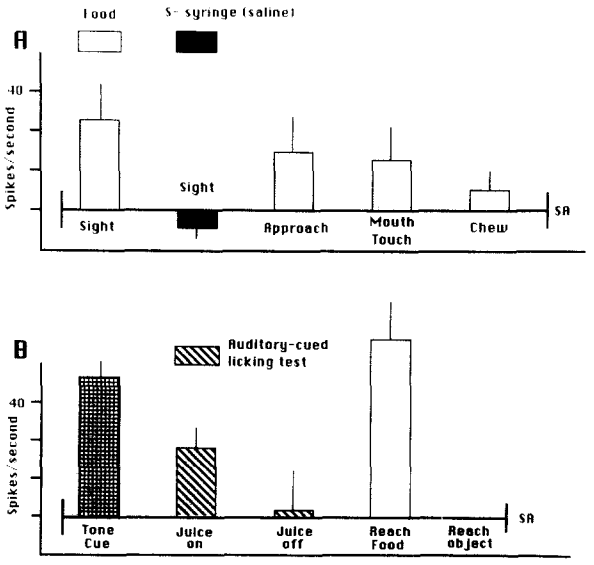


Fig. 8. Responses in the clinical tests (neurone No. 23). In (A) this neurone responded to the sight of food with an increase in firing rate, with increasingly smaller responses to the approach of food, to the touching of the mouth with food and during chewing. The sight of a saline-filled syringe resulted in a decrease in firing, opposite to the response to the sight of food. The neurone responded differentially in the two discrimination tasks: VDC (S+ vs S–: 36 vs 7 spikes/s), and VDS (S+ vs S–: 60 vs 24 spikes/s). In (B) the neurone responds well to the auditory cue signalling availability of juice, but less so when juice is withheld whilst the monkey licks continuously. The neurone also responds strongly to the tone cue (presented during the tasks) and whilst the monkey reaches for food and for a non-food object. This neurone projected to the motor cortex and thus is part of the basal nucleus of Meynert.

differential neuronal responses, it is possible that the presentation of reinforcers such as nuts and fruit might also activate the differential neurones. Data on the

TABLE V

*Responses to the sight of foods, the S+ and the S– in clinical tests*

Stimuli were presented either using the electromagnetic shutter or through the aperture in the clinical tests. The largest proportion of *S+ neurones* respond to the sight of foods and the S+, and are least responsive during chewing. Conversely, *S– neurones* are unresponsive to the sight of foods and the S+. The percentages of responsive neurones are expressed in parentheses.

| | *Substantia innominata* | | *Diagonal band of Broca* | |
|---|---|---|---|---|
| | *Neuronal type* | | *Neuronal type* | |
| | *S+* | *S–* | *S+* | *S–* |
| *Shutter:* | | | | |
| Sight of Foods | 16/19 (84) | 2/15 (13) | 5/7 (71) | 1/3 (33) |
| *Clinical:* | | | | |
| Sight of Foods | 20/26 (77) | 2/6 (33) | 6/10 (60) | 0/3 (0) |
| Sight of S+ | 14/24 (58) | 0/6 (0) | 5/9 (55) | 0/1 (0) |
| Sight of S– | 1/18 (0.05) | 3/5 (60) | 0/6 (0) | 1/1 (100) |
| Approach | 24/37 (64) | 3/12 (25) | 7/11 (64) | 0/2 (0) |
| Mouth touch | 12/25 (48) | 1/10 (10) | 7/11 (64) | 0/2 (0) |
| Drinking | 9/19 (47) | 2/12 (17) | 5/11 (45) | 0/1 (0) |
| Chewing | 8/24 (33) | 3/10 (30) | not tested | not tested |

neuronal responses to foods were obtained in two ways. Firstly, foods were presented using the electromagnetic shutter during the performance of the visual discrimination task. Lick responses to foods presented in this way were reinforced. Secondly, in clinical tests foods and juice (S+) and saline (S–) filled syringes were presented and delivered to the monkeys through an aperture in the primate chair. In these tests, lick responses were irrelevant and the monkeys learned not to make such responses. In some experiments the lick tube was removed

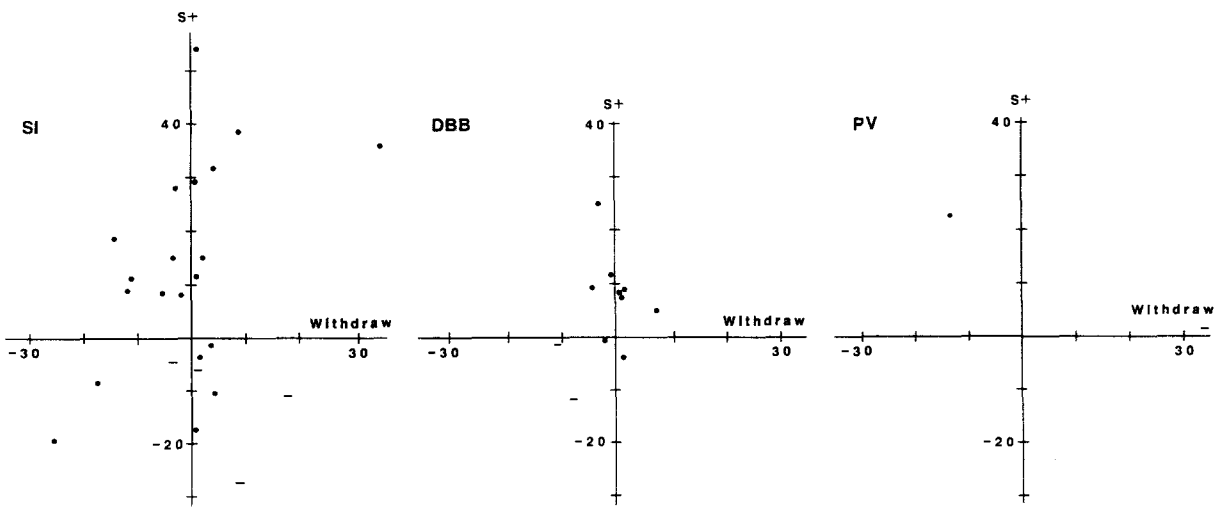


Fig. 9. A comparison of the responses to the sight and withdrawal of the S+ in the clinical tests. Each data point represents the mean responses of one neurone to sight (ordinate) and withdrawal of the S+ (abscissa). The spontaneous firing rate of each neurone is subtracted from the responses to show the magnitude and direction of the neuronal responses. Neurones are classified into *S+ neurones* (filled circles) and *S– neurones* (–). Many *S+ neurones* show a biphasic response to the stimuli: e.g. an increase in firing rate to the sight of the S+ and a decrease in firing rate at the withdrawal of the S+. The opposite pattern is found for *S– neurones*.

completely which had no effect on the neuronal responses.

During the clinical tests, counts of neuronal firing rate were taken during the sight and approach of stimuli toward the monkey, during the manipulation of the mouth with the stimulus, and during chewing and drinking. The responses of one neurone in the clinical tests are shown in Fig. 8. The neurone (No. 23) responded differentially in the visual discrimination task, and is quite typical (for comparison, see Table V). This neurone was antidromically driven at a constant latency (2.8 ms) following electrical stimulation of the motor cortex. Stimulation pulses triggered by spontaneous action potentials resulted in collision with the spontaneous spike, and this antidromic response identifies the neurone as belonging to the basal nucleus of Meynert.

The data for the clinical tests are presented in Table V. A neurone was taken to be responsive if the response to a stimulus was greater than a 50% change in the spontaneous firing rate of the neurone. From the data in Table V, several trends are apparent in the responses of the neurones. Firstly, it is clear that differential neurones respond well to the presentation of foods, presented either using the shutter and/or in clinical tests. Secondly, it is clear that *S+* and *S– neurones*, identified by their responses in the discrimination tasks, respond very differently to foods, and they are thus separated in the analysis. For example, the majority of *S+ neurones*

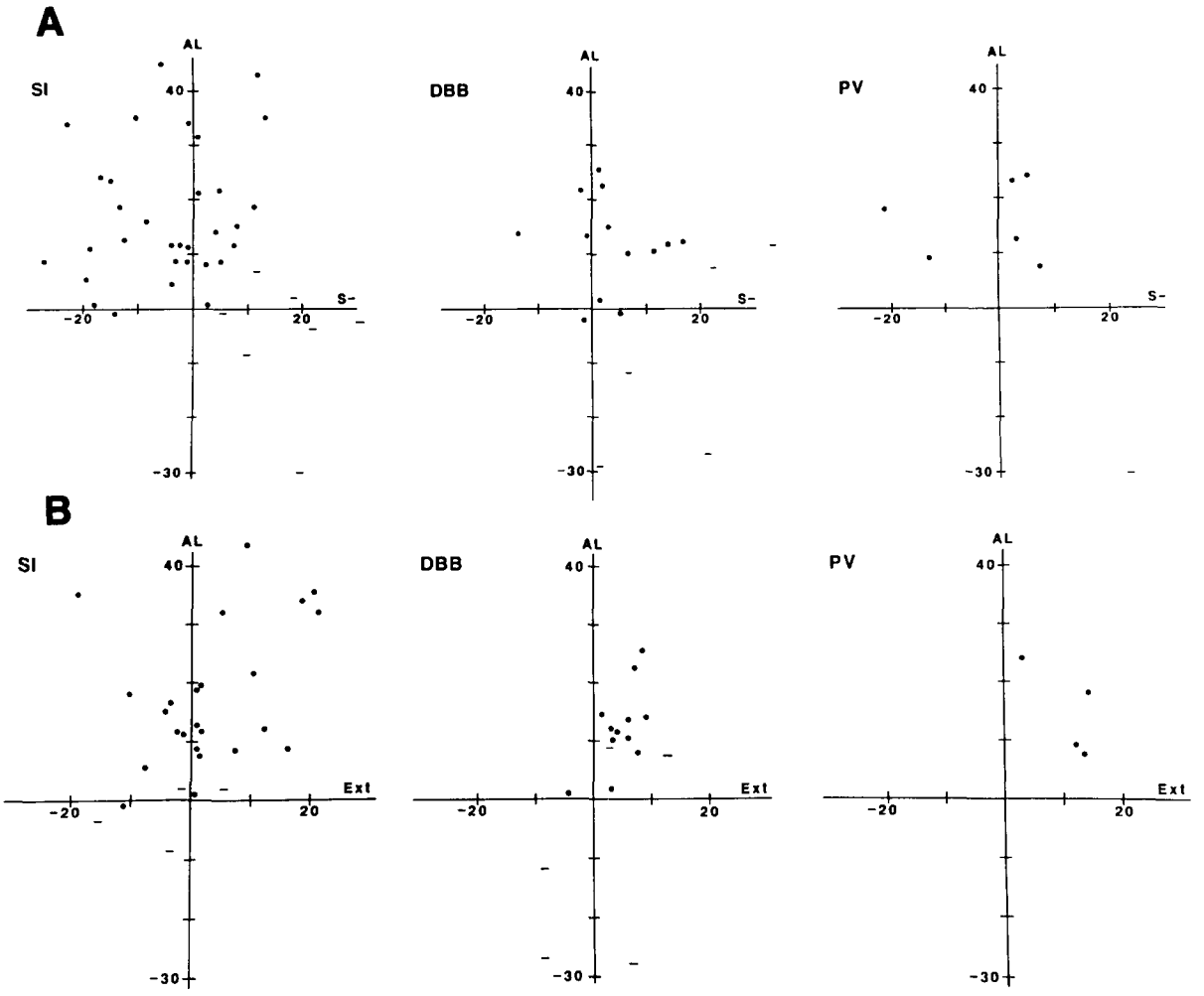


Fig. 10. A comparison of the responses to the auditory cue with the sight of the S– (A) and during extinction (B) in the clinical tests. In (A) each data point represents the mean responses of one neurone to the auditory cue (ordinate) and the sight of the S– (abscissa). Many *S+ neurones* show a biphasic response to the stimuli: e.g. an increase in firing rate to auditory cue and a decrease in firing rate at the sight of the S–. The opposite pattern is found for *S– neurones*. In (B) each data point represents the mean responses of one neurone to the auditory cue (ordinate) and extinction when juice is withheld (abscissa). Many *S+ neurones* show a biphasic response to the stimuli, e.g. an increase in firing rate to auditory cue and a decrease in firing rate during extinction. The opposite pattern is found for *S– neurones*. In this figure, the spontaneous firing rate of each neurone was subtracted from the responses to show the magnitude (spikes/s) and direction of the neuronal responses. Neurones are classified into *S+* (filled circles) and *S–* type (–). A regression line represents the responses of neurones in the DBB for which a significant correlation was obtained between the responses to the auditory cue and the extinction condition: DBB (*S+ neurones*: $y = 1.4x + 5.6$, $r = 0.66$, $P < 0.02$, $n = 12$).

respond to the sight of foods with increases in firing rate, while *S– neurones* show no change or a decrease in firing rate to the stimuli. Further, the sight of a saline-filled syringe elicits responses in *S– neurones* but not in *S+ neurones*. A third trend is discernible in the proportions of neurones that respond in the different phases of the protocol. The sight of reinforcing stimuli is most effective in eliciting a response, and particularly when the stimuli were presented in the task. Fewer neurons (Table V) were active, or were less responsive, when the monkeys were consuming the food, or drinking from the syringe (e.g. Fig. 8). Fourthly, the responses of differential neurons in the SI and DBB respond similarly during these tests.

Firing rate was also measured when the S+ syringe was removed from the monkey's mouth during drinking, to a distance of 30 cm. The syringe was not returned to the mouth, but was held in full view of the monkey for several seconds. In this test the firing rate of *S+ neurones* generally decreased, often below spontaneous firing rate, upon withdrawal of the syringe; in contrast, the firing rate of *S– neurones* remained unchanged or increased upon withdrawal of the syringe. The scatter plots in Fig. 9 compare the responses of differential neurones to the sight of the S+ and S– with the response to the withdrawal of the syringe. The responses of *S+ neurones* tend to cluster around the ordinate, indicating that these neurones respond with a decrease in firing rate during the withdrawal of the syringe. The responses of *S– neurones* are decreases to the sight of the S+ and in some cases, increases in response to syringe withdrawal. These response patterns were seen in the 3 regions of the basal forebrain.

*(5) Responses to non-food objects*

In some cases, the responses of differential neurones were measured when the monkeys were presented with, but were not able to obtain, non-food objects. The minority of neurones were active in this situation: 12/33 neurones (SI) and 0/9 neurones (DBB). It is possible that the monkey had learned that the presentation of objects was not followed by their delivery and that this may have determined the lack of responsiveness. In a situation in which objects could be obtained by arm movements made by the monkey, neurone No. 23 responded to the sight and during reaching for a non-food object and foods (Fig. 8).

*(6) Responses to auditory and gustatory cues*

The data obtained in the discrimination tasks and clinical tests indicate that basal forebrain differential neurones are responsive to visual stimuli that the monkeys have learned are reinforcing. A test was used that allowed the same neurones to be assessed for their responsiveness to auditory cues. During this test, an auditory cue (a click) was presented, signalling to the monkey that fruit juice was continuously available if licking was initiated and maintained for 15–30 s. Spontaneous firing rate was recorded before the cue and compared with the response to the cue and the following 2 s period. For some neurones, at some variable time during the continuous licking response, the flow of juice was turned off, and after another variable period of time, juice was turned on again without the auditory cue. This on/off procedure was repeated several times during the 30 s period. Following the auditory cue the monkey licked continuously for the 30 s period, having learned that cessation of juice was followed by the eventual reinstatement of the flow of juice. Thus an auditory cue was used to initiate licking and gustatory information indicated the presence or absence of juice to the monkey.

During these tests, most differential neurones (e.g. Fig. 8) responded to the auditory cue with a phasic burst of activity, the response usually declining during subsequent licking and the delivery of juice, and largely disappearing when juice was witheld — the 'extinction' condition. The response increased again when the flow of juice was reinstated. Fig. 10A shows the responses of all tested neurons to the auditory cue/juice delivery compared to the responses to the sight of the S– presented in

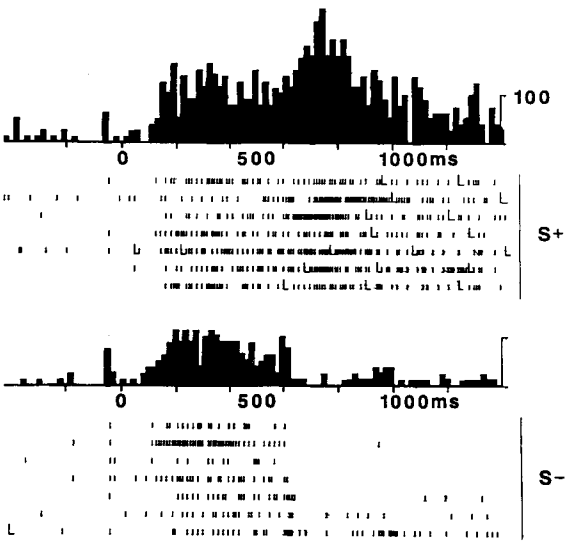


Fig. 11. Responses of a reinforcement-related neurone (No. 253) during the tone cue. The tone cue occurs at time 0, 500 ms before the presentation of the visual stimuli; each row represents the response to the presentation of the S+ or S–. The neurone (see Figs. 4 and 6) responds strongly during the tone cue and the S+, with a decrease in firing rate when the S– is presented. The L indicates the occurrence of the lick response. Note the erroneous lick response in the absence of a neuronal discharge in the intertrial interval during an S– trial. This event dissociates the neuronal response from the motor response. The scale at the right of the histogram represents a firing rate of 100 spikes/s.

the visual discrimination task. *S+ neurones* responded with increases in firing rate during the presentation of the auditory cue, with smaller responses or decreases in firing rate to the S–, and these points tend to cluster around the ordinate. In contrast, *S– neurones* respond more to the presentation of the S– than to the auditory cue, and tend to cluster around the abscissa. These patterns of responses were apparent in all 3 basal forebrain structures.

In Fig. 10B a comparison is made of the responses to the delivery of juice with the extinction condition when the juice is not delivered. Typically, *S+ neurones* are more responsive during the auditory cue and licking compared to the extinction condition, as shown by the clustering of the responses around the ordinate. In extinction the neurones are less active and may show a decrease in firing rate when juice is no longer delivered, even though the monkey continued to lick at the tube. *S– neurones* tend to respond with a decrease in firing rate to the auditory cue and during delivery of juice. These data suggest that a gustatory cue indicating the absence of reinforcement is able to modulate the responses of differential neurones. It is clear that lick responses, which occur both during the juice delivery and during extinction, are not responsible for the differential activity in these periods.

*(7) Responses during the tone cue*

The tone cue in the discrimination tasks was intentionally used to prepare the monkey for the presentation of the visual stimuli. Many differential neurones were responsive to this auditory stimulus. Fig. 11 shows the responses of one neurone (No. 253) during the presentation of the tone cue and the subsequent visual stimuli (see also Fig. 8). The neurone is active during the presentation of the tone and during the presentation of the S+; in contrast, the response to the S– is a decrease in firing rate. Note also that two erroneous lick responses occur in the intertrial interval before the presentation of the visual and auditory stimuli. These lick responses are not accompanied by neuronal activity and thus dissociate the behavioural and neuronal responses.

Fig. 12 represents the responses of individual neurones in the 3 basal forebrain regions to the tone cue compared to the stimuli used in the visual discrimination task. The data are separated into *S+* and *S– neurones*, and their respective responses to the tone cue. The data in this figure indicate that, for *S+ neurones*, the responses of many neurones to the tone cue and the S+ are approximately equal in magnitude. However, for *S– neurones* the response to the tone cue is, in general, a decrease in firing rate and substantially less than the response to the S–, similar to the decrease in response to the S+ for this type of neuron. These data points are clustered around the ordinate, indicating a response to the S–. Thus the neuronal responses to the tone cue resemble responses to the S+, but are dissimilar to the responses to the S–, as shown in Fig. 11. These two patterns of responses were observed for the three neuronal populations.

Response latencies to the tone cue are found in Table V. Responses to the tone cue were in most cases longer than the differential response latencies to the visual stimuli. It is important to note that auditory stimuli that

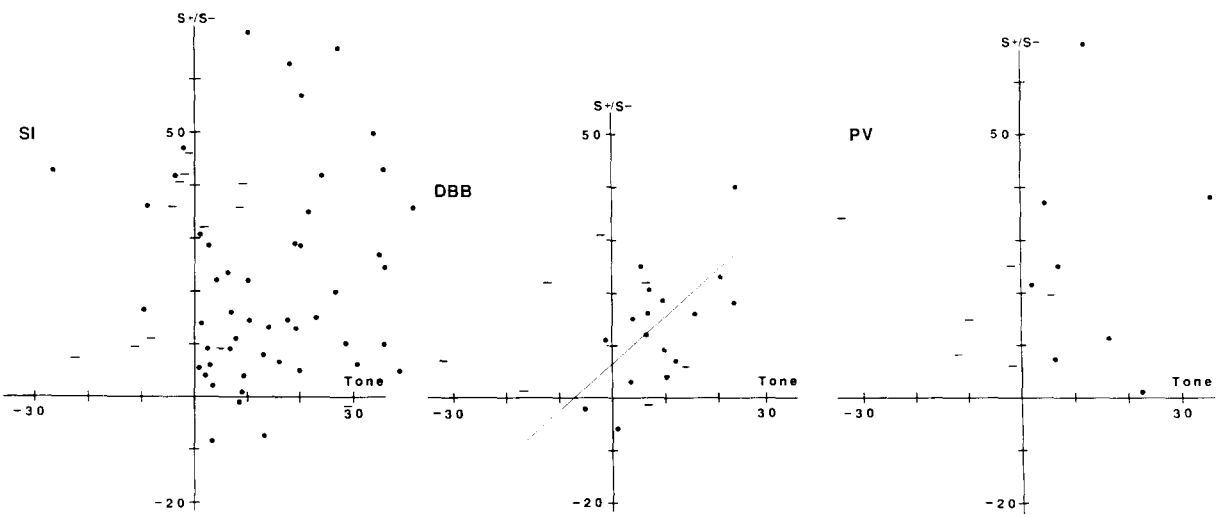


Fig. 12. A comparison of neuronal responses to the tone cue, the S+ and the S–. Each data point represents the mean responses of one neurone to the tone cue on the abscissa and the sight of the S+ (*S+* type) or the S– (*S–* type) on the ordinate. The spontaneous firing rate of each neurone was subtracted from the responses to show the magnitude and direction of the neuronal responses. Neurones are classified into *S+* type (filled circles), and *S–* type (–). Many *S+ neurones* respond to both the tone cue and the S+. In contrast, the *S– neurones* respond well to the S– stimulus, but respond with a decrease in firing rate to the tone cue. Thus the response to the tone cue is different for *S+ and S– neurones*. A regression line represents the responses of neurons in the DBB for which a significant correlation was obtained between the responses of the tone cue and the S+: DBB (*S+ neurones*: $y = 0.9x + 6.4$; $r = 0.67$, $P < 0.01$, $n = 17$).

did not signal reinforcement did not elicit neuronal responses. In the experiment a line printer was audible at the completion of every trial, but none of the reinforcement-related basal forebrain neurones recorded ever responded to this stimulus.

*(8) Arm movements and differential neuronal activity*

Neuronal activity was measured whilst the monkey made arm movements to obtain peanuts concealed in the hand of the experimenter (e.g. Fig. 8). The majority of the reinforcement-related neurones were responsive in this situation: 20/28 neurones in the SI, 7/9 neurones in the DBB and 2/4 neurones in the PV region. Typically, *S+ neurones* responded with increases in firing rate during reaching and licking initiated by an auditory cue. Conversely, *S– neurones* responded with decreases in firing rate during these motor acts.

*(9) Controls for arousal*

Typical basal forebrain neurones responded in all of the tasks in which reinforcement of the stimuli was manipulated. Although these neurones are generally responsive to reinforcing stimuli, they are not simply related to the arousal state of the monkey, nor to movements. Arousal was generated in several ways during the experiments. The unexpected delivery of saline is highly arousing to the monkeys, as judged by the ensuing vocalisations and body movement, but this event did not elicit a neuronal response, as shown by lick responses in the intertrial interval (e.g. Fig. 11), or erroneous responses[77]. Similarly, touching the limbs and trunk of the monkeys was an arousing stimulus, but the majority of neurones tested (SI: 13/16; DBB: 7/9) were unresponsive or showed a decrease in firing rate opposite to the responses to the reinforcing stimuli in the tasks. The 5 neurones responsive during the touch test were also active when the monkeys used arm movements to obtain reinforcement.

*(10) Other types of neuronal activity in the basal forebrain*

In addition to the reinforcement-related neurones, other types of neurones were observed in the basal forebrain regions (Table I). Two groups of neurones responded on the basis of the novelty or familiarity of the stimuli in recognition memory tasks and are described elsewhere[58,76]. A large proportion of basal forebrain neurones were active in relation to the tests, but were not differentially responsive to the reinforcing stimuli. A consistent finding was that many non-differential neurones responded during the presentation of the tone cue and/or the during the presentation of visual stimuli. These non-selective neurones responded similarly in this respect to the differential reinforcement-related neurones, but did not show statistically significant differential responses based on the reinforcement value of the stimuli. Approximately half of all neurones recorded in the basal forebrain were unresponsive in any of the tasks.

## DISCUSSION

The first major issue addressed by this study was the possibility that the responses of reinforcement-related basal forebrain neurones could be accounted for by a sensitivity to sensory properties such as the shape and colour of the reinforcing stimuli. We found that the responses of these basal forebrain neurones were not determined by the sensory properties and sensory modality of the reinforcing stimuli. The majority of neurones tested in the two versions of the visual discrimination tasks responded differentially in both tasks, demonstrating that the reinforcement value of the stimuli, and not their sensory properties, was important for the neuronal response. This conclusion is supported by the finding[77] that the *same* neurones responded differentially during the acquisition and reversal of a third discrimination task in which the monkey had to learn which of two stimuli signalled juice or saline, and to subsequently reverse this recently learned discrimination. In this task the neurones responded differentially to the same stimulus dependent upon its current learned reinforcement value. Furthermore, in a recognition memory task in which lick responses to novel stimuli elicited saline, and responses to the *same* stimuli shown as familiar elicited juice, the same reinforcement-related neurones responded differentially to novel and familiar presentations of the *same* stimuli on the basis of their reinforcement value. In the clinical tests, these neurones responded to foods and to syringes the monkey had learned were used to deliver fruit juice, but not to syringes used for the delivery of saline. Auditory stimuli that signalled the availability of juice also elicited neuronal responses, further strengthening the conclusion that the reinforcement-related neuronal responses were not determined by the sensory properties or even the sensory modality of the stimuli. These differential neurones also responded to a tone cue used to signal the onset of the trial and during certain mouth and arm movements which the monkey used to obtain reinforcement. The differential neurones were found in the SI, the DBB and in the PV region, and the responses of the neurones in the three different regions were similar in most respects. These data indicate that the basal forebrain is part of, or has access to mechanisms that allow monkeys to learn that previously unrelated stimuli and responses, selected by an experimenter, can be used to obtain reinforcement.

The activity of neurones with reinforcement-related activity is dissociable from arousal. Both the S+ and S– syringes generate arousal and movement, eliciting approach and avoidance behaviours respectively. During training the monkeys were able to reach for the S+ to obtain juice, while the response to the S– was a turning of the head and body away from this stimulus. Although all the discriminative stimuli used in the tasks were arousing for the monkeys, the neurones responded differentially to these stimuli, depending upon their current reinforcement value. Further, arousing stimuli in general did not elicit neuronal responses: the presentation of faces, the manipulations of the trunk and limbs, the ingestion of saline on error trials and the consumption of foods were not effective in eliciting neuronal responses. Indeed, neuronal responses were largest when the monkey prepared for, or was viewing the reinforcer, not when reinforcement was being consumed. These responses appeared as phasic bursts at the presentation of visual and auditory reinforcing stimuli.

Similarly, the differential neuronal responses can be dissociated from movements. The differential neuronal responses to the S+ and the S– occurred in the clinical tests in which lick responses were not made and were irrelevant for the delivery of the reinforcer. Indeed, in both the discrimination tasks and the clinical tests the maximal responses occurred at the sight of the stimulus, preceding the delivery of food or juice by up to several seconds. Movements also occurred in the absence of neuronal activity: neuronal responses did not accompany erroneous lick movements occurring in the intertrial interval; erroneous lick responses on S– trials were often not accompanied by neuronal responses; the extinction phase of the licking tests was not accompanied by neuronal activity although the monkey licked continuously; and movements made after the ingestion of saline were not associated with neuronal activity. Conversely, differential neuronal activity occurred in the absence of movements: differential neuronal responses occurred at least 150 ms prior to accurate lick responses, especially when the monkey had consumed large quantities of juice and in some cases failed to make a behavioural response to the S+; some neurones responded during both mouth and arm movements and it is unlikely that these neurones could control the two sets of muscles independently. Eye movements do not account for differential neuronal activity, as described elsewhere[77].

Although movements can be dissociated from differential responses, we found that differential neurones were active when the monkeys made mouth and arm movements to obtain reinforcement. Certain neurones in the lateral hypothalamus are responsive during bar pressing for food[40,41] as well as to the sight of food[16], and other studies have shown that basal forebrain neurones respond strongly when rats attempt to retrieve food[19,35]. However, the likelihood of obtaining reinforcement, rather than movement per se, appears to be crucial for the occurrence of the neuronal response, as conclusively shown by Richardson et al.[49] who found that basal forebrain neurones are active even when monkeys must inhibit behavioural responses in order to obtain reinforcement.

The differential response latencies reported here agree with a previous study[56]. These values, obtained from reinforcement-related neurones, should be distinguished from the response latencies of non-differential basal forebrain neurones at the presentation of visual and auditory stimuli, and which often precede differential responses latencies. The onset latencies of non-differential neurones ranged from 100 to 150 ms, comparable to the values reported by Mitchell et al.[38] for visual stimuli.

*The nature of effective reinforcers*

The second major question addressed by this study was whether differential neurones are active in relation to both liquid and solid foods, or only to one type of reinforcer. We found that these two types of reinforcer were equally effective at eliciting differential neuronal activity, as also found in a recent study of hypothalamic neurones[16]. Travis and Sparks[66] found that neurones located at the border of the internal capsule and globus pallidus responded differentially to two cues signalling food or electric shock; and reinforcement-related neurones responding to the S– in a visual discrimination task also responded to a stimulus that the monkey had learned delivered an aversive puff of air to the face[56]. These observations suggest that the responses of reinforcement-related neurones reflect the dimension of reward and aversion, rather than the encoding of specific properties, such as sweetness or texture, of the stimuli. However, certain neurones may respond selectively to the sight of food or to stimuli used to deliver juice, as described by Rolls et al.[56].

Feeding and drinking are controlled, in part independently, by specific mechanisms sensitive to factors such as blood sugar and angiotensin. However, the reinforcement-related neurones described here responded during both feeding and drinking, and thus are likely to play a general role in the control of motivated behaviour. Indeed, it is possible that these neurones mediate other, non-consummatory types of behaviour in which the basal forebrain plays a role, as shown by the effects of electrical stimulation in rats and monkeys, which can elicit feeding, drinking, vocalisation, the acquisition of non-food objects and object-carrying, nest-building, maternal and hoarding behaviour[26,45,52,53], sometimes from the same

electrode site[67]. Electrical stimulation of the basal forebrain does not appear to elicit hunger per se, for ingested food and objects are stored in the cheek pouches, rather than being eaten[53]. The stimulation appears to engage prepotent behavioural responses modulated by the current sensory environmnent. Thus it is possible that reinforcement-related neurones might respond to non-food reinforcers when monkeys are placed in a situation in which other forms of motivated behaviour are required.

In future experiments, it will be important to determine the range of motivated behaviours in which basal forebrain neurones are responsive. One reason for this is the necessity to establish how the loss of these neurones might affect behaviour in patients with Alzheimer's disease. It is likely that the reinforcement-related neurones form part of the basal nucleus of Meynert, and this structure is known to be damaged in Alzheimer's disease. Given the global nature of the cognitive deficits in this disease, it would be expected that the basal nucleus of Meynert plays a role in many types of behaviour, e.g. in the response to novelty and familiarity, as well as in the control of regulatory functions such as feeding or drinking. Indeed, neurones responding specifically on the basis of stimulus novelty and familiarity are observed in the basal forebrain[58,76]. The present experiments found that a minority of neurones tested were responsive to the presentation of non-food objects, as previously reported[55]. However, it is possible that this lack of responsiveness to objects is due to the experimental condition that the monkeys were unable to obtain the objects which were presented to them; we found that during drinking, when the S+ was withdrawn from the monkey making reinforcement unavailable, the neurones ceased to respond to this stimulus as well. Mitchell et al.[37] have reported that basal forebrain neurones do respond to non-food objects when the monkey is able to obtain them. These data suggest that the reinforcement-related neurones may well be active in situations when the monkeys are working for non-food reinforcers.

*Responses of basal forebrain neurones to stimuli in different sensory modalities*

A third issue addressed by this study concerned the responsiveness of basal forebrain neurones to stimuli in different sensory modalities. We found that motivationally relevant stimuli in both the visual and auditory modalities activate reinforcement-related neurones. An auditory cue signalling the availability of juice elicited responses from the neurones: further, differential neurones also responded to the auditory tone used to cue the monkey to the impending presentation of a reinforcing visual stimulus. It should be noted that other auditory stimuli that were not correlated with reinforcement (e.g. a line printer) never elicited neuronal responses. Thus only auditory stimuli that signalled the availability or proximity of reinforcement elicited responses from differential neurones. It is also possible that gustatory information influences these neurones as neuronal firing rate changed when the flow of juice was terminated in the auditory cued licking tests. Several studies[8,11,16,49] have observed neurones that respond to the sight of and at the delivery of reinforcers, and Mitchell et al.[38] have observed basal forebrain neurones responsive to visual and tactile stimuli that monkeys have learned are important in obtaining reinforcement. The present results show that stimuli in both the visual and auditory modalities are able to activate reinforcement-related neurones, provided that the monkey has learned that the stimulus signals the availability of reinforcement.

*The distribution of reinforcement-related neurones*

The fourth issue addressed by this study concerned the hypothesis that reinforcement-related neurones would be found in the SI, the DBB and the PV region. There were a number of reasons for this hypothesis. Although a great deal of evidence has shown that the hypothalamus is important in the control of feeding, it is known that adjacent structures may also serve related functions. Several studies have provided evidence of functional and anatomical similarities between the regions of the basal forebrain. Firstly, it is known that electrical stimulation of the SI, the DBB and the hypothalamus produces synergistic motivational acts such as feeding, drinking and supports self-stimulation behaviour[4,53,57,59], and that neurones responsive to the sight of food are found in the hypothalamus and substantia innominata[55]. Fibre systems traversing the basal forebrain appear to provide part of the anatomical substrate for reinforcement, with cell bodies in the SI, the DBB and the hypothalamus contributing to this fibre system[18]. Secondly, it has been shown that the cell bodies constituting the basal nucleus of Meynert are located throughout the basal forebrain and are embedded within the fibres of the medial forebrain bundle[25,33]. Thirdly, Aigner et al.[1] have found that combined lesions of the SI and the DBB are necessary to produce a deficit in the performance of an object recognition task, suggesting that these structures work in a complementary fashion. The finding that differential reinforcement-related neurones are distributed throughout the basal forebrain also suggests that the functions of these 3 regions are similar, at least with respect to the performance of the visual discrimination tasks. The data provided in the tables show that there are no striking differences in the proportions of responsive neurones and their properties recorded in the 3 regions.

However, reinforcement-related neurones are not found in all brain structures. Studies in the amygdala have found neurones that respond differentially in visually discrimination tasks, but they differ from basal forebrain neurones in terms of their responses to the tone cue, in the incidence of responses to the S+ compared to the S–, and in their responses in reversal and recognition memory tasks[71,74].

*Responses to the tone cue: implications for the basis of the neuronal responses*

Many differential neurones responded to the tone cue. These responses resembled those elicited by the visual stimuli signalling juice availability, but differed from the responses elicited by aversive stimuli, even though the tone cue does not specifically signal availability of juice; it is equally correlated with the presentation of the S+ (juice) and S– (saline) stimuli. However, the tone cue, like the S+, signals an increase in the proximity of reinforcement and thus some probability of juice delivery, whereas the S– unconditionally signals the availability of saline. Thus the neuronal response to the tone cue appears to reflect the same state as that elicited during the presentation of the S+.

The neuronal responses to the discriminative stimuli and to the tone cue suggest that the activity of the differential neurones reflects the expected availability of reinforcement brought about through learning the task contingencies and the preparation for the behavioural responses. This is indicated by other observations. For example, in clinical tests in which the S+ is withdrawn from the monkey, the neuronal response to this event is opposite to that elicited by the presentation of S+. In both cases, the S+ is in full view, but the monkey has learned that reinforcement is no longer available when the S+ is withdrawn. A second example is the finding that relatively few neurons were active during the consumption of food compared to the visual presentations of the stimuli. This finding is in agreement with the obervation that hypothalamic neurones are not in all cases responsive during eating[55], and suggests that expectation of the reinforcer and preparation for a response is the basis for the neuronal responses.

*The functional outputs of the reinforcement-related neurones*

The three regions of the basal forebrain appear to provide very similar functions, at least as far as the present tests have been able to determine. A complete account of how these neurones affect behaviour depends upon a knowledge of the way in which the neuronal responses affect efferent structures. Some evidence has been presented to show that the reinforcement-related neurones described in this paper are part of the cholinergic basal nucleus of Meynert: the location of the recorded neurones is similar to the basal nucleus as determined in anatomical studies; and the demonstration that reinforcement-related neurones are driven antidromically by cortical stimulation is consistent with this hypothesis. Thus the output of some reinforcement-related neurones is directed to the cerebral cortex (see also ref. 54).

Anatomical studies have demonstrated basal forebrain projections to many cortical regions[12,27] and that there is a crude topography between cortex and region of basal forebrain[33,43]. As reinforcement-related neurones were found throughout the basal forebrain, the output of these neurones, reflecting the expected availability of reinforcement brought about through learning, may be directed at diverse cortical regions with sensory, motor or associative functions. As such, *the phasic responses of basal forebrain neurones to reinforcing stimuli may provide an enabling mechanism that complements the specific functional role of cortex that receives this output.* Such a function would be expected on the basis of studies that have shown that the cholinergic innervation of cortical neurones acts to facilitate their responsiveness to other inputs[6].

Studies in the visual and somatosensory systems have shown that the receptive field properties of cortical neurones are modulated by ACh[29,63]. There is also substantial evidence that basal forebrain projections facilitate motor responses: hypothalamic stimulation potentiates motor reflexes elicited by stimulation of the motor cortex or the superior laryngeal nerve[39,69] and will powerfully increase conditioned neuronal responses to a labella tap[79]. These effects may be mediated by direct projections as electrical stimulation of the basal forebrain elicits monosynaptic, orthodromic responses in cortical neurones whose activity is related to behavioural responses and which project through the pyramidal tract[3,9,17,41]. It is even possible that these effects are mediated by the release of ACh in cortex. Aou et al.[2] applied ACh to neurones in the orbitofrontal cortex of behaving monkeys, finding that the majority of neurons activated by ACh were related to bar press responses made by the monkeys. In other studies, Lamour et al.[28] showed that neurones in somatosensory cortex that projected through the pyramidal tract were particularly likely to respond to ACh. Thus it is possible that the activity of reinforcement-related neurones facilitates or enables certain responses, particularly learned responses, to be carried out in situations when monkeys are motivated to achieve a goal and when the information available suggests that reinforcement is probable. The role of basal forebrain neurones in memory function may be a facilitation of the

learning process, as indicated by the finding that lesions of the basal forebrain impair the performance and learning of visual discrimination tasks[50,51]. However, it is unlikely that the basal forebrain is solely responsible for discrimination learning, as lesion deficits are neither total nor permanent, and there is abundant evidence that structures afferent to the basal forebrain play a major role in learning and memory and may be responsible for the learning reflected in the activity of basal forebrain neurones.

*The role of the afferent structures of the basal forebrain*

The data from anatomical and neuropsychological studies indicate that the basal forebrain is the recipient of information provided by limbic cortical and subcortical structures, particularly the ventromedial regions of the temporal and frontal lobes[73,76,77], regions known to receive information from several sensory systems[24] and to be involved in object recognition[36]. Indeed, visual discrimination performance in this study required such mechanisms, as the discriminanda displayed on the video monitor differed in their shape, while colour, size and brightness were equated. It is notable that many reinforcement-related neurones are distributed around fibre tracts such as the anterior commissure, internal capsule and ansa peduncularis, as are cells of the basal nucleus of Meynert[22,33,42]. The proximity of differential neurones to these fibre tracts may indicate possible functional connections with temporal and prefrontal structures and provide a basis for the neuronal responses to both visual and auditory reinforcing stimuli in the basal forebrain.

Ventromedial structures projecting to the basal forebrain are known to be involved in the mediation of motivated behaviour. In humans, lesions of the orbital and medial surface of the prefrontal cortex produce profound deficits in motivation such as generalised apathy, in social and sexual disorders, and often in conjunction with memory deficits[14,30,31,64]. Damage to the medial temporal lobes produces similar symptoms, as shown in the patient H.M., whose amnesia is accompanied by docility, impairments in regulating feeding and drinking, and a deficiency in responsiveness to pain[21].

Lesion studies in monkeys have shown that the orbital and medial prefrontal cortex and the amygdala are important for the performance of visual discrimination tasks and for the reversal of such tasks[23]. Neuronal activity related to the performance of these tasks has been recorded in both the amygdala and orbitofrontal cortex[61,65,74,75], and these neurones are characterised by the specificity of the stimuli to which they respond, contrasting with the broad range of stimuli to which reinforcement-related neurones in the basal forebrain respond. Two further differences are that basal forebrain neuronal responses change when the reinforcement contingency changes in a reversal task, and these neurones also respond differentially to novel and familiar stimuli when this information can be used to obtain reinforcement[74,77]. In contrast, amygdala neurones that respond differentially in a visual discrimination task do not show reversal or show differential responses to novel and familiar stimuli. It is possible that the responses of basal forebrain neurones to a wide range of reinforcing stimuli result from a concentration of inputs from the selectively responsive neurones in orbital cortex and amygdala.

The ventromedial prefrontal cortex is a major afferent of the basal forebrain[34,60,76] and contributes to the mechanisms of reinforcement. Stimulation and lesion studies in monkeys have indicated the importance of this region for social and sexual behaviour[13,46], vocalisation[26,32,52] and feeding and drinking[53]. Thus the range of motivated behaviours to which the ventromedial prefrontal cortex contributes is similar to that of the basal forebrain, a condition necessary for the hypothesis that the responses of basal forebrain neurones are, in part, due to inputs from ventromedial limbic cortex, and the proposition that reinforcement-related neurones participate in many forms of motivated behaviours.

*Reinforcement-related neuronal activity and Alzheimer's disease*

The activity of neurones in the basal forebrain reflects the learned reinforcement value of sensory stimuli and possibly the intention to respond to these stimuli. Reinforcement-related neurones do not respond to particular reinforcers, but to stimuli useful in obtaining food or juice, and these neurones also respond appropriately to non-appetitive stimuli signalling aversive shock and air puff[56,66]. These reinforcement-related neurones may respond to a wide range of appetitive and non-appetitive stimuli, but this remains to be tested. However, the available data suggest that the function of reinforcement-related neurones is an enabling, facilitating process directed to diverse, functionally specific cortical mechanisms.

This functional analysis of the basal forebrain is in general consistent with the reduced competence of patients with Alzheimer's disease. Although these patients are not obviously impaired in their ability to regulate feeding and drinking, they are impoverished in a wide range of cognitive functions, with a reduction in information processing speed[15]. It is conceivable that a loss of cortical facilitation mediated by the basal forebrain could result in the deterioration of cognitive function found in the disease. In addition, it is likely that

damage to the ventromedial regions of the temporal and frontal lobes is particularly important for the deficits observed in Alzheimer's disease, with damage to other association areas such as the parietal cortex contributing to the deficits[44]. As noted in this paper, the limbic cortical regions provide the input to the basal forebrain, and damage to these regions results in disordered cognitive and emotional behaviour resembling that seen in patients with Alzheimer's disease. These disordered mechanisms seem to be paralleled by the nature of the information reflected in the activity of basal forebrain neurones, and thus we suggest that the responses of these neurones, based on information from limbic cortical regions, provide a facilitation of diverse functions throughout the cerebral cortex, and that the basal forebrain participates in many different types of learned and motivated behaviour.

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REFERENCES

1 Aigner, T., Mitchell, S., Aggleton, J.P., DeLong, M., Strubble, R., Wenk, G., Price, D. and Mishkin, M., Recognition deficit in monkeys following neurotoxic lesions of the basal forebrain, *Soc. Neurosci. Abstr.*, 10 (1984) 116.11.
2 Aou, S., Oomura, Y. and Nishino, H., Influence of acetylcholine on neuronal activity in monkey orbitofrontal cortex during bar press feeding task, *Brain Research*, 275 (1984) 178–182.
3 Aou, S., Oomura, Y., Woody, C.D. and Nishino, H., Effects of behaviorally rewarding hypothalamic electrical stimulation on intracellularly recorded neuronal activity in the motor cortex of awake monkey, *Brain Research*, 439 (1988) 31–38.
4 Brady, J.V., Temporal and emotional factors related to electrical self-stimulation of the limbic system. In H.H. Jasper (Ed.), *Reticular Formation of the Brain*, Little and Brown, Boston, 1958, pp. 689–703.
5 Briese, E. and Olds, J., Reinforcing brain stimulation and memory in monkeys, *Exp. Neurol.*, 10 (1964) 493–508.
6 Brown, D.A., Slow cholinergic excitation — a mechanism for increasing neuronal excitability, *Trends Neurosci.*, (1983) 302–307.
7 Bruning, J.L. and Kintz, B.L., *Computational Handbook of Statistics*, 2nd edn., Scott/Foresman, Glenview, Illinois, 1977.
8 Burton, M.J., Rolls, E.T. and Mora, F., Effects of hunger on the responses of neurones in the lateral hypothalamus to the sight and taste of food, *Exp. Neurol.*, 51 (1976) 668–677.
9 Canedo, A., Pericruciate cortex unit activity during intentional movement. Effect of subcortical electrical stimulation, *Brain Research*, 247 (1982) 269–276.
10 Coyle, J.T., Price, D.L. and DeLong, M.R., Alzheimer's disease: a disorder of cortical cholinergic innervation, *Science*, 219 (1983) 1184–1190.
11 DeLong, M.R., Activity of pallidal neurons during movement, *J. Neurophysiol.*, 34 (1971) 414–427.
12 Divac, I., Magnocellular nuclei of the basal forebrain project to the neocortex, brain stem, and olfactory bulb. Review of some functional correlates, *Brain Research*, 93 (1975) 385–388.
13 Dua, S. and MacLean, P.D., Localisation for penile erection in medial frontal lobe, *Am. J. Physiol.*, 207 (1964) 1425–1434.
14 Eslinger, P.J. and Damasio, A.R., Severe disturbance of higher cognition after bilateral frontal lobe ablation: Patient EVR, *Neurology*, 35 (1985) 1731–1741.
15 Flicker, C., Ferris, S.H., Crook, T., Bartus, R.T. and Reisberg, B., Cognitive function in normal aging and early dementia. In J. Traber and W.H. Gispen (Eds.), *Senile Dementia of the Alzheimer type*, Springer, Berlin, 1985, pp. 269–282.
16 Fukuda, M., Ono, T., Nishino, H. and Nakamura, K., Neuronal responses in monkey lateral hypothalamus during operant feeding behavior, *Brain Res. Bull.*, 17 (1986) 879–884.
17 Funahashi, S., Responses of monkey prefrontal neurons during a visual tracking task reinforced by substantia innominata self-stimulation, *Brain Research*, 276 (1983) 267–276.
18 Gallistel, C.R., Gomita, Y., Yadin, E. and Campbell, K.A., Forebrain origins and terminations of the medial forebrain bundle metabolically activated by rewarding stimulation or by reward-blocking doses of pimozide, *J. Neurosci.*, 5 (1985) 1246–1261.
19 Hamburg, M.D., Hypothalamic unit activity and eating behavior, *Am. J. Physiol.*, 220 (1971) 980–985.
20 Heath, R., Electrical self-stimulation of the brain in man, *Am. J. Psychiatr.*, 120 (1963) 571–577.
21 Hebben, N., Corkin, S., Eichenbaum, H. and Shedlack, K., Diminished ability to interpret and report internal states after bilateral medial temporal resection: case H.M., *Behav. Neurosci.*, 99 (1985) 1031–1039.
22 Hedreen, J.C., Struble, R.G., Whitehouse, P.J. and Price, D.L., Topography of the magnocellular basal forebrain system in human brain, *J. Neuropathol. Exp. Neurol.*, 43 (1984) 1–21.
23 Jones, B. and Mishkin, M., Limbic lesions and the problem of stimulus-reinforcement associations, *Exp. Neurol.*, 36 (1972) 362–377.
24 Jones, E.G. and Powell, T.P.S., An anatomical study of converging sensory pathways within the cerebral cortex of the monkey, *Brain*, 93 (1970) 793–820.
25 Jones, E.G., Burton, H., Saper, C.B. and Swanson, L.W., Midbrain, diencephalic and cortical relationships of the basal nucleus of Meynert and associated structures in primates, *J. Comp. Neurol.*, 167 (1976) 385–420.
26 Jurgens, U., Reinforcing concomitants of electrically elicited vocalisations, *Brain Research*, 26 (1976) 203–214.
27 Kievet, J. and Kuypers, H.G.J.M., Basal forebrain and hypothalamic connections to prefrontal and parietal cortex in the rhesus monkey, *Science*, 187 (1975) 660–662.
28 Lamour, Y., Dutar, P. and Jobert, A., Excitatory effect of acetylcholine on different types of neurons in the first somatosensory neocortex of the rat: laminar distribution and pharmacological characteristics, *Neuroscience*, 7 (1982) 1483–1494.
29 Lamour, Y., Dutar, P., Jobert, A. and Dykes, R.W., An iontophoretic study of single somatosensory neurons in rat granular cortex serving the limbs: a laminar analysis of glutamate and acetylcholine effects on receptive-field properties, *J. Neurophysiol.*, 60 (1988) 725–750.
30 Lhermitte, F., Pillon, B. and Serdaru, M., Human autonomy and the frontal lobes. Part 1: imitation and utilisation behavior: a neuropsychological study of 75 patients, *Ann. Neurol.*, 19 (1986) 326–334.
31 Luria, A.R., *The Working Brain*, Basic Books, New York, 1973.
32 McLean, P.D. and Newman, J.D., Role of midline frontolimbic cortex in production of the isolation call of squirrel monkeys, *Brain Research*, 450 (1988) 111–123.
33 Mesulam, M.-M., Mufson, E.J., Levey, A.I. and Wainer, B.H., Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata) and hypothalamus in the rhesus monkey, *J. Comp. Neurol.*, 214 (1983) 170–197.
34 Mesulam, M.-M. and Mufson, E.J., Neural inputs into the

nucleus basalis of the substantia innominata (CH4) in the rhesus monkey, *Brain*, 107 (1984) 257–274.
35 Mink, J.W., Sinnamon, H.M. and Adams, D.B., Activity of basal forebrain neurons in the rat during motivated behaviors, *Behav. Brain Res.*, 8 (1984) 85–108.
36 Mishkin, M., A memory system in the monkey, *Philos. Trans. R. Soc. London Ser. B*, 298 (1982) 89–95.
37 Mitchell, S.J., Richardson, R.T., Baker, F.H. and DeLong, M.R., Electrophysiological and functional characteristics of neurons in the nucleus basalis of Meynert in macaque monkeys, *Soc. Neurosci. Abstr.*, 8 (1982) 57.14.
38 Mitchell, S.J., Richardson, R.T., Baker, F.H. and DeLong, M.R., The primate nucleus basalis of Meynert: neuronal activity related to a visuomotor tracking task, *Exp. Brain Res.*, 68 (1987) 506–515.
39 Murphy, J.P. and Gellhorn, E., The influence of hypothalamic stimulation on cortically-induced movements and on action potentials of the cortex, *J. Neurophysiol.*, 8 (1945) 339–364.
40 Ono, T., Oomura, Y., Sugimori, M., Nakamura, T., Shimizu, N., Kita, H. and Ishibashi, S., Hypothalamic unit activity related to lever pressing and eating in the chronic monkey. In D. Novin, W. Wyrwicka and G. Bray (Eds.), *Hunger: Basic Mechanisms and Clinical Implications*, Raven, New York, 1976, pp. 159–170.
41 Oomura, Y., Ono, T., Ocha, M., Nishino, H., Shiizu, N., Ishibashi, S., Kita, H., Sasaki, K., Nicolaidis, S. and Van Atta, L., Neuronal activities in feeding behavior of chronic monkeys. In Y. Katsuki, M. Sato, S.F. Takagi and Y. Oomura (Eds.), *Food Intake and Chemical Senses*, Tokyo University Press, 1977, pp. 505–524.
42 Parent, A. and DeBellefeuille, L., Organisation of efferent projections from the internal segment of the globus pallidus in the primate revealed by the fluorescence retrograde labeling method, *Brain Research*, 245 (1982) 201–213.
43 Pearson, R.C.A., Gatter, K.C., Brodal, P. and Powell, T.P.S., The projections of the basal nucleus of Meynert upon the neocortex in the monkey, *Brain Research*, 259 (1983) 132–136.
44 Pearson, R.C.A., Esiri, M.M., Hiorns, R.W., Wilcock, G.K. and Powell, T.P.S., Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer's disease, *Proc. Natl. Acad. Sci. U.S.A.*, 82 (1985) 4531–4534.
45 Phillips, A., Cox, V.C., Kakolewski, J.W. and Valenstein, E.S., Object-carrying by rats: an approach to the behavior produced by brain stimulation, *Science*, 166 (1969) 903–905.
46 Raleigh, M.J. and Steklis, H.D., Effects of orbitofrontal and temporal neocortical lesions on the affiliative behavior of Vervet monkeys, *Exp. Neurol.*, 73 (1981) 378–389.
47 Reeves, A.G. and Plum, F., Hyperphagia, rage, and dementia accompanying a ventromedial hypothalamic neoplasm, *Arch. Neurol.*, 20 (1969) 616–623.
48 Richardson, R.T. and DeLong, M.R., Nucleus basalis of Meynert neuronal activity during a delayed response task in monkey, *Brain Research*, 399 (1986) 364–368.
49 Richardson, R.T., Mitchell, S.J., Baker, F.H. and DeLong, M., Responses of nucleus of Meynert neurons in behaving monkeys. In C.D. Woody, D.L. Alkon and J.L. McGaugh (Eds.), *Cellular Mechanisms of Conditioning and Behavioral Plasticity*, Plenum Press, New York, 1988, pp. 161–173.
50 Ridley, R.M., Baker, H.F., Drewett, B. and Johnson, J.A., Effects of ibotenic acid lesions of the basal forebrain on serial reversal learning in marmosets, *Psychopharmacology*, 86 (1985) 438–443.
51 Ridley, R.M., Murray, T.K., Johnson, J.A. and Baker, H.F., Learning impairment following lesion of the basal nucleus of Meynert in the marmoset: modification by cholinergic drugs, *Brain Research*, 376 (1986) 108–116.
52 Robinson, B.W., Vocalisation evoked from forebrain in macaca mulatta, *Physiol. Behav.*, 2 (1967) 345–354.
53 Robinson, B.W. and Mishkin, M., Alimentary responses to forebrain stimulation in monkeys, *Exp. Brain Res.*, 4 (1968) 330–366.
54 Rolls, E.T., Neuronal activity related to the control of feeding. In S. Ritter and C.D. Barnes (Eds.), *Feeding Behaviour: Neural and Humoral Controls*, Academic Press, New York, 1986, pp. 163–190.
55 Rolls, E.T., Burton, M.J. and Mora, F., Hypothalamic neuronal responses associated with the sight of food, *Brain Research*, 111 (1976) 53–66.
56 Rolls, E.T., Sanghera, M.K. and Roper-Hall, A., The latency of activation of neurones in the lateral hypothalamus and substantia innominata during feeding in the monkey, *Brain Research*, 164 (1979) 121–135.
57 Rolls, E.T., Burton, M.J. and Mora, F., Neurophysiological analysis of brain-stimulation reward in the monkey, *Brain Research*, 194 (1980) 339–357.
58 Rolls, E.T., Perrett, D.I., Caan, A.W. and Wilson, F.A.W., Neuronal responses related to visual recognition, *Brain*, 105 (1982) 611–646.
59 Routtenberg, A., Gardner, E.L. and Huang, Y.H., Self-stimulation pathways in the monkey, macaca mulatta, *Exp. Neurol.*, 33 (1971) 213–224.
60 Russchen, F.T., Amaral, D.G. and Price, J.L., The afferent connections of the substantia innominata in the monkey, macaca fascicularis, *J. Comp. Neurol.*, 242 (1985) 1–27.
61 Sanghera, M.K., Rolls, E.T. and Roper-Hall, A., Visual responses of neurons in the dorsolateral amygdala of the alert monkey, *Exp. Neurol.*, 63 (1979) 610–626.
62 Schaltenbrand, G., The effects of stereotaxic electrical stimulation in the depth of the brain, *Brain*, 88 (1965) 835–840.
63 Sillito, A.M. and Kemp, J.A., Cholinergic modulation of the functional organisation of the cat visual cortex, *Brain Research*, 289 (1983) 143–155.
64 Talland, G.A., Sweet, W.H. and Ballantine Jr., T.H., Amnesic syndrome with anterior communication artery aneurysm, *J. Nerv. Ment. Dis.*, 145 (1967) 179–192.
65 Thorpe, S.J., Rolls, E.T. and Maddison, S., The orbitofrontal cortex: neuronal activity in the behaving monkey, *Exp. Brain Res.*, 49 (1983) 93–115.
66 Travis, R.P. and Sparks, D.L., Unitary responses and discrimination learning in the squirrel monkey: the globus pallidus, *Physiol. Behav.*, 3 (1969) 187–196.
67 Valenstein, E.S., Cox, V.C. and Kakolewski, J.W., Reexamination of the role of the hypothalamus in motivation, *Psychol. Rev.*, 70 (1970) 16–31.
68 Vincent, J.D., Arnauld, E. and Bioulac, B., Activity of osmosensitive single cells in the hypothalamus of the behaving monkey during drinking, *Brain Research*, 44 (1972) 371–384.
69 Weerasuriya, A., Bieger, D. and Hockman, C.H., Basal forebrain facilitation of reflex swallowing in the cat, *Brain Research*, 174 (1979) 119–133.
70 Whitehouse, P.J., Price, A.W., Struble, R.G., Clark, A.W., Coyle, J.T. and DeLong, M.R., Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain, *Science*, 215 (1982) 1237–1239.
71 Wilson, F.A.W., *Neuronal Activity Related to Novelty, Familiarity and Reinforcement*, D. Phil. Thesis, University of Oxford, 1985.
72 Wilson, F.A.W., Rolls, E.T., Yaxley, S., Thorpe, S.J., Williams, G.V. and Simpson, S.J., Responses of neurons in the basal forebrain of the behaving monkey, *Soc. Neurosci. Abstr.*, 10 (1984) 37.8.
73 Wilson, F.A.W., Riches, I.P. and Brown, M.W., Neuronal activity in the inferomedial temporal cortex compared with that in the hippocampal formation: implications for amnesia of medial temporal lobe origin. In C.D. Woody, D.L. Alkon and J.L. McGaugh (Eds.), *Cellular Mechanisms of Conditioning and Behavioral Plasticity*, Plenum Press, New York, 1988, pp. 313–328.
74 Wilson, F.A.W. and Rolls, E.T., Reinforcement-related neuronal activity in the basal forebrain and amygdala, *Soc. Neurosci. Abstr.*, 15 (1985) 160.1.

75 Wilson, F.A.W. and Rolls, E.T., Habituation and stimulus-specific neuronal responses recorded from the amygdala of the monkey, *Soc. Neurosci. Abstr.*, 17 (1987) 305.6.
76 Wilson, F.A.W. and Rolls, E.T., Neuronal responses related to the novelty and familarity of visual stimuli in the substantia innominata, diagonal band of Broca and periventricular region of the primate basal forebrain, *Exp. Brain Res.*, in press.
77 Wilson, F.A.W. and Rolls, E.T., Learning and memory is reflected in the responses of reinforcement-related neurons in the primate basal forebrain, *J. Neurosci.*, in press.
78 Woodward, R.R. and Goldsmith, P.L., *Cumulative Sum Techniques. Mathematical and Statistical Techniques for Industry*, ICI monographs, No. 3. Oliver and Boyd, Edinburgh, 1964.
79 Woody, C.D.., Kim, E. and Berthier, N.E., Effect of hypothalamic stimulation on unit responses recorded from neurons of sensorimotor cortex of awake cats during conditioning, *J. Neurophysiol.*, 49 (1983) 780–791.