

## RESPONSES OF STRIATAL NEURONS IN THE BEHAVING MONKEY. 1. HEAD OF THE CAUDATE NUCLEUS

E.T. ROLLS, S.J. THORPE and S.P. MADDISON

*Department of Experimental Psychology, Oxford University, South Parks Road, Oxford (U.K.)*

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### SUMMARY

The activity of 394 neurons in the head of the caudate nucleus and the most anterior part of the putamen was analyzed in 3 behaving rhesus monkeys in order to analyze the functions of this part of the striatum. Of these neurons, 64.2% responded in the tests used in relation to, for example, environmental events, movements made by the monkey, the performance of a visual discrimination, or during feeding. However, only relatively small proportions of these neurons had responses which were unconditionally related to visual (9.6%), auditory (3.5%), or gustatory (0.5%) stimuli, or to movements (4.1%). Instead, the majority of the responsive neurons had activity in relation to stimuli or movements which was conditional, in that the responses occurred in only some test situations, and were often dependent on the performance of a task by the monkeys. Thus, it was found in the visual discrimination task that 14.5% of the neurons responded during a 0.5 sec tone/light cue period which signalled the start of each trial; 31.1% responded in the period in which the discriminative visual stimuli were shown, with 24.3% of these responding more to either the visual stimulus which signified food reward or to that which signified punishment; and 6.2% responded in relation to lick responses. Yet these neurons typically did not respond in relation to the cue stimuli, to the visual stimuli, or to movements, when these occurred independently of the task, or when performance of the task was prevented. Comparably, of the neurons tested during feeding, 25.8% responded when the food was seen by the monkey, 6.2% when he tasted it, and 22.4% during a cue given by the experimenter that a food or non-food object was about to be

presented. However, only few of these neurons had responses to the same stimuli presented in different situations.

It is concluded that many neurons in the head of the caudate nucleus and the most anterior part of the putamen respond in relation to events which are used as cues to prepare for the performance of tasks, including feeding, in which movements must be initiated. Other neurons respond in relation to the stimuli used and the movements made in these tasks. However, the majority of these neurons do not have unconditional sensory or motor responses. It is therefore suggested that the anterior neostriatum contains neuronal mechanisms which are important in the process by which environmental cues are used in the preparation of behavioral responses, and in the initiation of particular behavioral responses made in particular situations to particular environmental stimuli. Deficits in the initiation of movements following damage to striatal pathways may arise in part because of interference with these functions of the anterior neostriatum.

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## INTRODUCTION

Despite rapid recent advances in knowledge of the anatomy of the striatum, and the disruption of behavior produced by damage to the striatum, the functions of the striatum are still poorly understood, with some investigators proposing motor [31], and others cognitive functions [12, 39]. To investigate striatal function, recordings have been made from single neurons in different regions of the striatum during the types of behavior known to be disrupted by striatal damage, as described in this and the following papers [6, 51]. The striatum can be divided into the neostriatum, consisting of the caudate nucleus and putamen, and the ventral striatum, consisting of the nucleus accumbens, olfactory tubercle and islands of Calleja [18]. In this paper the responses of neurons in the head of the caudate nucleus and the adjoining most anterior part of the putamen are described.

Anatomically, the neostriatum receives major inputs from almost all areas of the neocortex, and has major efferent connections with the globus pallidus, which in turn is connected to the ventral group of thalamic nuclei and thus to the motor and premotor cortex, and also has connections to brainstem motor regions [7, 17, 22, 23, 36, 37]. This pattern of connections suggests that the striatum provides one important route through which the cortex can influence motor structures [12, 39]. Studies in the monkey show that there is some topography in the cortico-striatal projection, in that for example the prefrontal cortex projects to the caudate nucleus, the motor cortex (area 4) and somatosensory cortex (areas 3, 1 and 2) project somatotopically to the putamen, and the temporal cortex projects to regions in the tail and head of the caudate nucleus [16,

21–23, 26–29, 56]. In view of the large input to the caudate nucleus from the prefrontal cortex [16, 28, 29], which includes projections from the ventral prefrontal cortex and orbitofrontal cortex to the ventral part of the head of the caudate nucleus [3, 61], in the present study the activity of neurons in the head of the caudate nucleus was recorded in situations (see methods) which included those known to activate orbitofrontal neurons [55], so that processing in these two connected regions could be directly compared. Although studies with autoradiography indicate that each region of the cortex projects to a wider region of the striatum [16, 61] than originally shown by the fiber degeneration method [22], nevertheless considerable topography is retained. For example, the fact that in the primate, the sensorimotor cortex projects almost exclusively to the putamen, and the prefrontal cortex almost exclusively to the caudate, suggests that the information processed by these different parts of the striatum may be different. It was therefore one of the aims of the present series of neurophysiological investigations [6, 44, 47, 48, 50, 51] to compare the activity of single neurons in different regions of the striatum under the same testing conditions. The striatum also receives projections from the substantia nigra, pars compacta, via the nigrostriatal bundle, which is largely dopaminergic, and from the intralaminar thalamic nuclei, and has a projection to the substantia nigra, pars reticulata.

Damage to the striatum produces effects which suggest that it is involved in orientation to stimuli and in the initiation and control of movement. Lesions of the dopamine pathways which deplete the striatum of dopamine lead to a failure to orient to stimuli, a failure to initiate movements which is associated with catalepsy, and to a failure to eat and drink [32]. In man depletion of dopamine in the striatum is found in Parkinson's disease, in which there is tremor and akinesia, that is a lack of voluntary movement [19]. Extensive lesions of the caudate nucleus itself in the cat lead to a syndrome in which the signs appear to be the opposite of those produced by nigrostriatal bundle damage, and include an increased tendency to orient to and 'lock on' to environmental stimuli, with little habituation to such stimuli, so that there is 'compulsory approach' to auditory and especially visual stimuli, and hyperactivity [57–60]. Similar effects have been reported in monkeys with smaller ablations [11]. There is some evidence that selective effects related to the function of the cortex from which a particular region of the caudate receives its major input can be produced by selective caudate lesions. For example, in the monkey, lesions of the anterodorsal part of the head of the caudate nucleus disrupted delayed alternation performance, which is also impaired by the corresponding cortical region, the dorsolateral prefrontal cortex. In contrast, lesions of the ventrolateral part of the head of the caudate nucleus (as of the orbitofrontal cortex which projects to it), impaired the reversal of a visual discrimination. Lastly, lesions of the tail of the caudate nucleus (as of the inferior temporal visual cortex which projects to this part of the caudate) produced a visual discrimination deficit [13, 20]. Because of these effects of striatal lesions the

activity of striatal neurons was recorded in the present investigations during the initiation of behavior, for example during the initiation of feeding; during visual discrimination performance and its reversal; and during the presentation of visual and other stimuli.

In the putamen, neurons have been described which altered their firing rates in relation to movements [2, 8–10, 30]. In the caudate nucleus, neuronal activity has been described which altered during a simple delayed response task when the light which signalled the start of a trial occurred, during the 6.5 sec delay period, during pulling of the response lever by hand, or during the delivery of the fruit juice reward [54], or was related to arm and finger movements, or sometimes apparently to the presentation of food [4, 5].

One aim of the present investigations was to investigate the functions of the striatum by analyzing the activity of striatal neurons during the types of behavior known to be impaired by striatal lesions, such as during the initiation of feeding, during visual discrimination performance and its reversal, and during the presentation of visual and other stimuli. A second aim was to obtain evidence on the possible localization of function within the striatum by comparing the activity of neurons in different regions of the striatum during the performance of the same set of tasks. A third aim was to investigate the role of the striatum in feeding by comparing the activity of striatal neurons with that of neurons in the hypothalamus and related structures where neuronal responses are found which precede and predict feeding behavior initiated to the sight of food [41, 42, 44, 46, 49]. This aim follows from the evidence that alteration of striatal function impairs feeding, that striatal neurons may respond to food (see above), and that there is a projection from the hypothalamus to the substantia nigra, pars compacta, through which hypothalamic feeding-related neurons might influence striatal function and thus feeding [35]. A fourth aim was to compare the activity of striatal neurons with those of orbitofrontal neurons during tasks known to be impaired by orbitofrontal damage, to analyze the relation between the cortical and striatal processing involved in these tasks. To enable this comparison, striatal responses were recorded in (i) a Go/No Go visual discrimination task with reversals, (ii) extinction and passive avoidance of an ad libitum licking response, and (iii) the presentation of a range of aversive and rewarding stimuli [55]. It should be emphasized that there has been very little previous investigation of the activity of neurons in different regions of the striatum in relation to behavior. In this paper, the activity of single neurons in the head of the caudate nucleus in the behaving monkey is described.

## METHODS

The methods used were similar to those described previously [44–46, 52, 55], and are presented here as briefly as possible, except where they differ.

### *Recording*

Three male rhesus monkeys, weighing 4.0–5.5 kg were implanted under thiopentone sodium anesthesia with stainless-steel holders on which an adaptor could be fitted for later daily single-unit recording sessions using glass-coated tungsten microelectrodes (after Merrill and Ainsworth, ref. 34, but without the platinum plating). The signal from the microelectrode was passed through a FET buffer amplifier mounted on the microdrive, amplified by conventional band-pass filtered amplifiers, and displayed on an oscilloscope. Data were analyzed using an on-line PDP-11 computer, which was programmed to produce peristimulus time histograms with the additional presentation of every trial individually as a dot display, or to compute the mean firing rate (and its S.E.) of the neurons during stimulus presentations or control periods.

### *Analysis of neuronal responses*

(i) *'Clinical' tests.* These tests provided a first screen for whether neuronal responses were related in any way to feeding, or to the presentation of aversive objects. Various food, non-food and aversive objects were presented and brought towards the animal, and in the case of foods fed to the animal. Measurements of the firing rate of the neuron were taken in consecutive periods according to the following standard protocol: (1) when the animal was sitting quietly (spontaneous activity); (2) as the experimenter reached behind a screen to retrieve an object from a tray that was out of the animal's sight; (3) as the experimenter's arm was gradually brought back into view; (4) as the object was introduced into the animal's field of view at a distance of about 1 m; (5) as the object was gradually brought towards the animal; (6) while the object was held close to the animal's mouth; (7) as the animal was fed the object (if it was food or delivered saline); and finally (8) as the object was removed. On some trials, the object was removed before the animal had had a chance to taste it. The objects tested included foods such as banana, peanuts, and a 2 ml syringe from which the monkey was fed blackcurrant juice, neutral stimuli such as gratings and laboratory objects, and aversive stimuli such as a 1 ml syringe from which the monkey was given mildly aversive hypertonic saline to drink. This sequence of counts used in the standard protocol allowed initial assessment of whether neuronal responses were to the sight of food, were gustatory or olfactory, or were movement-related [44, 55].

(ii) *Shutter tests.* This test situation was designed to measure whether neurons had visual responses, and to show the latency of visual responses. A 6 cm diameter electromagnetically operated shutter (Compur 5FS) was positioned in a circular aperture in a screen 30 cm away from the animal, and was opened to reveal the visual stimuli. The animal's fixation could be observed by viewing the animal through a peephole in the side of the screen. Correct fixation was usually obtained by providing a 0.5 sec cue period immediately before the opening of the shutter during which a 450 Hz tone was sounded and a small red light mounted just above

the shutter came on. In addition, the shutter open time was kept relatively short (1.5 sec), and in the 8.5 sec intervals between stimuli the monkey could see only the screen. The latency of the neuronal responses was measured in a peristimulus time histogram relative to the time of the opening of the shutter. Neurons with visual responses typically had response latencies of less than 200 msec, and showed time locking to the period in which the shutter was open, whereas neurons with movement-related responses either did not respond in the shutter situation, or had inconsistent responses with latencies which were typically longer than 250 msec.

(iii) *Go/No Go visual discrimination task.* A 6 cm diameter electromagnetically operated shutter positioned 30 cm in front of the monkey opened to reveal one of two stimuli. One of the stimuli indicated that if the animal licked a tube positioned in front of his mouth he would obtain a reward of approximately 0.2 ml of fruit juice. The other stimulus indicated that if he licked the tube he would obtain 0.2 ml of aversive hypertonic saline. By licking on the appropriate trials the animal normally obtained between 1500 and 2000 rewards during a 4 h recording session. Several different pairs of discriminative stimuli were used, including a red and green plaque, colored syringes, and vertical and horizontal gratings. The stimuli themselves were mounted on the arms of a rotor which was moved by the computer to bring the appropriate stimulus according to a pseudo-random sequence behind the shutter before the start of each trial. In order to ensure that the animal was fixating the shutter when it opened the shutter opening was preceded by a 0.5 sec signal cue period during which a 450 Hz tone sounded and a small red light (LED) mounted over the shutter came on. The monkeys' response latencies measured from time 0 when the shutter opened to reveal the positive discriminative stimulus until the time of tongue contact with the lick tube were typically 350–450 msec.

In order to measure the time relations between neuronal activity related to reaching, which was found in some neurons, and the arm movement, one monkey could be required to reach to press a small illuminated panel to start a trial of the visual discrimination task.

(iv) *Reversal task.* The experimenter instructed the computer to reverse the meaning of the two discriminanda in the Go/No Go visual discrimination task, so that the previously rewarded stimulus was now negative and vice versa. The monkey learned to reverse his behavioral responses quickly, in that if he obtained saline when he licked to a stimulus which had previously been associated with reward, on subsequent trials he did not lick to that stimulus in order to avoid saline, but did lick to the previously punished stimulus to obtain reward.

#### *Localization of recording sites*

The locations of the neurons described in this paper were determined in two ways. First, at the end of every track, X-radiographs were taken of the frontal and

lateral views of the head to determine the position of the tip of the recording electrode relative to permanently implanted reference electrodes, whose positions were later determined histologically. Second, at the end of the recording period, lesions were made through the tip of the recording electrode to mark typical neurons. This was done by passing either anodal or cathodal current of 100  $\mu$ A for 100 sec. Following tranquilization with ketamine and then a lethal i.p. dose of pentobarbitone sodium the animal was perfused with 0.9% saline followed by formal-saline. After equilibration in sucrose-formalin, serial frozen 50  $\mu$ m brain sections were cut and stained with thionin. Then reconstructions, to a final accuracy of approximately 0.5 mm, were performed of all the recording sites on projected sections of the histology using the marker microlesions and the tips of the recording electrodes in the histology, and the corresponding X-radiographs for each track.

## RESULTS

A total of 394 single neurons was recorded in the anterior neostriatum of three rhesus monkeys. Of these, 253 (or 64.2%) were found to respond in one or more of the testing situations, as summarized in Table I. The reasons for the responses of the neurons in these different test situations were analyzed as described below, and are considered under four main headings: responses to sensory stimulation; responses related to movements performed by the animal; responses during the performance of the visual discrimination task; and other responses seen during clinical testing.

### *Responses to sensory stimulation*

Although many neurons responded when stimuli were presented to the monkey in one or other of the test situations (see Table I), such responses were often specific to a combination of the particular testing situation and the stimulus presented, so that in only a relatively small number of cases (54, 13.7%) could the responses of neurons in the head of the caudate nucleus be classified as sensory.

### *Visual responses*

A total of 38 units (that is, 9.6% of the total sample) was classified as having visual sensory responses. To be classified as visual a neuron had to satisfy at least one of the following criteria: (1) respond to the presentation of visual stimuli both in the shutter and in the clinical testing situations; and (2) respond selectively to different visual stimuli shown using shutter presentation, with no response when the monkey's view of the shutter was blocked. (These criteria were not intended to encompass every type of visual response which might be found, but if met provided useful evidence that a neuron was responding to visual stimuli, rather than responding in a more complex way in relation to the performance of a task.)

TABLE I

*Summary of neuronal responses in the anterior neostriatum*

	<i>Tested</i>	<i>Response</i>	<i>%</i>
Neurons recorded	394		
Visual discrimination – cue period	365	53	14.5
Visual discrimination – shutter period	370	115	31.1
Visual discrimination – lick-related	370	23	6.2
Shutter presentation – cue period	94	10	10.6
Shutter presentation – shutter period	107	52	48.6
Clinical – prepresentation	348	78	22.4
Clinical – sight/approach	353	91	25.8
Clinical – during feeding	352	22	6.2
Clinical – removal	194	6	3.1

Most of these neurons (26, or 68.4% of the 38 with visual responses) had non-selective visual responses, in that they responded to visual stimuli almost independently of the nature of the stimulus used. Of the 12 selective neurons, two responded selectively to foods with latencies of 150–200 ms, but unlike hypothalamic neurons with responses associated with the sight of food [46], they did not respond differentially in the visual discrimination to the stimulus associated with the availability of food. Two neurons responded selectively to aversive visual stimuli, but one responded to aversive stimuli only in the shutter situation and not clinically, and the other had a long response latency of 340 msec, so that even these responses were unlike the visual responses found in the hypothalamus or orbito-

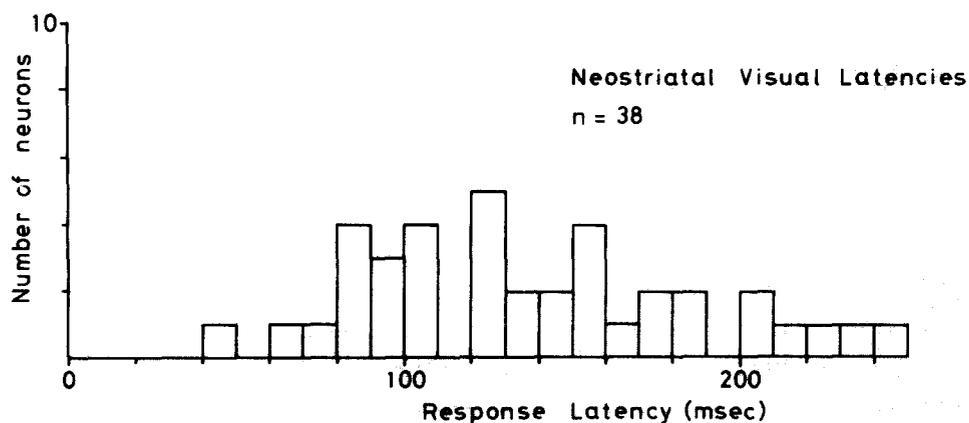


Fig. 1. The response latencies to visual stimuli of neurons in the anterior neostriatum classified as having visual responses (see text).

frontal cortex. Three neurons responded selectively to novel visual stimuli, and the remainder had visual responses selective for other stimuli. The response latencies for the 38 visual units are illustrated in Fig. 1. The mean response latency of the non-selective neurons (122.4 msec) was significantly shorter ( $P < 0.02$ , two-tailed  $t$ -test) than that of the selective units (167.8 msec).

#### *Gustatory responses*

Only two striatal units (0.5% of the total sample) were classified as having gustatory responses. These neurons responded when the animal was feeding, but not if the animal was simply making mouth movements. One of these units responded to the taste of glucose, banana and blackcurrant juice during clinical testing, but not to water or saline, and the magnitude of the neuronal response depended on the concentration of the glucose tasted. The other responded to the taste of chocolate-flavored glucose during clinical feeding tests, and also after the animal had licked and obtained fruit juice in the visual discrimination task. A number of other units showed responses during feeding but these were usually shown to be associated with mouth movements made by the monkey.

#### *Auditory responses*

Although these were not a primary topic in this investigation, a number of neurons were found with responses which were clearly dependent on an auditory input. Fourteen neurons (3.5% of the total sample) were classed as having auditory responses, in that they either responded to the noise of the shutter opening (when it was obscured from view) or they responded to one or more auditory stimuli but not to general behavioral activation. Three of the neurons responded to the opening of the shutter, with latencies of 20–30 msec. An example of such a neuron is shown in Fig. 2. This neuron also showed a small response to the onset of the tone, which was largest with tone frequencies of 800 Hz, and responded to clicks. The other 11 neurons responded to various auditory stimuli. Particularly effective was the sound of the laboratory door being opened which was found to evoke responses in 7 of the units.

#### *Movement-related responses*

Activity that was unconditionally related to particular movements was uncommon in the anterior striatum, with only 16 neurons (4.1% of the total sample) showing such responses. Even for these units, the correlation between neuronal activity and movements was usually only fairly general, with responses occurring, for example, only when the monkey made vigorous body movements. One neuron in the head of the caudate nucleus had responses related to arm extension (see Fig. 2 of ref. 47), and one was of the type common in the putamen [51] with responses related to the monkey's lick responses.

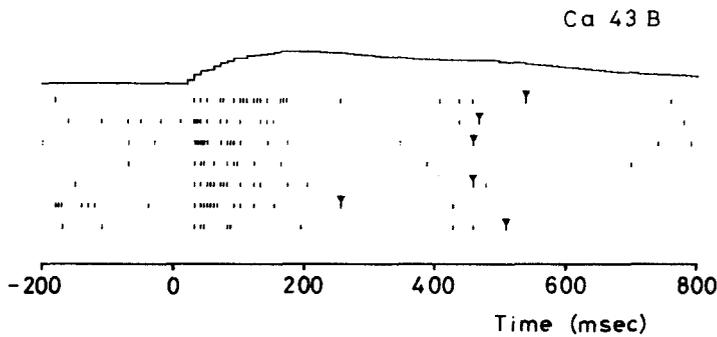


Fig. 2. An auditory response of a neuron in the head of the caudate nucleus. The neuron responded 40 msec after the sound at time 0 of the shutter opening, even when it was obscured from view (see text). Each spike is represented by a vertical line, each trial in the task is represented by one row, and licks which the monkey made on some trials are represented by inverted triangles. The top trace is the cumsum (see text) computed from the responses on these 7 trials.

### *Task-related responses*

Many neurons in the head of the caudate nucleus responded during the performance of the visual discrimination task (see Table I), but did not have unconditional sensory or motor responses of the type described above.

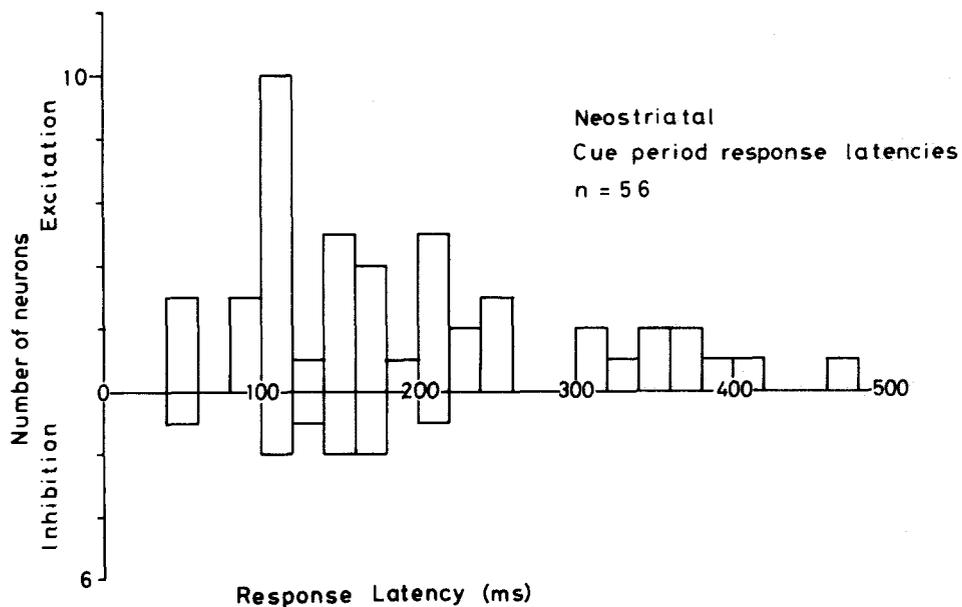


Fig. 3. The response latencies to the 0.5 sec tone and light cue which preceded and signalled the start of each trial of the visual discrimination are shown for cue-responsive neurons in the anterior neostriatum.

### Cue-related responses

Fifty-three of the 365 units tested (i.e. 14.5%) responded during the 0.5 sec cue period which preceded and signalled the opening of the shutter in the visual discrimination task. (Two others responded to the cue in the shutter tests, but were not tested in the visual discrimination task.) One other neuron responded during the cue period in the shutter presentation situation but did not respond in the visual discrimination. The latency distribution for the 56 neurons relative to the start of the cue is given in Fig. 3, which shows that response latencies of between 100 and 200 msec are common, and that 83.9% of the neurons responded by increasing their firing rate. Normally two cues, a 450 Hz tone and a small red LED positioned just above the shutter, were given together in the 0.5 sec cue period. Of 11 neurons tested with the cues separately, 9 responded to either the tone or the LED alone, and 2 responded only to the LED. An example of a unit that responded strongly independently of the modality of the cue is shown in Fig. 4. Most of the units maintained their activity until after the opening of the shutter (see e.g. Fig. 4).

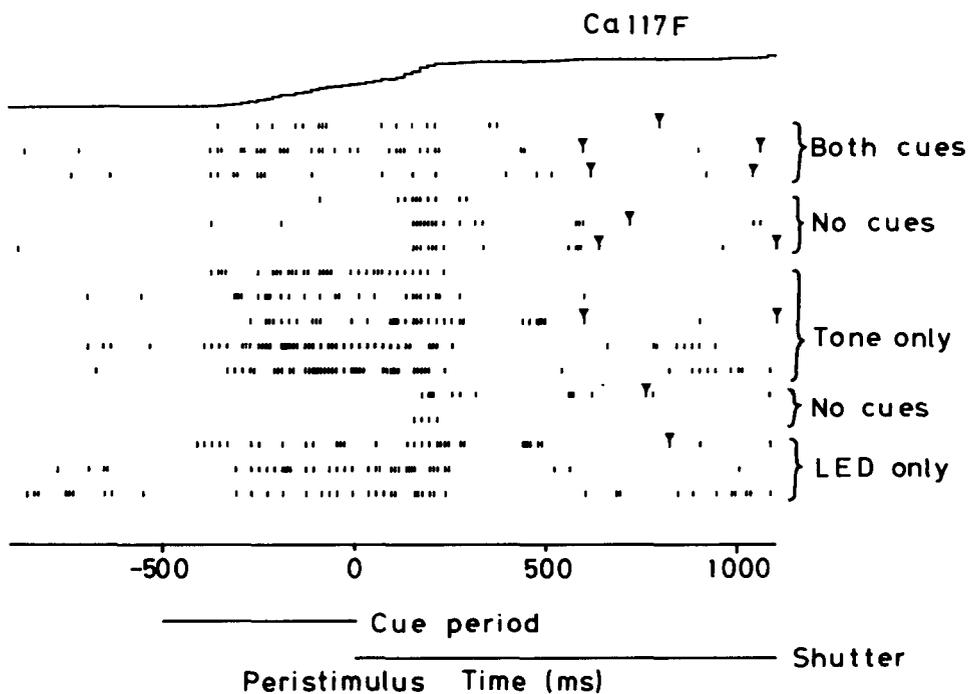


Fig. 4. Responses of a cue-responsive neuron in the head of the caudate nucleus to either the tone or to the light emitting diode (LED) cue which signalled the start of each trial of the visual discrimination task. Peristimulus time is shown relative to the onset of the visual stimuli at time 0. The cue period started 500 msec before the visual stimuli were shown by the opening of the shutter, and ended at time 0. The period in which the visual stimuli were shown is indicated by the line labeled shutter. If no other cue indicated the start of each trial ('no cues'), the neuron responded to the first cue available for the start of the trial, namely the opening of the shutter. Other conventions as in Fig. 2.



*Neuronal responses occurring after the shutter opened*

One hundred and fifteen of the 370 units tested in the visual discrimination task (31.1%) responded in relation to the opening of the shutter. The response latencies relative to the shutter opening are shown in Fig. 6. Because response latencies were in many cases shorter when the tone or LED cue preceded the shutter opening than when no cue was used, only neurons tested in the no-cue condition are shown in Fig. 6. The response latencies of 22 of 26 neurons tested with and without cues were decreased by 10–110 msec if the cue was used. These latency differences, and the short latencies of some of the responses, especially when a cue was used, are consistent with the fact that the responses of many of these neurons could not be classified as sensory, and suggest that the neuronal responses could be related to the preparation for responses or to anticipatory responses.

For one unit, the effect of making the opening of the shutter unsignalled was dramatic. This is illustrated in Fig. 7. The top four trials show the responses of the unit in the visual discrimination task when the opening of the shutter was uncued. There is a clear burst of firing from about 90 to 300 msec. If the animal was able to initiate the trials himself (as illustrated in the bottom 8 trials), there was no response to the opening of the shutter, even though the sensory event was the same. The difference between the two situations is presumably related to the fact that in the unsignalled condition, the opening of the shutter is the first cue that the animal has that a trial has commenced. In the self-start situation on the other hand, the opening of the shutter is not so important as a cue.

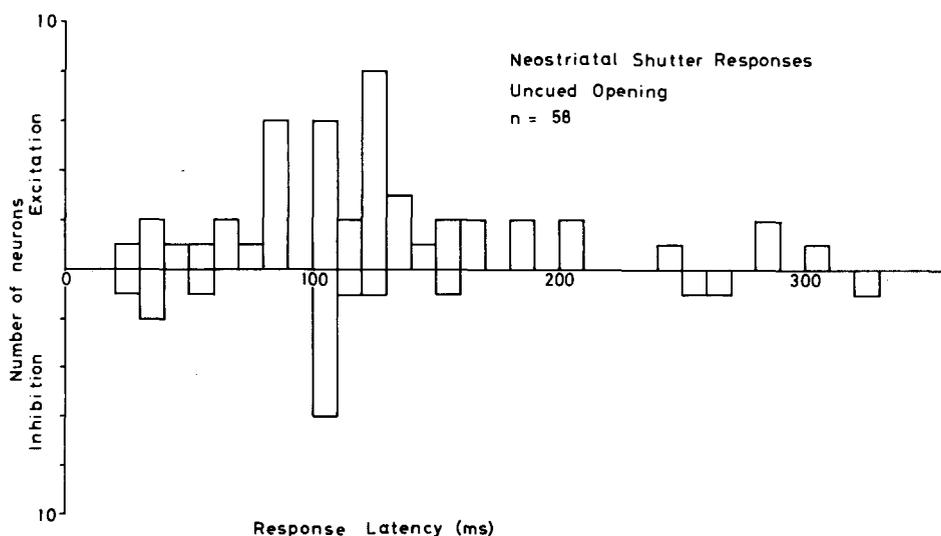


Fig. 6. The response latencies of neurons which responded after the shutter opened in the visual discrimination task. The latencies are shown relative to the time of shutter opening.

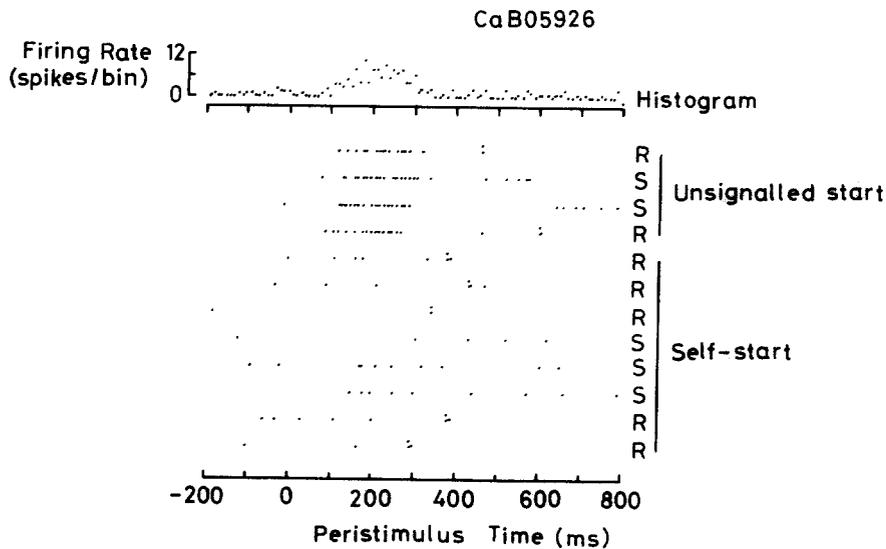


Fig. 7. Activity of a neuron which responded after the shutter opened in the visual discrimination task. This neuron responded only if the opening of the shutter was unsignalled by the 0.5 sec tone/LED cues (upper 4 trials), and did not respond when the monkey initiated each trial by pressing an illuminated panel to start each trial (self-start, lower 8 trials). Conventions as in Figs. 2, 4 and 5. The shutter opened at time 0. The trials have been regrouped for clarity in this and other figures, and were originally presented in random order.

### *Differential responses*

Twenty-eight neurons had responses that were different on reward and saline trials in the visual discrimination. Examples of the responses of one of these neurons are shown in Fig. 8, in which the trials (which were presented in pseudo-random order) have been rearranged for clarity. In Fig. 8A it is shown that without cues, the neuron started to respond on both reward and saline trials at approximately 170 msec after the shutter opened, and that on saline trials the unit stopped responding at about 230 msec, but that on reward trials at about the same time the neuron increased its firing rate. In Fig. 8B it is shown that if a cue was present, the neuron started to show non-differential activity to the cue before the shutter opened, and showed differential activity at approximately 190 msec after the shutter opened. Another example of one of these neurons, which started to respond even before the tone cue sounded if the monkey could start the trial by reaching out to press an illuminated panel, is shown in Fig. 9. Because the neuron responded tonically throughout the pre-differential period, and even after this was not phasically related to mouth movements, it is probable that the neuron was not involved in the performance of particular motor acts, but was instead involved in a more general control of task performance. This was a general finding, in that only 4 of the 28 differential neurons responded phasically during the licks, and they also responded during *ad libitum* licking to obtain fruit juice or during mouth

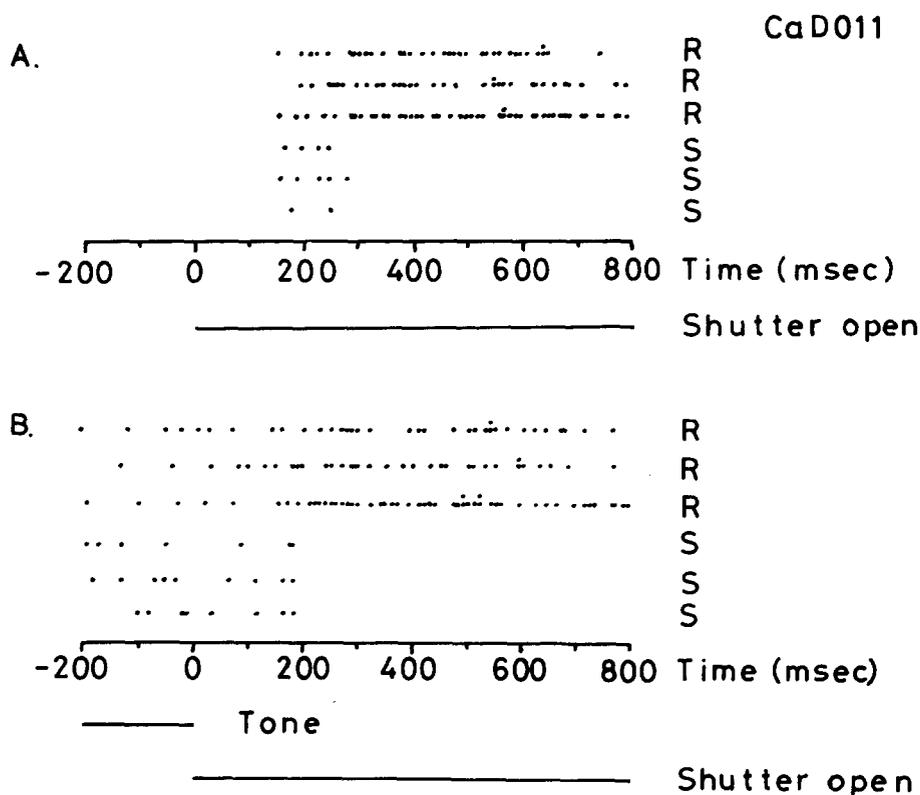


Fig. 8. Activity of a neuron with differential responses in the visual discrimination task. A: no cues present in the 0.5 sec period which preceded the opening of the shutter at time 0 to reveal the visual discriminanda. B: the 0.5 sec tone/LED cues were present. Action potentials are represented by dots, and licks by a raised dot. Other conventions as in previous figures. The responses were differential, with more activity on reward (R) than on saline (S) trials, from a latency of 200–230 msec. A low level of non-differential firing preceded the differential response, starting in the cue period (lower traces, B), and after the shutter opened if no other cue for the start of the trial was given (upper traces, A).

movement. The latencies at which the differential activity started in these neurons was in the range 120–400 msec (Fig. 10) compared to latencies of lick responses of approximately 450 msec in these monkeys. It is also shown in Fig. 10 that most of these neurons (29 out of 35, or 83%) responded more on reward than on saline trials. A number of these neurons with differential responses in the discrimination period had started to respond (non-differentially) in the cue period, as illustrated in Figs. 8 and 9.

When the association of the visual stimuli with reward was reversed, it was found that the majority of the differential neurons tested (5/7) reversed their responses, proving that the responses of these neurons were related to the significance of the stimuli or to the response performed, and were not specific to a particular stimulus. For one neuron the evidence was inconclusive. For the other

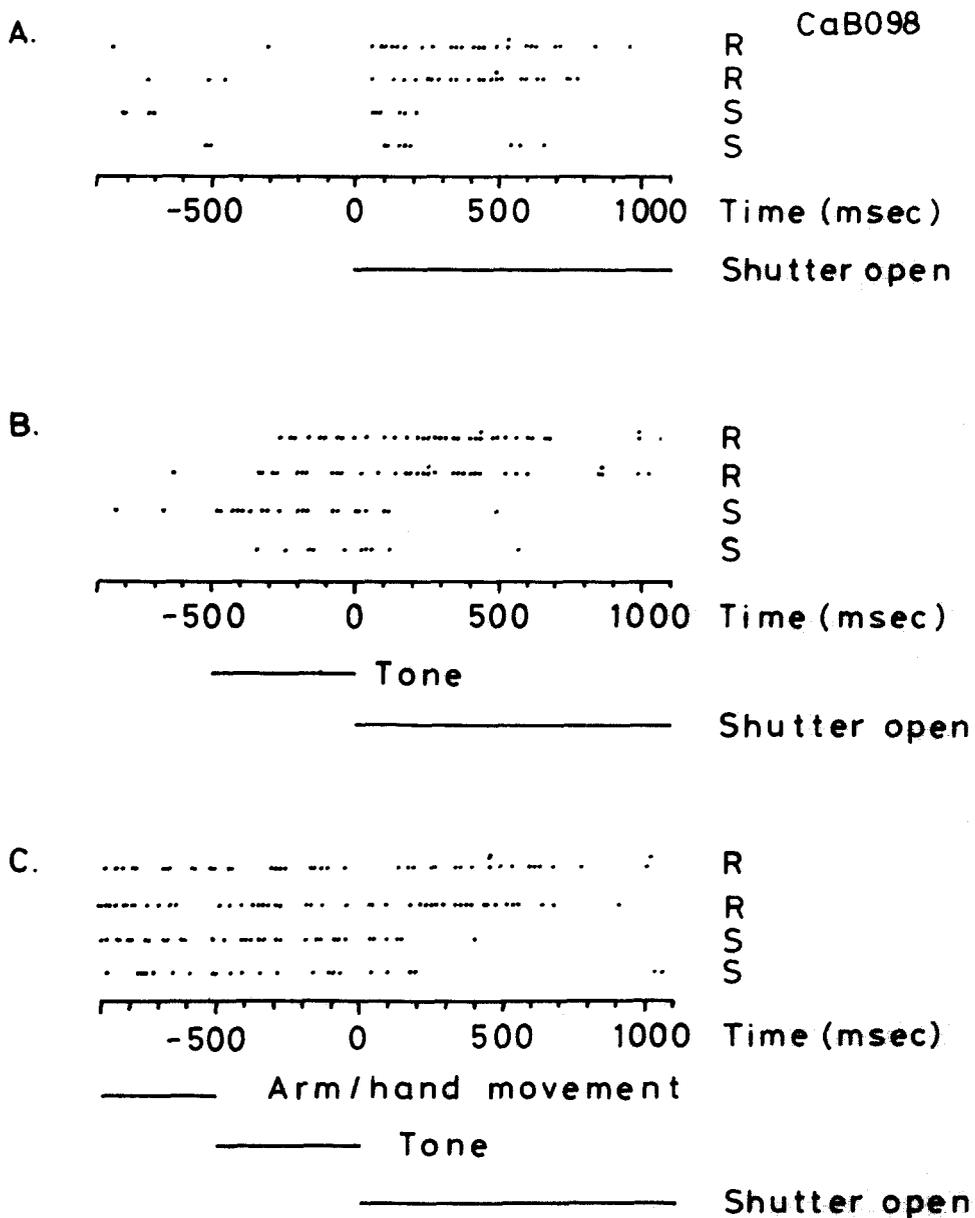


Fig. 9. Activity of another neuron with differential responses in the visual discrimination task. A: no cues present in the 0.5 sec period which preceded the opening of the shutter at time 0 to reveal the visual discriminanda. B: The 0.5 sec tone/LED cues were present. C: the monkey was allowed to initiate the trial himself by reaching to press an illuminated panel which started the 0.5 sec tone cue. Conventions as in previous figures. The responses were differential, with more activity on reward (R) than on saline (S) trials, from a latency of 150–200 msec. Non-differential firing preceded the differential response, starting as soon as the monkey initiated a trial (C), in the cue period (B) if the tone was the first cue for the start of a trial, and after the shutter opened if no other cue for the start of the trial was given (A).

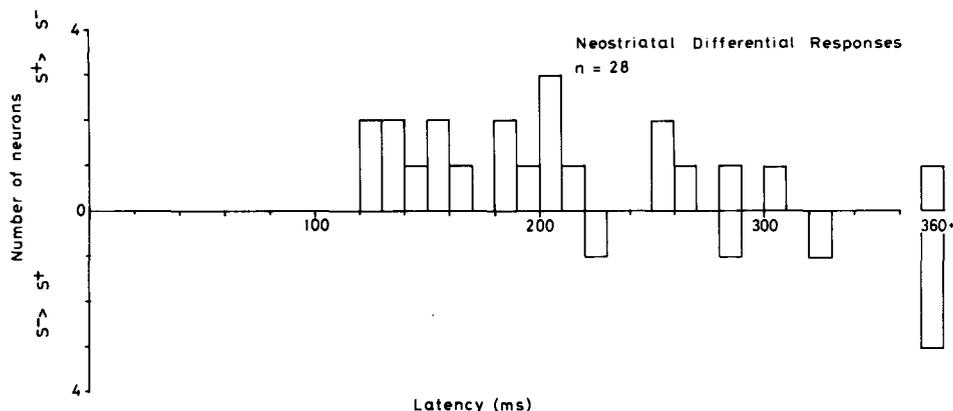


Fig. 10. The latencies at which the differential activity was present in anterior neostriatal neurons with differential responses in the visual discrimination. Neurons which responded more to the reward-related discriminative stimulus (S+) are shown as raised bars, and those which responded more to the punishment-related discriminative stimulus (S-) as descending bars. The latencies are shown relative to the time at which the discriminative stimuli were revealed by the opening of the shutter.

neuron the differential response was non-reversible, in that it responded selectively to the green discriminative stimulus, whether it was treated as rewarding or aversive. This indicated that the differential activity was dependent on a sensory feature of the green discriminandum, but interestingly the neuron did not respond to the same green stimulus when it was presented in the standard shutter presentation situation, so that it did not have an unconditional sensory response. Consistent with this, the differential response latency for this neuron varied between 120 and 280 msec. No neurons had activity related in any of the other ways found in the orbitofrontal cortex [55] to reversal or extinction.

#### *Post-lick responses*

Twelve neurons (3.2% of the 370 tested) responded after the licks were made in the visual discrimination task. The responses of the majority of these neurons were affected by whether food was obtained, in that for 6 of 8 neurons tested the response was greater when fruit juice reward rather than saline was delivered. Also 5 of 6 neurons tested also responded when the monkey licked out of the task to obtain fruit juice ad libitum, and 7 out of 11 units tested also responded during feeding in the clinical testing situation. However the responses of these neurons were not usually unconditional (i.e. independent of the testing situation), and selective for food, in that only one was classified as showing gustatory responses.

*Responses during clinical testing*

Many neurons responded during clinical testing, as indicated in Table I. Some responded to, for example, the sight or approach of food or non-food visual stimuli ('sight' responses, Table I), and some (27.5%) of these had selective responses for food as compared to non-food stimuli (see e.g. Fig. 3 of ref. 47). Of the neurons which responded during the sight or approach of visual stimuli in the clinical test situation, 35.2% were classified as having visual sensory responses (see above). The remaining 64.8% did not have visual sensory responses, in that they did not respond to visual stimuli in the shutter tests of visual sensory responsiveness, or to the visual stimuli in the visual discrimination task. These neurons thus had responses which were conditional on the situation in which the stimuli were presented. The responses of these neurons could be related to particular behavioral responses being made to the stimuli in some testing situations (see Discussion). None of these neurons had unconditional movement-related responses. Of the neurons which responded during feeding, 91% were classified as not having gustatory responses, in that their responses could not be shown to be selective for certain fluids, or to be concentration-dependent, but were sometimes situation-specific, not responding, for example, during ad libitum licking for the same fluid, or having movement-related activity.

A considerable proportion (22.4%) of neurons in the head of the caudate responded before the food or non-food object was actually shown to the monkey in the clinical testing situation. These neurons responded when the experimenter reached behind a screen to retrieve food from a tray which was hidden from the monkey's view, but typically did not respond when the food was shown (for 65.4% of the neurons), as the food was brought towards the monkey, during feeding, or during mouth, limb or body movements made by the monkey (see e.g. Fig. 11). For different neurons, these responses were associated with the reaching movement towards the food tray (35 neurons), with the movement as the experimenter brought his arm back in preparation for presenting the food to the monkey (18 neurons), or during both movements (25 neurons). These movements by the experimenter were termed prepresentation arm movements. The responses of these neurons were usually excitatory (in 87.2% of the cases).

Given that the prepresentation arm movements were an important cue that an object, which might be food, was about to be presented from behind the screen, it was of interest to determine how specific the neuronal responses were to that particular cue. It was found that of 17 neurons tested, 12 responded only when the experimenter's arm movements were towards the tray which held the objects, and not during his arm movements above, below, or towards the right. Four neurons were less specific in that they responded whenever the experimenter reached out of the monkey's field of view, irrespective of the direction, and one neuron responded only when the experimenter made a reaching movement

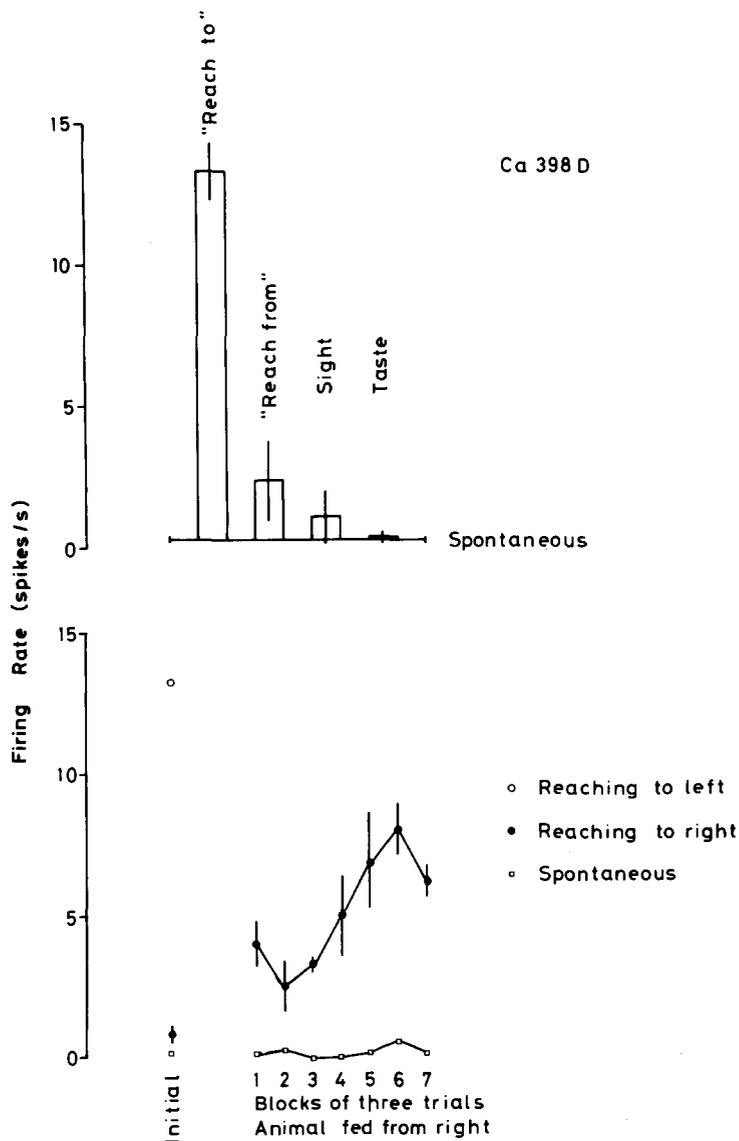


Fig. 11. Presentation responses of a neuron in the head of the caudate nucleus. The mean and standard error of the firing rate of the neuron are shown. Top: the neuron responded before a food or non-food object was shown to the monkey as the experimenter was reaching behind a screen to obtain the object, but did not respond to the sight of food (Sight), or during eating (Taste). This neuron responded to one part of the prepresentation sequence, namely reaching by the experimenter towards ('Reach to') but not away from ('Reach from') the tray on which the foods and non-food objects were placed behind the screen. Bottom: the same neuron responded initially only to presentation movements by the experimenter towards the left, the normal position of the tray, but came gradually to respond to the experimenter's movements to the right when the tray was instead placed on the right.

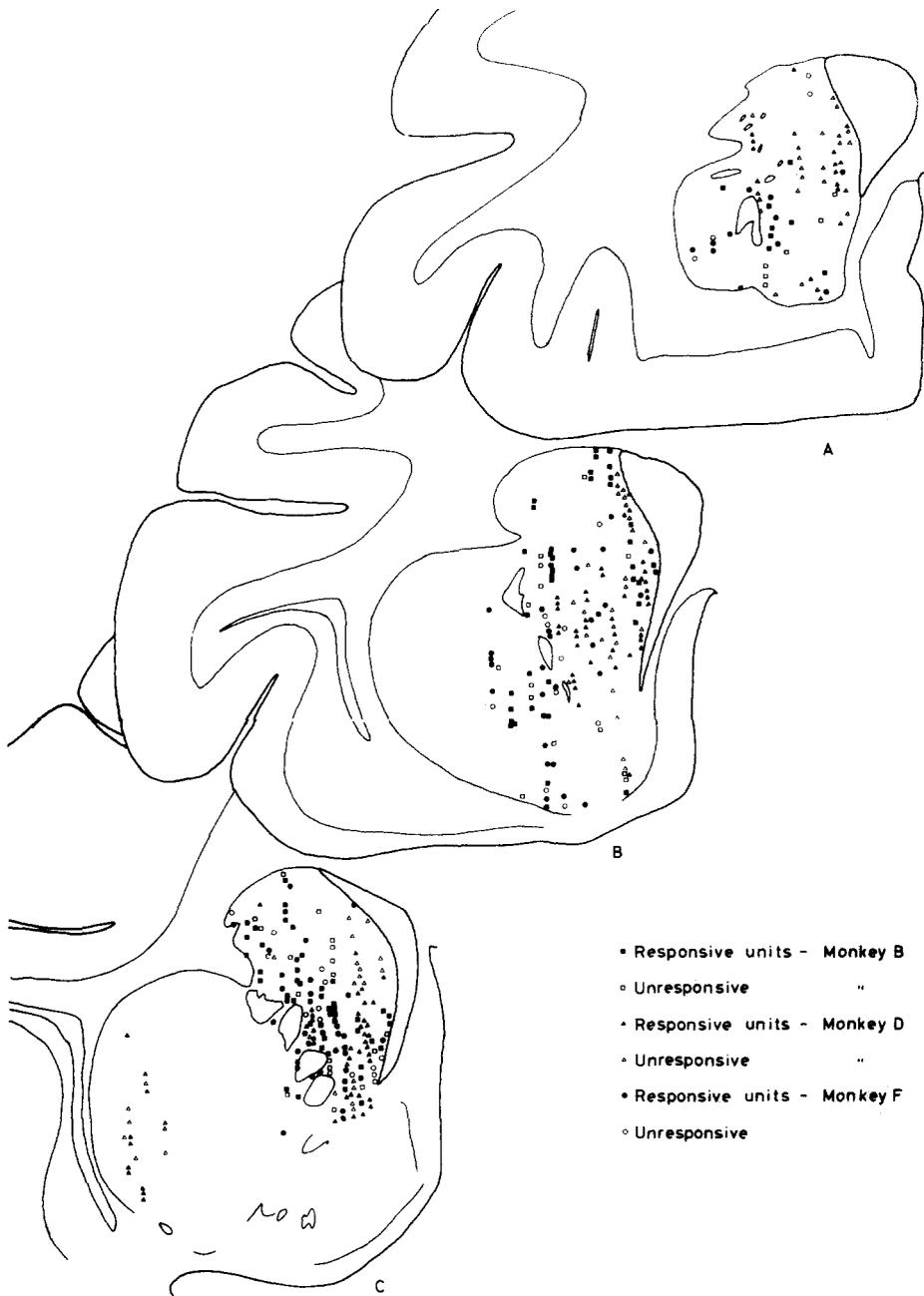


Fig. 12. The locations in the anterior striatum at which the neurons described here were recorded. Sections A, B and C corresponded in these rhesus monkeys to approximately 24, 22 and 20 mm anterior to the interaural plane.

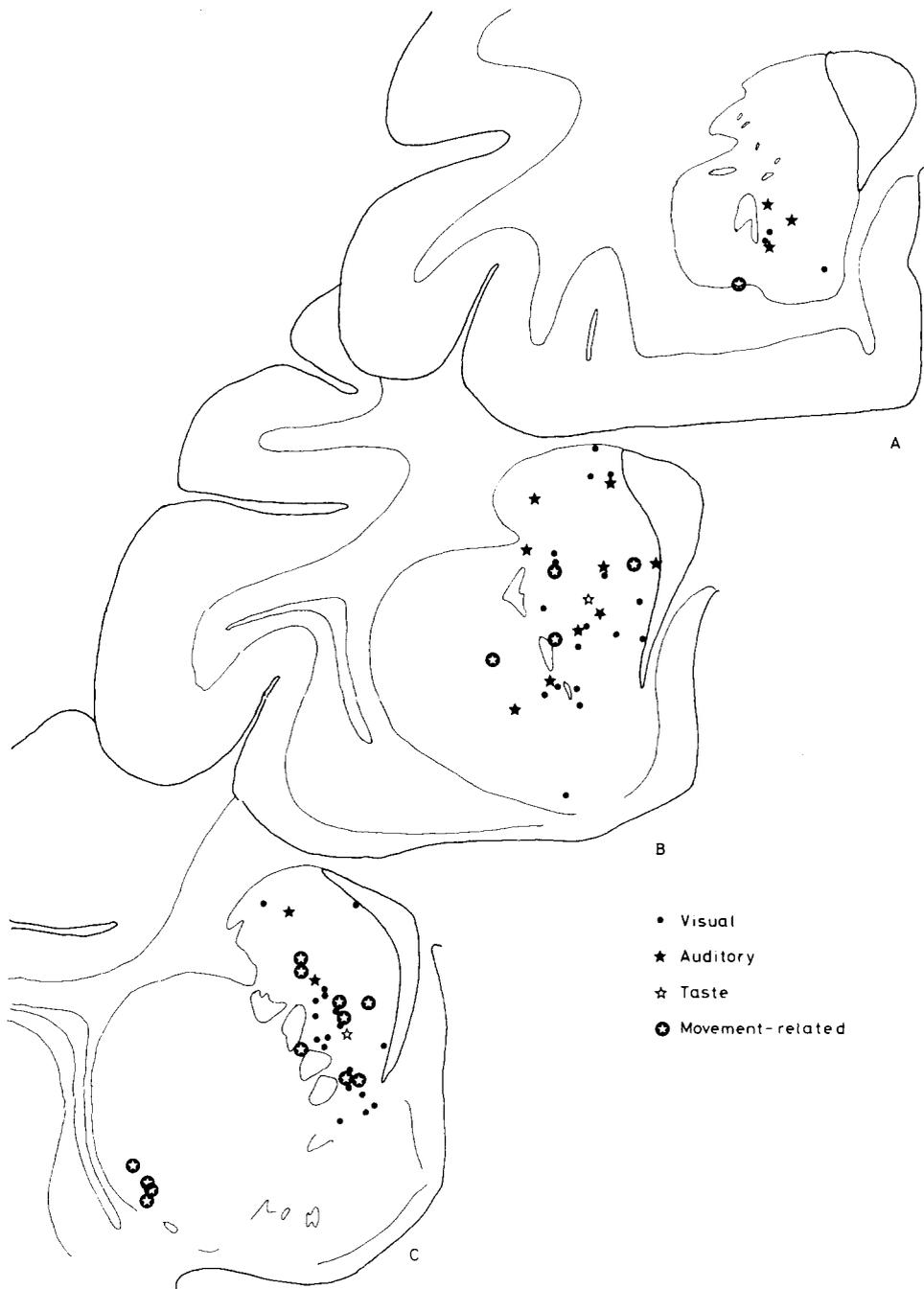


Fig. 13. The locations in the anterior neostriatum at which neurons with responses classified as visual, auditory, gustatory or movement-related were recorded.

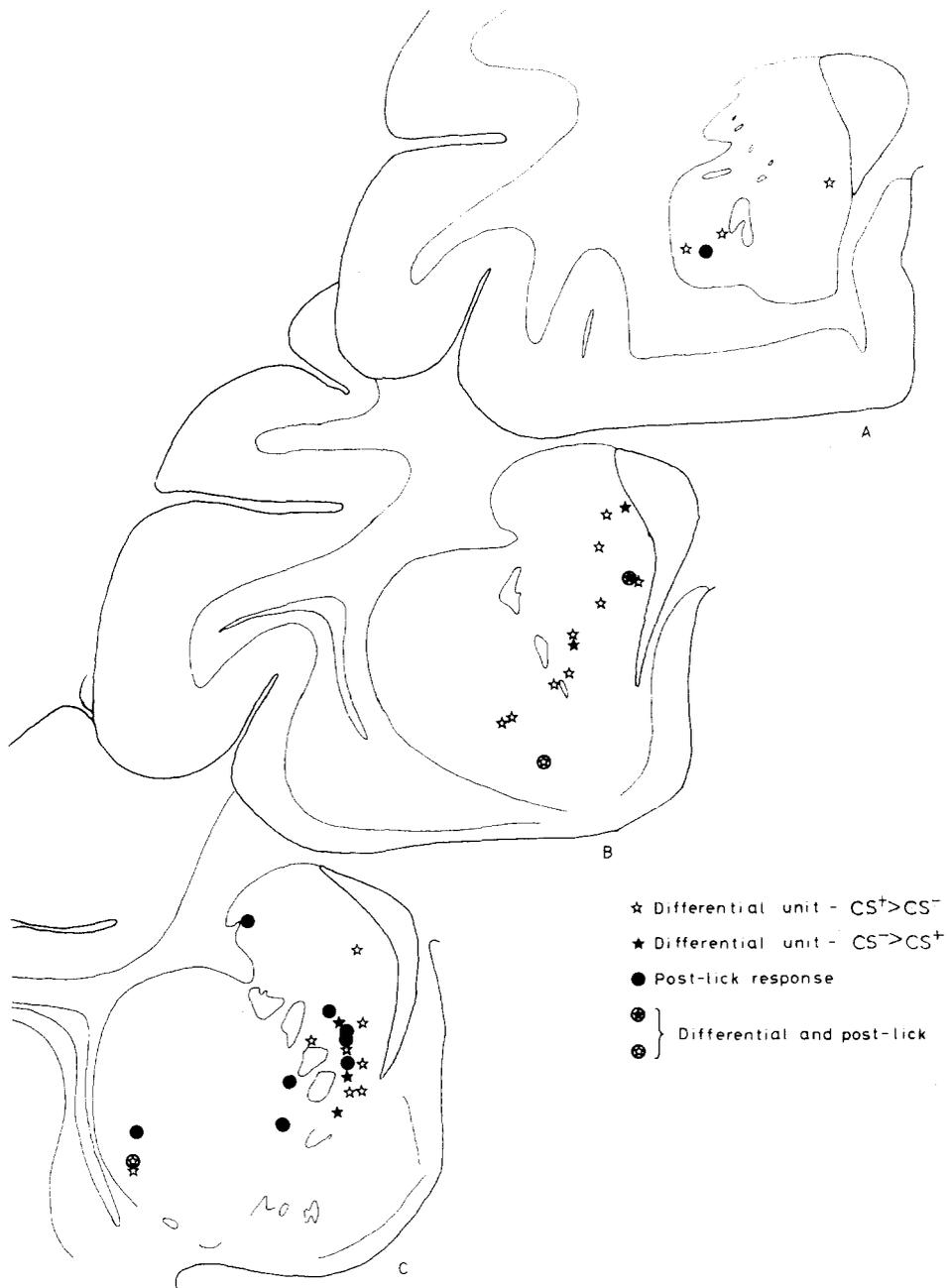


Fig. 14. The locations in the anterior neostriatum at which neurons were recorded with responses which occurred differentially in the visual discrimination task on rewarded trials ( $CS^+ > CS^-$ ) or on punished trials ( $CS^- > CS^+$ ), or occurred after the lick responses made in the task.

towards the right of the monkey. Evidence that these neurons did not respond because of a moving stimulus in the visual field was that many of these neurons showed no response to movement of the experimenter's hand and arm within the animal's visual field, but showed a pronounced response as soon as the experimenter started reaching behind the screen. Support for this conclusion is that some neurons also responded vigorously even if the experimenter merely looked in the direction of the food tray. It was also clear that the response was not simply due to eye-movements made by the monkey, because the neurons could respond well even if the animal was not tracking the experimenter's arm movement.

To investigate the role of experience in setting up these neuronal responses to cues which had regularly preceded the presentation of objects which might be foods, extinction was attempted by making the arm movement repeatedly without the presentation of an object. For the 5 neurons tested there was no evidence for habituation over 20–30 trials, perhaps because the association had been based on so much previous experience. In another test, some neurons (5/7 tested) which initially only responded to the experimenter reaching towards the food tray on the left, started to respond to reaching in another direction if this was consistently followed by the presentation of food. An example of a unit which was apparently modulated by such learning is shown in Fig. 11, bottom.

Since the experimenter's prepresentation arm movements were important cues for the monkey, it was of interest to find that such units could respond to cues in other situations, such as the cues which signalled each trial in the visual discrimination task. Of 71 neurons with prepresentation responses tested in the visual discrimination task, 24 (33.8%) responded during the cue period of the task, a proportion which is considerably higher than the average for striatal units (14.5%).

#### *Location of the recorded neurons*

The positions of the 394 neostriatal units recorded in the present study are shown in Fig. 12. The units are plotted on representative sections of one hemisphere at three different coronal planes. The three planes are labeled A, B and C and correspond to positions of approximately 24, 22 and 20 mm anterior to the interaural plane. Units were sampled between 18 and 25 mm anterior to the interaural plane, but the majority lay between 20 and 24. It is clear from the diagram that the majority of the units recorded were in the head of the caudate nucleus ( $n = 331$ ), with a number also recorded in the most anterior part of the putamen ( $n = 63$ ). The locations of the neurons with responses classified as sensory or movement-related are shown in Fig. 13, and of the neurons with differential or post-lick responses in Fig. 14.

## DISCUSSION

Although a large number of the anterior striatal neurons recorded in the present study responded in one or more of the testing situations, relatively few were classified as sensory. This was because although many neurons responded when, for example, a visual stimulus was presented clinically (see also refs. 1, 4, 5, 33, 38), they often responded in only some testing conditions, and did not respond unconditionally to the stimuli, independently of context. Thus, for example, although 91 of the 353 units tested (i.e. 25.8%) responded when objects were presented to the animal in the clinical testing situation, only a small proportion of these also responded when the same object was presented to the animal behind the glass screen of the electronically controlled shutter used to measure the latency of visual responses successfully in such regions as the inferior temporal visual cortex [45], the amygdala [52], the hypothalamus [46], and the orbitofrontal cortex [55]. The relatively small proportion (9.6%) of neurons in the head of the caudate nucleus which passed the relatively strict criteria for being visual, and the finding that most of these were non-selective, suggest that this part of the neostriatum is not particularly involved in the actual processing of sensory input. The finding that many of the neurons responded to environmental stimuli only in certain contexts suggests rather that this part of the striatum is involved in the processes whereby particular responses occur to such stimuli. The relatively high proportion of neurons with responses to external stimulation in the anesthetized animal, which may arrive in the caudate via the centromedian thalamic nucleus from polysensory regions in the reticular formation and tectum [25, 40], could reflect fragments of arousal responses occurring under these conditions which are not present in the normal awake animal. The relatively small number of neurons in the present study in the awake monkey which did appear to respond selectively to auditory stimulation often appeared to respond to stimuli, such as the sound of the laboratory door opening, which are particularly important as cues to the animal that events are taking place in the environment. Buser et al. [4, 5] have also found neurons in the head of the caudate nucleus of the monkey which responded to similar environmental events.

In the present study very few neurons (4.1% of the sample) in the anterior part of the neostriatum, and particularly in the head of the caudate nucleus, appeared to respond in relation to particular movements made by the monkey. In some previous studies a larger proportion of movement related responses was found in the striatum, but the recordings were in the putamen or in more posterior parts of the caudate [8–10, 30]. Indeed, we have also found a high proportion of neurons with movement-related responses in the putamen [51], so that their infrequency in the head of the caudate nucleus in this study was not due to the testing methods used, but rather reflected a topographical difference in the responses in these different parts of the striatum. This is in line with the anatomical

evidence that the putamen receives its major cortical inputs from the motor and somatosensory cortex, whereas the head of the caudate nucleus receives its cortical inputs primarily from the prefrontal cortex [22, 26–29] in which neuronal activity is often related to cognitive processing performed on environmental stimuli rather than to movements [15, 55]. In some other studies which have reported movement related activity in the head of the caudate nucleus [4, 5, 14, 24, 53], the neuronal responses were in many cases related only generally to the performance of the task required, rather than being clearly phase locked to particular movements. Indeed, in the study by Schneider et al. [53] in which the activity of cat caudate units was recorded while the animal was drinking milk from a tube, no units were found that were clearly movement-related, although 25% of the units had activity that was time locked to drinking. Thus, all the studies, including the present one, are in general agreement that in the head of the caudate there are remarkably few units that are clearly related to particular movements, although many may be more generally involved in motor performance. In more posterior regions of the caudate, and more particularly in the putamen, clear movement related activity is much more common [51].

Although only few neurons in the anterior striatum were classified as having unconditional sensory or motor responses, many of the neurons were active in the test situations, for example, during the cue period (see Fig. 3) or when the shutter opened (see Fig. 6), at which time the monkeys had to prepare for and initiate behavioral responses. Many of these neurons thus had responses which were related to cues which the monkey could use to prepare for the initiation of behavioral responses. Examples are the neurons which responded during the tone/LED period which signalled the opening of the shutter in the visual discrimination or the latency testing situation, and the neurons which responded during the prepresentation movements made by the experimenter which indicated that an object, which might be food, was about to be presented. The monkeys had been given experience over thousands of trials of the cue value of these environmental events, and it was in this context that such a high proportion (110 of 394 tested, i.e. 27.9%) of anterior striatal neurons responded to at least one of these cues. The responses of other anterior striatal neurons to other significant environmental events such as the opening of the laboratory door may well reflect a situation in which many anterior striatal neurons are tuned to respond to different environmental events to which it may be important to make behavioral responses. The question then arises of the extent to which these cue-related responses are sensory, or motor.

A small number of the cue-related responses appeared to be closely related to sensory events. For example, in the task two out of 11 neurons tested responded to the LED cue but not to the tone cue, so that their responses were probably not related to the cue value of the stimuli or to any behavioral reaction to the stimuli, but were probably modality-specific sensory responses. Consistent with this, the

response latencies of these neurons, and of a small number of other neurons, to the cue stimuli were relatively short (in the range 4–100 msec, see Fig. 3). However, most of the neurons with cue-related responses had longer response latencies (see Fig. 3), responded to the cue regardless of whether it was auditory or visual (in 9 of 11 cases tested), and for 7 of 15 units tested only responded during the cue period if the monkey was performing the visual discrimination task (not responding in the cue period if the shutter opened to reveal visual stimuli in the tests for visual responsiveness). Thus most of the units with cue-related activity did not have unconditional sensory responses, but instead the responses were conditional on the stimuli acting as cues. The cue-related neuronal responses were also independent of identifiable movements of for example the limbs, face and mouth, to which neuronal activity in a different part of the striatum, the putamen, could in a great number of cases be clearly related, showing that the present testing methods were capable of identifying neurons with activity related to such movements (see also ref. 51). Although the responses of some of these cue-related neurons could have been related to postural movements, as has been suggested for some neurons in the putamen [2, 14], the cue-related neurons described here in the head of the caudate nucleus did not alter their activity even during a wide range of body movements made when the task was not being performed. Nevertheless, without extremely extensive EMG recordings from many axial muscles [10], it is not possible to completely exclude the possibility that the activity of these cue-related neurons was related to postural adjustments made in response to the cues. Indeed, the most parsimonious explanation of the responses of these cue-related neurons which can be advanced at present is that they respond to stimuli which are cues for the animal to prepare himself to make a response, and that these neuronal responses are involved in the different preparations made to respond, which may well include postural adjustments as well as attention towards the shutter through which the discriminative stimuli are about to appear. Indeed, evidence that such neurons may be important in preparing an animal to respond is that if the function of this system is disrupted by damage to the dopamine pathways, responses are not initiated appropriately to environmental stimuli, and the animal is described as akinetic (see e.g. ref. 32). It will be a fascinating aim for future work to determine exactly where in relation to sensory input and motor output systems neurons with such cue-related responses are placed, for the present work suggests that they are neither unconditionally sensory nor motor, but are at an intermediate stage of processing and are on a pathway important in enabling animals to utilize environmental cues in order to prepare for the initiation of motor responses.

In a similar way, the neurons with conditional responses to other environmental stimuli such as food may reflect processing which can neither be described as unconditionally sensory or unconditionally motor. Such neuronal responses may be important in the initiation of particular movements to particular stimuli

in particular situations. These neuronal responses could reflect relatively stable connections formed as the result of previous experience and used in rapid, relatively fixed, well-learned motor responses to particular stimuli. These may be called stimulus–response connections. This type of neuronal response is thus different to that which occurs in some hypothalamic neurons to a wide range of visual stimuli which signify for example food reward, and on the basis of which any behavioral response appropriate for obtaining the reward could be initiated [43]. Neurons with responses which could allow such flexibility of behavioral response are considered next.

The responses of neurons in the head of the caudate nucleus are indeed very different from those in the hypothalamus during feeding and visual discrimination. In the lateral hypothalamus and substantia innominata, neurons were found which responded to the sight of food irrespective of whether it was shown clinically or in the shutter testing situation used to measure latency, and also responded to the stimulus associated with food in the visual discrimination [44, 46]. In contrast, although some neurons in the head of the caudate nucleus appeared to respond to food in one of these situations, their responses were at least partly situation-specific or ‘conditional’. Thus, their responses probably reflected at least in part the generation of behavioral responses occurring in particular situations to food, and were not responses associated just with the sight of food-related stimuli. In particular, the responses of the striatal neurons which occur when food is presented clinically to the monkey (refs. 4, 5, 38, 47 and this study), of which the majority have been shown in this study to be specific to that testing situation, thus appear to be related to preparing for and executing particular behavioral responses made in a particular situation to food. A similar conclusion follows for the considerable numbers of striatal neurons which responded differentially in the shutter situation or in the visual discrimination on trials on which a food or food-related stimulus was shown, in that the majority of these neurons did not respond to the sight of food during clinical testing. Thus these neurons may be involved in rapid, well-learned, almost automatic responses to discriminative stimuli, whereas a more general-purpose decoding is represented at the hypothalamic level, in that a food in any of these testing situations may activate such hypothalamic neurons, so that any appropriate response can then be initiated. The neurons in the head of the caudate nucleus with responses which occur to the cues provided in the visual discrimination and clinical situations, but do not usually occur to the sight of food or during feeding, are probably also important in preparing the animal to make responses, and because of this are important in feeding.

The responses of neurons in the head of the caudate are also different from those in the orbitofrontal cortex, from which it receives projections. Thus the orbitofrontal cortex contains a higher proportion of clear sensory responses than the anterior part of the striatum. For instance, 32.4% of orbitofrontal neurons

were classified as being visually responsive compared with only 9.6% in the anterior striatum. Also, visual responses in the striatum were less likely to be selective, in that only 31.6% of the small number of neurons with visual responses were selective, whereas in the orbitofrontal cortex, 66.9% were selective. Further, orbitofrontal neurons recorded in the same three animals were often selective even for particular foods or aversive stimuli [55], and this degree of selectivity was not found in these anterior striatal neurons. This indicates that whereas the orbitofrontal cortex contained information required for computations specific to particular stimuli, the anterior neostriatum is unlikely to be involved in the fine differentiation of stimuli. Further, information about whether reinforcement had been received was represented in the responses of 36 orbitofrontal neurons (7.9%) with gustatory responses [55], whereas only two (0.5%) were found in the anterior neostriatum. Also, unlike the orbitofrontal cortex, no units were found in the neostriatum with clear bimodal sensory responses to, for example, the sight and taste of the same food [55]. In the visual discrimination task, although neurons in the orbitofrontal cortex did respond in the cue period, and the cue related responses of anterior striatal neurons could be derived partly from these, a number of classes of orbitofrontal neurons with activity related to reversal behavior were not found in the anterior striatum. These orbitofrontal neurons included neurons which responded when an error was made and punishment was obtained in reversal or non-reward was obtained in extinction, and neurons which responded selectively to a particular visual stimulus, but only when it was associated with reward. Thus neuronal responses present in the orbitofrontal cortex and which could be used for the alteration of behavioral responses to stimuli no longer associated with reinforcement [55], are not found in the striatum. This difference supports the view that complex neuronal mechanisms involved in the performance of tasks such as visual discrimination reversal are situated in cortical regions such as the orbitofrontal cortex, and that subcortical areas such as the head of the caudate nucleus are not directly involved, but may relay the results of such cortical decision making to the motor system. Thus although lesions in both areas might disrupt performance on a visual discrimination reversal task [13], the reason for the disruption of performance is not the same. It could be that after orbitofrontal lesions, the neuronal mechanism for the switching of central sets is damaged, whereas after neostriatal lesions it is the pathways by which this mechanism actually influences behavior that are disrupted. It is also of interest that since not all the response types seen in the orbitofrontal cortex are also seen in the head of the caudate (and this is especially true for gustatory responses), the cortico-striatal projection from orbitofrontal cortex must be a selective one, involving only certain classes of neurons. Such a distinction would be easy to understand if the different classes of orbitofrontal neurons were anatomically separate. For example, if all the neurons apparently involved in 'intermediate' processing in the visual discrimination task were all cortical interneurons, then this would explain why such responses are not seen in the striatum.

As suggested above, the responses of neurons in the anterior neostriatum appear to be involved in the preparation for the initiation of movements, and in particular movements initiated to particular environmental stimuli. It may be suggested that some of the effects of disruption of striatal pathways arise because of dysfunctions of these neuronal systems. Thus the akinesia or lack of voluntary movement produced by damage to the dopaminergic nigrostriatal bundle in animals and present in Parkinson's disease in man [19] may arise at least in part because of dysfunction of a system which normally is involved in utilizing environmental stimuli which are used as cues in the preparation for the initiation of movements [47, 48]. Such preparation may include for example postural adjustments. It may also be suggested that this type of movement disorder is due in part to the dysfunction of the neuronal system described here which appears to be involved in the generation of particular responses to particular environmental events (see also refs. 47, 48).

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