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RESPONSES OF STRIATAL NEURONS IN THE BEHAVING MONKEY. 3. EFFECTS OF IONTOPHORETICALLY APPLIED DOPAMINE ON NORMAL RESPONSIVENESS

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Abstract—In order to analyse the functions of dopamine, the effects of the iontophoretic application of dopamine on the responsiveness of striatal neurons to their normal inputs were investigated in the behaving monkey. It was shown that many neurons in the putamen had responses related to movements, of for example the mouth. Iontophoretically applied dopamine decreased the spontaneous firing rates of 178 of 267 neurons (67%) tested in the putamen, caudate nucleus, and the adjacent prefrontal cortex which also receives a dopaminergic projection. Trifluoperazine, applied iontophoretically to block dopamine receptors, increased the spontaneous firing rates of some of the neurons in the prefrontal cortex, suggesting that under normal conditions in the behaving animal the release of dopamine holds the firing rates of these neurons at a low level. The median was 9 spikes/s in the present sample of striatal neurons. Application of dopamine decreased the magnitude of the movement-related responses of the striatal neurons; this decrease in the responses was of approximately the same magnitude in spikes per second as the decrease in the spontaneous firing rate of the neurons produced by the same current of dopamine.

It is suggested that this type of effect of dopamine could influence the signal to noise ratio of processing within the striatum, and that changes in this signal to noise ratio produced by disturbances of dopaminergic function could contribute to the behavioral disorders produced by dysfunctions of the dopaminergic systems.

The caudate nucleus and putamen receive inputs from the cerebral cortex, and have outputs to motor structures via their projections to the globus pallidus and substantia nigra, pars reticulata, which in turn project via the thalamus to the premotor cortex as well as to the brainstem.[2,7,12,13,24] The caudate nucleus and putamen also receive a dopaminergic input from the substantia nigra, pars compacta. This dopaminergic nigrostriatal bundle is important for the function of the striatum, in that its degeneration in man occurs in Parkinson's disease in which there is akinesia (an inability to initiate voluntary movements),[9] and its destruction in animals leads to catalepsy and an inability to orient to environmental stimuli,[10,20,37] but as yet it is unclear how this dopaminergic input influences the normal functioning of the striatum. To investigate this, in the study described here the effects of dopamine, administered microiontophoretically, on the normal responses shown by neurons in the striatum of the behaving animal were determined. Microiontophoretic application was used in order to ensure that the effects observed were not due to altered behavior of the animal, which would be produced by systemic administration of dopamine agonists or antagonists, and would mean that any alteration of neuronal activity could be as a result of the altered behavior rather than of alteration of the dopamine in the region of the single neuron from which recordings were being made. The recordings were made in a non-human primate, the macaque monkey, in order to ensure that the results were as relevant as possible to understanding the normal functions and the dysfunctions of dopamine in man. The recordings were made in the behaving animal because only in these conditions could the effect of the dopamine be determined not only on the spontaneous activity of the neurons, but also on the normal responses of the neurons to their inputs. Only by determining how dopamine influences the responsiveness of striatal neurons to their normal inputs, as well as its effects on spontaneous activity, can the functions of dopamine in the striatum be determined. Although dopamine has been applied to striatal neurons in the anesthetized animal previously, and usually a decrease of spontaneous activity[3] and of responses evoked by electrical stimulation is obtained, some investigators have claimed that its action is excitatory.[14,25] This is the first study we know in which the effects of dopamine on the normal responses shown by striatal neurons in the behaving animal have been investigated.

The cortical inputs to the striatum have some topographic organization.[10,11] Thus the visual cortex in the temporal lobe projects into the tail of the caudate nucleus and adjoining part of the putamen,

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and in a previous study in this series, we have shown that visual responses to complex patterned visual stimuli are found in this part of the striatum.[1] The head of the caudate nucleus receives from cortex which includes the prefrontal cortex. In the head of the caudate nucleus we found neurons which responded to environmental stimuli used in the preparation for and initiation of movements, and probably reflected inputs from the prefrontal cortex.[32] The recordings described in this paper were made in a third part of the striatum, the putamen, which receives inputs from the sensorimotor cortex, areas 1, 2, 3, 4 and 6,[2,11,15–18] and part of the aim of making the recordings in this region was to enable comparison with the activity of neurons recorded in other parts of the striatum in the same testing conditions, in order to obtain further evidence on specialization of function within the striatum.[1,26,27,32–34]

EXPERIMENTAL PROCEDURES

The methods used were similar to those described previously[30,31,32] and are presented here as briefly as possible, except where they differ.

Recording

Two male macaque monkeys (one *Macaca mulatta* and one *Macaca fascicularis*), weighing 4.0–5.5 kg were implanted under thiopentone sodium anesthesia with stainless-steel holders which allowed access to the dura for later daily single unit recording sessions. For the recording sessions, an XY positioner and hydraulic microdrive which held the microelectrode were fitted to the holder and the microelectrode was introduced through the dura, which was anesthetized with xylocaine, with a guide tube. The signal from the microelectrode was passed through a FET source follower amplifier mounted on the microdrive, amplified by conventional band-pass filtered amplifiers, and displayed on an oscillosocpe. Data were analysed 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 SE) of the neurons during stimulus presentations or control periods.

The microiontophoretic recording electrodes were designed specially for use in the behaving animal. In order to optimize the recording properties of the microelectrodes, which must provide considerable recording stability for use in the behaving animal, we prepared our normal glass-insulated tungsten microelectrodes (after Merrill and Ainsworth,[21] but without the platinum plating) in a version small enough to fit inside an array of glass barrels for the microiontophoresis. This allowed separate optimization of the microiontophoretic and recording properties of the combined microelectrode. The microelectrodes were manufactured from one large (4 mm) central barrel, through which the recording microelectrode was later inserted, surrounded by 11–12 capillary tubes to be used for each of the drugs. Each of the capillary tubes was prefilamented, and also contained at least one additional filament inserted by hand, in order to ensure correct filling to the tip. This assembly was then pulled to a diameter of no more than 0.8 mm in a bunsen flame to form the shaft of the microelectrode. Its diameter was not less than 0.3 mm to ensure that the recording electrode could reach the tip, and to ensure that the solutions would fill correctly. The length of this shaft was 100 mm, as it had to pass through the guide tube. The last 2 mm of the iontophoretic electrode was then pulled in a conventional vertical electrode puller to reach a diameter of 15 μm at the tip, using beading if necessary. Finally, the recording glass-insulated tungsten microelectrode, which had an exposed tip of 5–10 μm, was inserted into the central barrel of the iontophoretic microelectrode array, advanced with a micromanipulator until its tip protruded 10–30 μm from the end of the ionotophoretic barrels and then fixed in this position with glue at the other end.

The iontophoretic barrels were filled with the electrode held in a vertical position using polythene tubing pulled in a bunsen to a diameter small enough to fit into a barrel as far as the pulled shaft. The solutions were made immediately before each recording sesson, and were filtered with a 0.4 μm millipore filter. They were as follows. (1) Dopamine: as a solution of dopamine hydrochloride (0.2 M) in ascorbic acid (0.5 mg/ml). (2) Noradrenaline: as a solution of noradrenaline hydrochloride (0.2 M) in the same ascorbic acid solution. (3) Trifluoperazine, a dopamine receptor blocking agent, as a 0.2 M solution in the same ascorbic acid solution. (4) Glutamate: as a solution of L-glutamic acid (0.2 M) in distilled water. (5) DL-homocysteic acid (0.02 M) as a solution in distilled water. (6). Sodium chloride: as a 2 M solution, used for current compensation and for current control. Each barrel was connected with silver wire to either a Neurophore iontophoretic current driver with current compensation using the sodium chloride barrel, or for early tracks to a purpose built current driver. Current effects were rare when current compensation was used, and any neuron showing an effect of current was excluded from the analysis. Backing currents of 3–5 nA were used to minimize leakage.

Analysis of neuronal responses

The responses of the neurons described here, most of which were in the putamen, were analysed using the same tests used for analysis of neuronal responses in the head[32] and tail[1] of the caudate nucleus so that neuronal responses in these different parts of the striatum could be compared. These tests are described only briefly here. After the responses of a neuron had been analysed using these different tests, the effects of iontophoretic application of the substances described above on both the spontaneous activity and the responses of the neuron were investigated. It was possible to measure the effects of these substances on both the spontaneous activity and the normal responses shown by the neuron by performing the iontophoresis while the monkey performed one of the tasks in which the neuron had been shown to respond.

"Clinical" tests. These tests provided a first screen for whether neuronal responses were related in any way to feeding, to the presentation of visual stimuli, or to movements. 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 a standard protocol designed to assess whether neuronal responses were to the sight of food, were gustatory or olfactory, or were movement-related.[30,32,36]

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) positioned in a circular aperture in a screen 30 cm away from the animal opened to reveal visual stimuli. The latency of neuronal responses was measured in a peristimulus time histogram relative to the time of the opening of the shutter. Neurons with visual responses typically have responses latencies of less than 200 ms in this situation, and show time locking to the period in which the shutter is open (see e.g. refs 1, 26, 32 and 36). In contrast, it was found that neurons in the putamen with movement-related responses either did not respond in the shutter situation or had inconsistent responses with latencies which were typically longer than 250 ms, so that this test was useful for differentiating visual from movement-related neuronal responses.

Go/nogo visual discrimination task. The shutter 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. In order to ensure that the animal was fixating the shutter when it opened, the shutter opening was preceded by a 0.5 s signal cue period during which a 450 Hz tone sounded and a small red light (LED) mounted over the shutter came on. This task allowed neurons with activity related to for example the signal cues, to the discriminative visual stimuli, or to the monkey's movements to be investigated (see refs 31, 32, 36). Because it was found that many neurons in the putamen had activity related to movements, this task was sometimes simplified to increase the number of movements obtained by allowing the monkey to initiate his lick movement on every tiral to obtain food as soon as the signal cue finished, irrespective of which visual stimulus was shown.

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

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 electrodes to mark typical neurons. This was done by passing either anodal or cathodal current of 100 μA for 100 s. Following tranquillization with ketamine and then a lethal i.p. dose of pentobarbitone sodium the animal was perfused with 0.9% saline followed by formalin–saline. After equilibration in sucrose–formalin, serial frozen 50 μm 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

Neuronal activity in the putamen

Of 234 neurons recorded in the putamen during the performance of the visual discrimination task and/or during the clinical feeding tests, 68 (29%) had activity which was phasically related to movements. A histogram showing the responses in the clinical feeding test situation of a neuron with activity related to mouth movements is shown in Fig. 1. The neuron responded when the monkey made licking movements to obtain fruit juice and during swallowing. The neuron did not have activity related to taste, in that it responded during tongue protrusion made to a food or non-food object. Nor did it have activity which occurred to the sight of food (count period 4) before the monkey started to make mouth movements to the food. The activity of a similar mouth movement-related neuron in the visual discrimination task is shown in Fig. 2. The neuron responded phasically with the lick made on reward trials, and did not respond on the saline

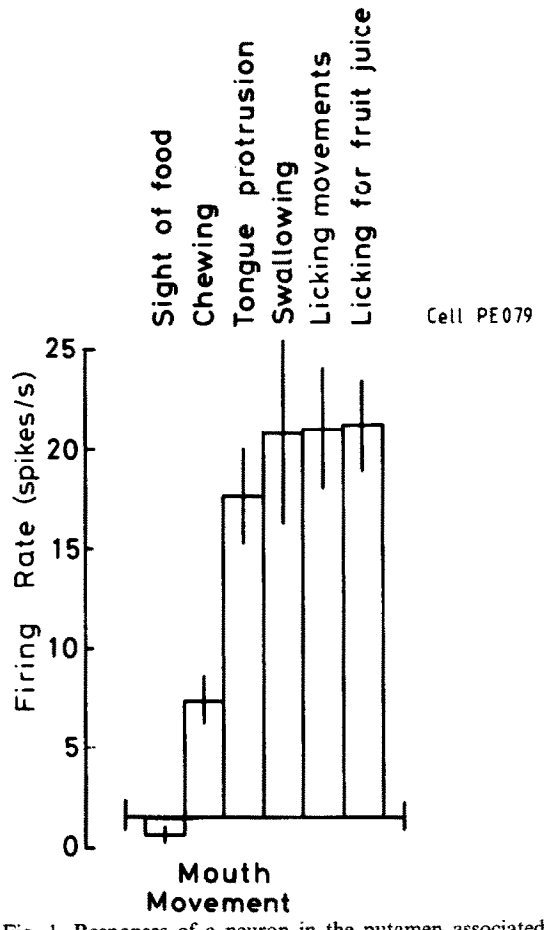

Fig. 1. Responses of a neuron in the putamen associated with mouth movements. The means and SEs of the responses and of the spontaneous activity are shown.

trials on which correctly the monkey did not lick. The latency of these movement-related neuronal responses relative to the onset of the visual stimuli was quite short, approximately 220 ms for lick movements in which the fruit juice tube was contacted at 350–450 ms (see Fig. 2). These neurons responded not only in relation to the licking mouth movements made in the visual discrimination task, but also responded when mouth movements were made during clinical testing when a food or non-food object was brought close to the mouth. Their responses were thus unconditionally related to movements, in that they responded in whichever testing situation was used, and were therefore different from the responses of neurons in the head of the caudate nucleus.[29]

Of the 68 neurons in the putamen with movement-related activity in these tests, 61 had activity related to mouth movements, and 7 had activity related to movements of the body. Of the remaining neurons, 24 (10%) had activity which was task related in that some change of firing rate associated with the presentation of the tone cue or the opening of the shutter occurred on each trial (see ref 32), 4 had auditory responses, 1 responded to environmental stimuli (see ref 32), and 137 were not responsive in these test situations.

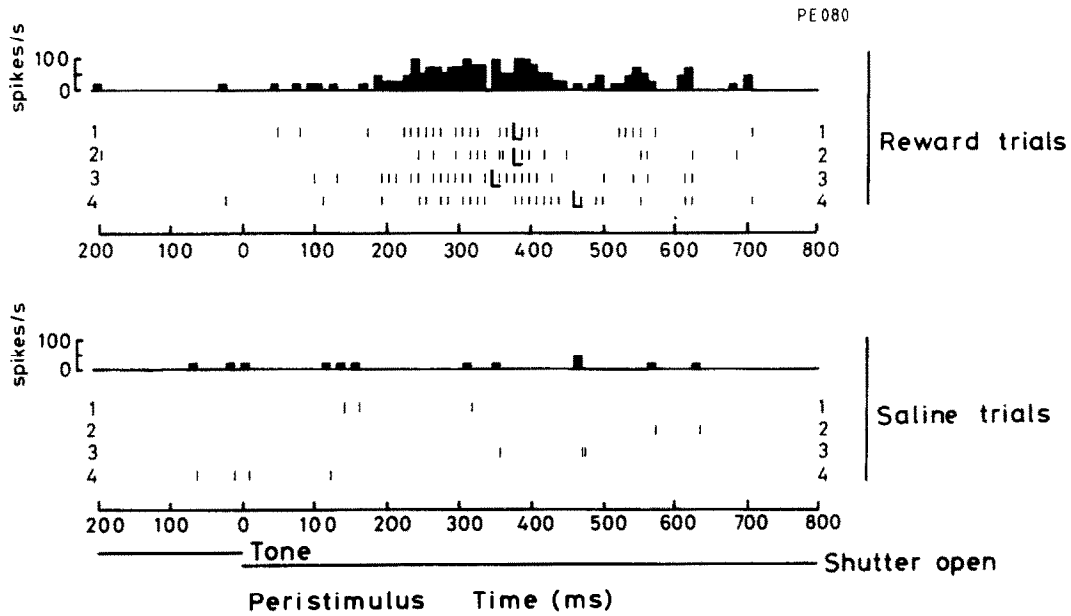

Fig. 2. Activity in the visual discrimination task of a neuron in the putamen with responses related to mouth movements. Each trial is represented by one row. The neuron fired a series of spikes (each spike is represented by a vertical line) associated with the lick responses (L) made on reward trials to obtain fruit juice. The neuronal responses started with a latency of approximately 220 ms after the visual stimuli were shown at time 0. On trials on which the visual stimulus which indicated that saline would be obtained if a lick was made, the monkey correctly did not lick and the neuron did not respond. The trials were run in random order, but are grouped for convenience.

Iontophoresis

A total of 340 neurons was studied using iontophoretic techniques in the two monkeys. The majority (194) of these neurons were located in the putamen, with some (25) in the head of the caudate nucleus and some (121) in the prefrontal cortex (see recording sites marked in Fig. 3).

Most of the cells studied were tested with one or both of the excitatory substances, glutamic acid and DL homocysteic acid. Most were also tested with iontophoretic dopamine, and many, for comparison, with another catecholaminergic transmitter, noradrenaline. The effects of the various substances on the spontaneous activity of units in the striatum and prefrontal cortex will be discussed first. Then, the effects of iontophoretically applied drugs on the normal responses of the neurons will be considered. Because similar types of response to the iontophoretically applied substances used here were obtained from neurons in the caudate, putamen, and prefrontal cortex in these experiments (and all receive a dopaminergic input), the results for these structures are not presented separately below.

Effects on spontaneous activity

Glutamate. A total of 157 neurons was tested with iontophoretically applied glutamate. All those units which were affected by the application (140, or 89%) responded with an increase in firing rate. The remaining 17 units were unaffected. No units were seen which exhibited a decrease in firing rate when glutamate was applied. The effective currents were nearly always in the range 10–20 nA, and it was found that the units would respond in a clearly dose-related manner to an increase in the iontophoretic current.

DL-*Homocysteic acid.* A total of 29 neostriatal neurons was tested with the iontophoretic application of DL-homocysteic acid. As with glutamate this was only ever found to produce excitation (seen in 28, or 96% of the units). For most of the study, the concentration used was 0.02 M (that is, ten times more dilute than that used with glutamate), but even then, the effects were often intense, with currents as low as 4 nA producing strong excitation, and higher currents often producing depolarization block. Because of this excessive excitation, and because unlike glutamate, DL-homocysteic acid is not a naturally occurring transmitter, the use of DL-homocysteic acid was not continued in later tracks in the study.

Dopamine. A total of 267 neurons was tested with iontophoretic dopamine. Of these, 178 (67%) were clearly inhibited, with the remaining 89 unaffected. No instances were seen of dopamine producing an increase in spontaneous firing. The currents used were typically larger than those used with glutamate. Typically, inhibition was seen with currents of 20–40 nA, and it was often found that the inhibitory effects were dose-dependent. An example of a decrease of firing rate produced by dopamine, with no response seen to the current control, is illustrated in Fig. 4.

Noradrenaline. Eighty units were tested with noradrenaline. As with dopamine, the only iontophoretic

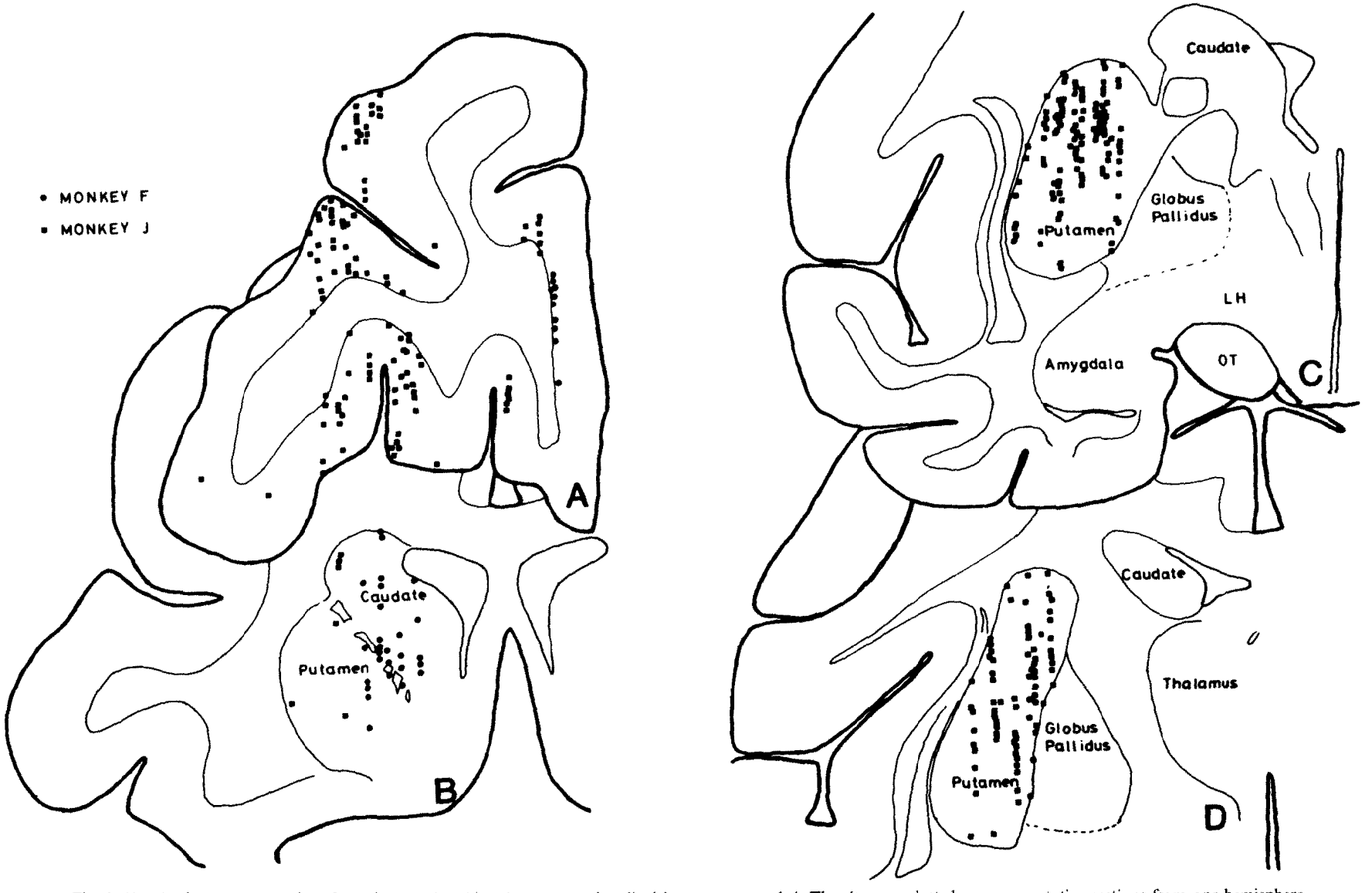

Fig. 3. Sites in the putamen and prefrontal cortex in which the neurons described here were recorded. The sites are plotted on representative sections from one hemisphere. Filled circles show the sites in one monkey; filled squares the sites in the other monkey. LH, lateral hypothalamus; OT, olfactoray tract.

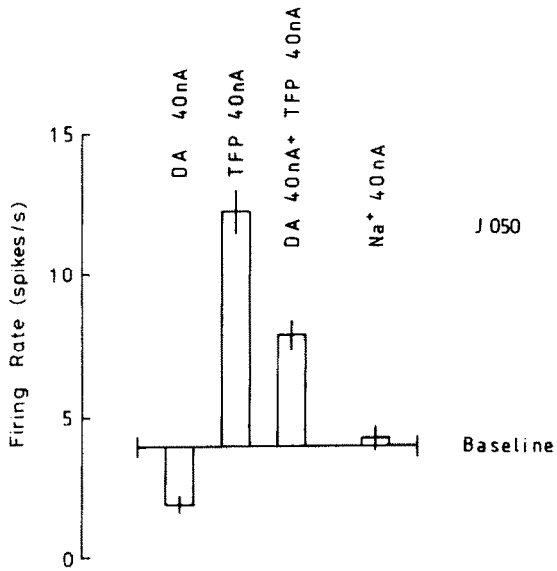

Fig. 4. Response of a neuron to iontophoretically applied dopamine (DA), trifluoperazine (TFP), and a combination of the two. The means and the SEs of the responses and the spontaneous baseline firing rate of the neuron are shown. The neuron did not respond to the current control (Na^+).

effect that was seen was inhibition, which was seen in 49 (61%) cases. The other 31 units were unaffected. The proportion of responsive neurons may be relatively high because noradrenaline was more likely to be tested on a neuron if it had already been shown to respond to dopamine.

In a number of cases, the same unit was tested with both iontophoretic dopamine and noradrenaline, in which case it was possible to quantitatively determine the relative effects of the two transmitters. This was possible for 60 units. Of these, 22 (37%) were found to respond approximately equally to both dopamine and noradrenaline. However, many other neurons were preferentially affected by dopamine. Thus, 29 (48%) responded more to dopamine, and 8 (13%) were only affected by dopamine. By contrast, only 1 unit was found which was preferentially affected by noradrenaline. Thus, despite the fact that both noradrenaline and dopamine were used at the same concentration of 0.2 M, dopamine was found to be considerably more effective in producing inhibition in the striatum than was noradrenaline.

Trifluoperazine. An example of a neuron whose spontaneous firing rate was decreased by the application of dopamine at a current of 40 nA, and increased by trifluoperazine (40 nA), is shown in Fig. 4. When trifluoperazine was applied in combination with the dopamine, it was able to reverse dopamine's inhibitory effect. Neither effect could be attributed to current artefacts since Na^+ ions at the same current had no effect. Thirty-one units (27 of which were in the prefrontal cortex) were tested with iontophoretically applied trifluoperazine. (A greater number of units could not be tested because it was found that the iontophoretic barrel filled with trifluoperazine tended to block.) In many cases, no clear effect was seen on spontaneous firing. However, in 6 neurons (which were in the prefrontal cortex) the application of trifluoperazine produced a clear increase in firing. Such an effect is consistent with the presence of endogenously released dopamine, whose inhibitory effect would be blocked by the presence of the antagonist drug. In 9 cases, trifluoperazine was applied to a neuron which was already being inhibited by iontophoretically applied dopamine. For 5 of these neurons, it was possible with this method to reverse the inhibitory effect of the iontophoresed dopamine.

Effects of dopamine on evoked activity

One of the major aims of the present study was to investigate how dopamine affects the normal response properties of neurons in the neostriatum and frontal cortex. The results already presented demonstrate that the only iontophoretic effect of dopamine on spontaneous firing in the unanesthetized monkey was one of inhibition. Next it is considered whether the effect of dopamine on the normal responses shown by these neurons is the same.

To answer this question, most of the neurons described above were tested for the effects of iontophoretically applied dopamine during the performance of a visual discrimination task or a modification of it. A total of 275 units was tested in the task while recordings were being made with iontophoretic electrodes. Of these, 109 (40%) were found to respond in relation to one or more aspects of the task. For example, 40 (15%) showed activity related to the onset of the 0.5 s duration cue period. A further 8 (3%) responded in relation to the opening of the shutter which revealed one or other of the two discriminanda. However, most common of all were the 61 units (22%) which responded in relation to the lick movements that the monkey made on reward trials in order to receive fruit juice reward.

Of these 109 neurons with task-related activity, 37 were found to have their spontaneous activity suppressed by iontophoretic dopamine. In addition to these neurons, there was a further neuron with a response during clinical testing which was also found to respond to iontophoretic dopamine. Thus, data are available on the relative effect of iontophoretic dopamine on spontaneous and evoked activity for 38 neurons. These data are primarily relevant to the functions of dopamine in the striatum, in that 28 of these neurons were in the putamen, 7 were in the caudate nucleus, and 3 were in the prefrontal cortex.

An example of the effect of iontophoretically applied dopamine on the normal responses shown by a neuron in the putamen is shown in Fig. 5 (PJ073). The lower histogram and set of raster displays show that the neuron responded by increasing its firing rate during the part of the task in which lick responses were being made. (In this simplified task, the monkey could make lick responses as soon as the shutter

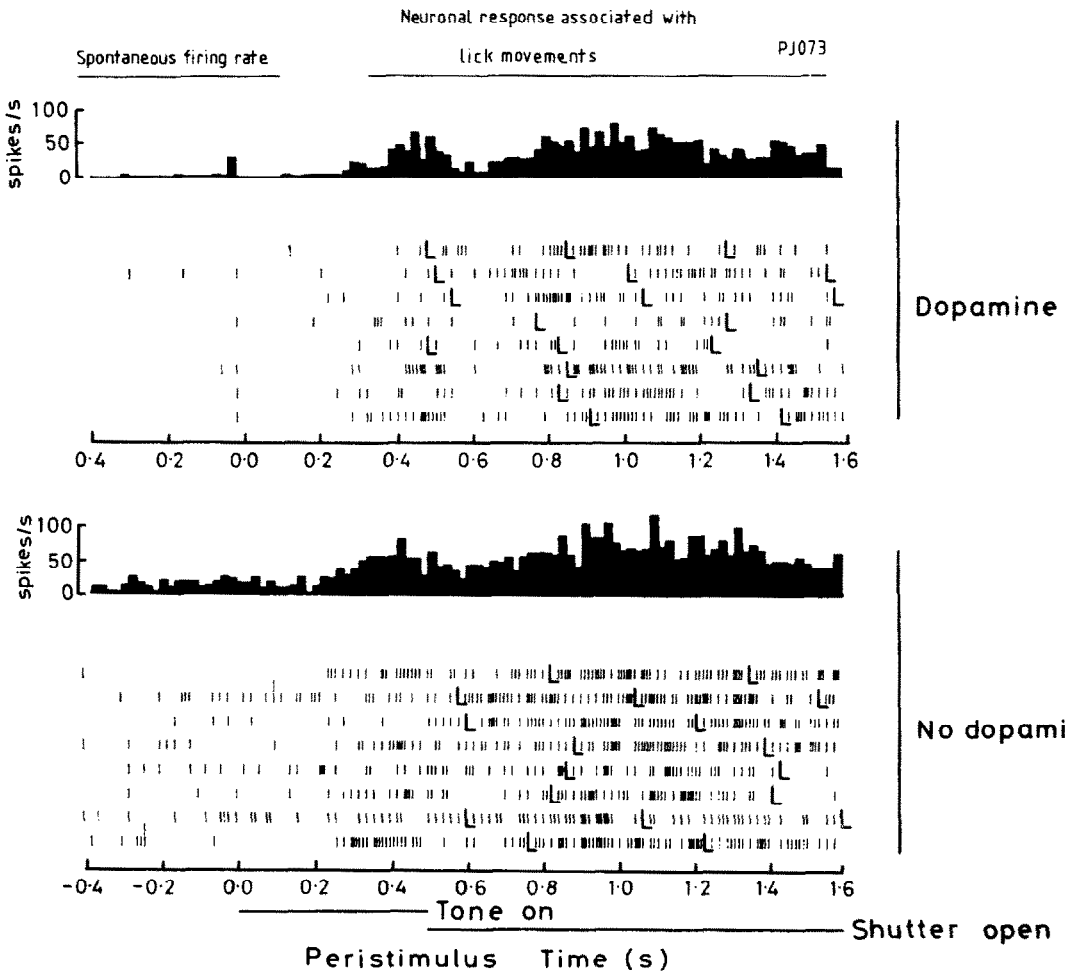

Fig. 5. Effects of dopamine on the spontaneous activity and the responses of a neuron in the putamen. Conventions as in Fig. 2. The lower rasters and histogram show that with no drug being applied the neuron fired spontaneously (before the signal tone for each trial) at a few spikes per second and responded by increasing its firing rate during the licking movements made by the monkey to obtain fruit juice after the shutter opened at time 0.5 s. The upper rasters and histogram show that iontophoresis of dopamine (100 nA) decreased both the spontaneous activity and the responses of the neuron.

opened after the 0.5 s tone). The upper histogram and raster displays show that while the dopamine was being applied iontophoretically, the spontaneous activity of the neuron was decreased, and so was the magnitude of the neuronal response associated with the lick movements. Another example is shown in Fig. 6 (PUT77J). Again, the dopamine decreased both the spontaneous activity of the neuron and the responses of the neuron associated with the lick movements being made in the task by the monkey. (For this neuron, a small amount of glutamate was being ejected continuously to produce a spontaneous firing rate of a few spikes per second in order to determine whether dopamine produced a similar effect on the spontaneous activity and on the responses of the neuron.)

Inspection of Figs 5 and 6 suggests that by reducing the spontaneous activity of the neurons, the dopamine tended to enhance the magnitude of the response relative to the spontaneous activity. If the spontaneous activity of the neuron is considered as noise, and the response of the neuron as the signal, then it might follow that the effect of the dopamine is to increase the signal to noise ratio of the neuron, by holding the spontaneous activity at a low level. In order to analyse quantitatively how dopamine effcts the activity of these neurons, the spontaneous firing rate with and without the iontophoretic application of dopamine, and the responses of the neuron both with and without the iontophoretic application of dopamine, were measured for each of the 38 neurons for which activity was available for many (4–25) trials with and without dopamine. An example of the spontaneous activity and of the responses of a neuron measured in this way with and without dopamine are shown in Fig. 7 (PJ088). In addition, it is shown in Fig. 8 that increasing the amount of dopamine ejected tended to decrease further both the spontaneous activity and the response of another neuron in the putamen (PJ077). (Throughout this paper, the re-

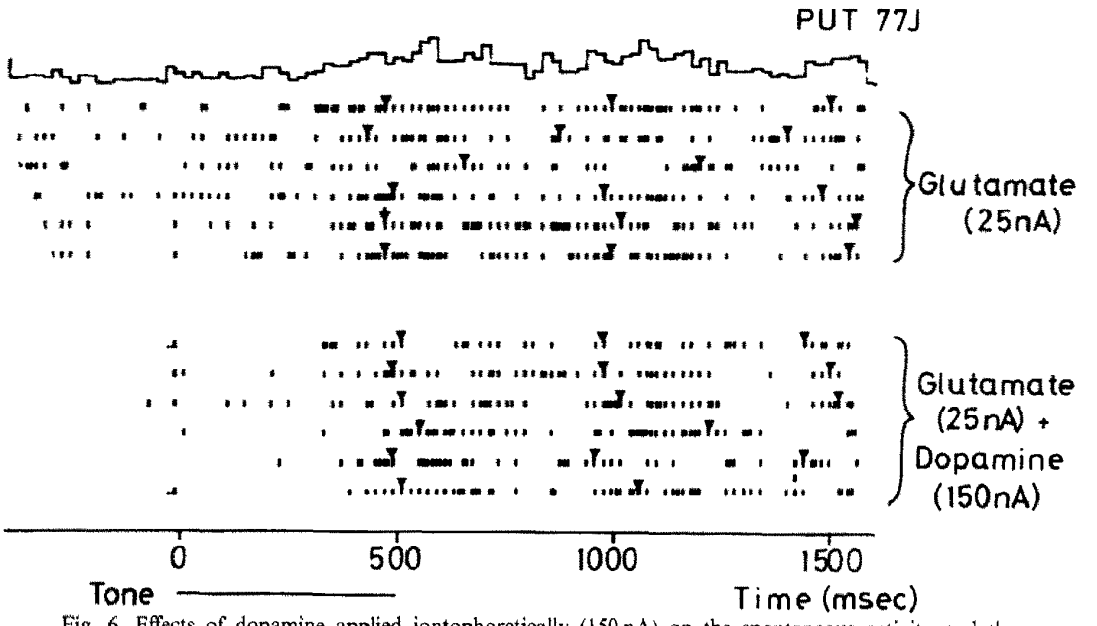

Fig. 6. Effects of dopamine applied iontophoretically (150 nA) on the spontaneous activity and the responses of another neuron in the putamen. Conventions as in Fig. 5, except that licks are represented by inverted triangles.

sponse of the neuron was measured as its firing rate in spikes per second during the period in which it was responding—see Discussion.)

One hypothesis suggested for consideration by the data shown in Figs 7 and 8 was that the effect of a given amount of dopamine was to reduce both the response of the neuron and its spontaneous firing rate by a similar number of spikes per second. This type of effect was that which best accounted for the data obtained across the whole population of neurons, as shown in Fig. 9, in which each point shows the reduction in the neuronal response compared to the reduction in the spontaneous activity for each neuron. In fact, the decrease in the response of the neurons produced by dopamine was 5.9 ± 0.99 (mean $\pm$ SEM) spikes/s, and the decrease produced in the spontaneous activity by the same current of dopamine was 6.52 ± 1.12 spikes/s. The similarity of these reductions was confirmed by the value of t obtained in a Student's t-test ($t = 0.67$, $df = 33$, paired test) and of T obtained in a Wilcoxon test ($T = 280$, $n = 34$, $z = 0.30$) for the comparison between the reductions produced by dopamine of the spontaneous activity and of the response of the neurons. (Four neurons were excluded from this comparison because their spontaneous firing rates

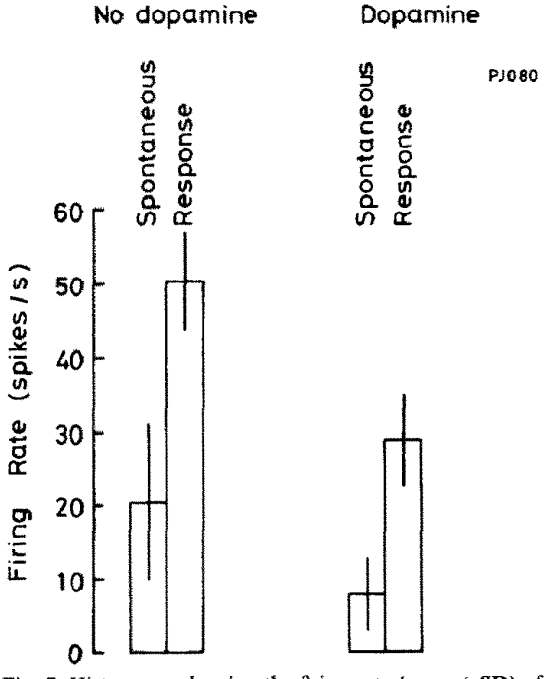

Fig. 7. Histograms showing the firing rate (mean $\pm$ SD) of the spontaneous activity and of the responses of another neuron in the putamen with and without the iontophoretic application of dopamine.

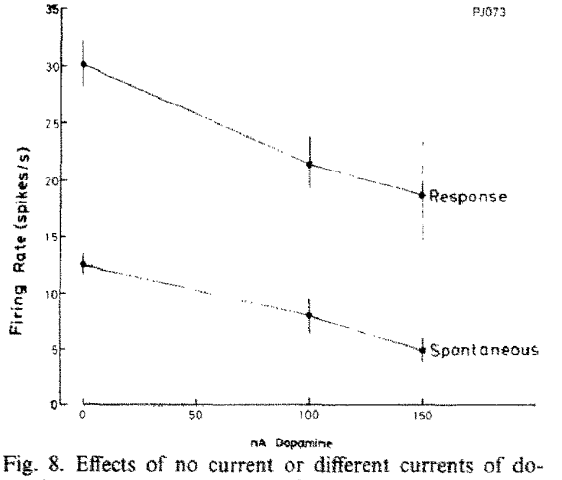

Fig. 8. Effects of no current or different currents of dopamine on the spontaneous activity (lower curve) and on the responses of the neuron shown in Fig. 5.

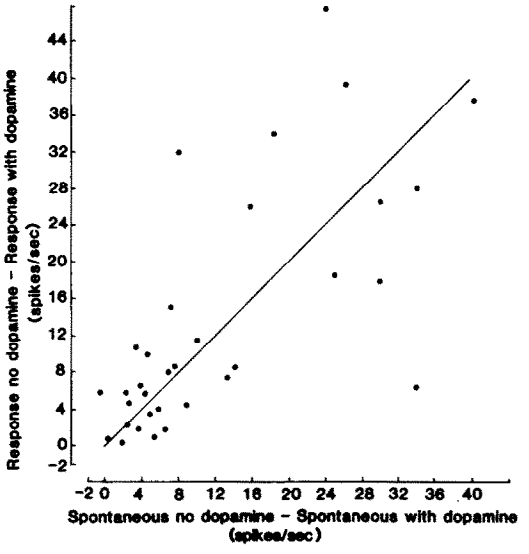

Fig. 9. The reduction in the responses of each neuron (spikes/s) produced by dopamine (ordinate) is plotted against the reduction in the spontaneous activity of that neuron produced by the same current of dopamine (abscissa). Each point provides data from one neuron. The line is drawn at 45°.

were so low that they were at a floor.) In that the reductions of the spontaneous and response-associated firing rates produced by dopamine were so similar, the most parsimonious explanation of the effect of dopamine is that it reduces the spontaneous firing rate and the response of the neurons equally.

The effects of dopamine on the responses relative to the spontaneous activity of the neurons can also be considered quantitatively in terms of its effects on the ratio of these values. This ratio (i.e. the response/the spontaneous firing rate), with and without dopamine, is shown for each neuron in Fig. 10, from which it is clear that dopamine tended to increase the value of this ratio. The mean ratio without dopamine was 1.92 ± 0.14 and with dopamine was 4.03 ± 0.67 ($t = 3.5$, $df = 33$, $P < 0.002$; $T = 65$, $n = 34$, $z = 3.97$, $P < 0.001$). Thus, if this ratio is considered analogous to the signal to noise ratio, this was significantly increased by the dopamine.

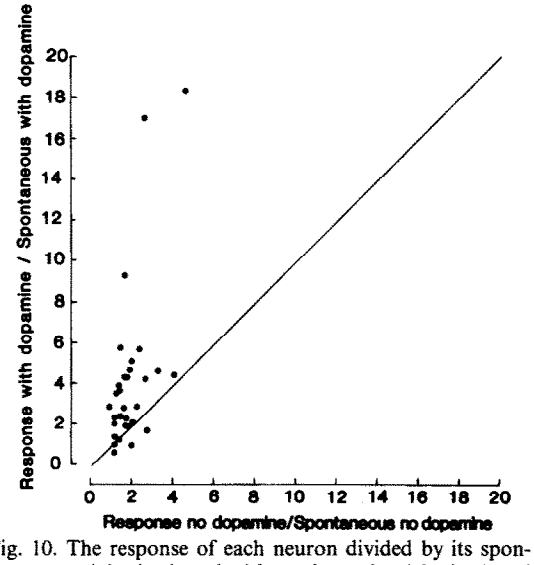

Fig. 10. The response of each neuron divided by its spontaneous activity is plotted without dopamine (abscissa) and with dopamine (ordinate). Each point provides data from one neuron. The line is drawn at 45°.

DISCUSSION

Anatomical and functional correlates of neuronal activity in different parts of the striatum

The present investigation provides further evidence on neuronal activity in the striatum, on differences between neuronal activity in different regions of the striatum, and that the inputs which activate these neurons are derived functionally (as well as anatomically[12,13]) from the cortex which overlies a particular region of the striatum. Thus in this investigation it was found that the majority of responsive neurons in the main part of the putamen (see Fig. 3) had responses related to movements made by the monkey (see also ref. 2). This is consistent with the inputs to these regions from sensorimotor cortex, areas 3, 1, 2, 4 and 6.[2,12,13] In contrast, though the same testing methods were used, neuronal activity related to visual stimuli and which showed rapid habituation was found in the tail of the caudate nucleus and adjoining part of the ventral putamen, which receive inputs from the inferior temporal visual cortex.[1] Also, neuronal activity related to the preparation for and initiation of behavioral responses in response to environmental cues was found in the head of the caudate nucleus,[32,33] whereas such neurons were relatively rare (10%) in the putamen, and instead neurons with activity unconditionally associated with movements made in the same test situations were common (29%) in the putamen. This difference in the type of neuronal response found in the putamen and the head of the caudate nucleus in the same testing situations provides further evidence that the responses of neurons in the head of the caudate nucleus are not unconditional movement-related responses, but are related to cues used in the preparation for and initiation of movements.[34] Again, a similarity in the responses of neurons in one part of the striatum to those in the cortical regions from which it receives is found, in that the head of the caudate nucleus receives projections from the prefrontal cortex (see ref. 32), in which neurons which respond to the same environmental cues are found (unpublished observations of G. Baylis and E. T. Rolls). Further, the activity of some neurons in the ventral striatum, which receives inputs from limbic structures such as the amygdala and hippocampus, occurs to stimuli related to emotional and novel environmental events[34] which are probably processed through limbic structures.[26,28]

The present study thus provides further evidence that neurons in different regions of the striatum have different types of response in the behaving primate.

Moreover, the results also provide further evidence that the processing in a given region of the striatum is related to the particular inputs it receives from the regions of cortex which project into it[12,13] and that it is these cortical inputs which are particularly important in producing the responses of striatal neurons normally shown when the system is operating physiologically in the behaving animal. The importance of this at least partial segregation of neuronal response types in different major parts of the striatum for our understanding of striatal function is that it shows that there is at least partial segregation of function within different regions of the striatum, and that it is not functionally homogeneous. A consequence of this is that damage to different regions of the striatum (including for example regional depletion of dopamine) would not be expected to necessarily lead to the same type of disorder. For example, in view of the results described here, it might be expected that movement disorders might be produced by depletion of dopamine in the putamen, but that other more complex disorders would result if there were depletion of dopamine in other regions of the striatum, such as the head of the caudate nucleus, the tail of the caudate nucleus, or the ventral striatum. Further issues important for our understanding of striatal function raised by the present results are whether within the striatum there is the possibility for different regions to interact and whether the partial functional segregation seen within the striatum is maintained in processing beyond the striatum. For example, is the segregation maintained throughout the globus pallidus and thalamus with projections to different premotor and even prefrontal regions reached by different regions of the striatum, or is there convergence at some state during this post-striatal processing? (see further ref. 29).

Effects of dopamine: functional implications

The results described here also show that dopamine, applied iontophoretically, decreases the normal responses shown by neurons in the neostriatum produced through their natural inputs, as well as decreasing the spontaneous firing rates of these neurons. Moreover, the quantitative analysis presented in Figs 7–9 indicated that the effect of dopamine on both the responses and the spontaneous firing rate was subtractive, in that dopamine decreased both the responses of each neuron and its spontaneous firing rate by a similar number of spikes per second.

The effect of this action of dopamine on how information is processed within the striatum will be considered in two ways. First, the effect of dopamine on signal to noise ratio will be considered. The signal to noise ratio can be represented by the ratio of signal plus noise to noise.[4,8,19] If the signal to noise ratio of the neuron is represented by the ratio of the response of the neuron to the spontaneous firing rate, then dopamine can be considered to increase the signal to noise ratio of the neurons (see Fig. 10). (Note that the response of the neuron is therefore represented by the firing rate of the neuron while the neuron is responding, rather than this firing rate minus the spontaneous rate, in order to be analogous to signal plus noise.) This result is what is obtained if the effect of the dopamine is to decrease the spontaneous activity and the response of the neurons in a subtractive way, for as the spontaneous activity tends to zero, so this signal to noise ratio tends to a high value. Indeed, if this analysis is followed, it may be proposed that one of the functions of dopamine in the striatum is to actively set the spontaneous firing rate of striatal neurons to its normal low level, so that effectively the signal to noise ratio of the information transmission system is maximal. This maintenance of the firing rate at a low level may require the continuous release of dopamine under normal conditions in the behaving animal, in that it was possible to show in at least some cases for neurons in the prefrontal cortex, which also receives a dopaminergic input, that the application iontophoretically of the dopamine receptor blocking agent trifluoperazine increased the firing rate of the neurons (see e.g. Fig. 4). Second, the effect of dopamine on signal detectability can be considered. In signal detection theory, the discriminability of the signal from noise, d', can be represented by the mean value of the signal minus the mean value of the noise all divided by a measure of the SD of the noise and signal distributions.[4,8,19] For a neuron, this could be represented by the mean firing rate when the neuron is responding minus the mean spontaneous firing rate all divided by the SD of these firing rates (and making appropriate adjustments if the SDs are different[4,8]). If this analysis is used, the subtraction of a constant from the spontaneous and the response firing rates, which is the effect of dopamine implied by the data shown in Fig. 9, would not normally affect the discriminability of the signal from the noise. However, if a relatively large amount of dopamine decreased the spontaneous activity of the neuron to zero, and the response firing rate of the neuron to a low value, then d' would be reduced to a low value. Thus, if analysed in this way, dopamine could influence transmission through the striatum by setting the threshold.

These two ways of considering the effect of dopamine on transmission through the striatum can be exemplified using the data shown in Fig. 7, in which SDs of the firing rates are shown. Given that the response-related and the spontaneous firing rates of the neuron were 50.4 and 20.6 spikes/s without dopamine, and 29.2 and 8.0 spikes/s with dopamine, the signal to noise ratio without dopamine was 2.45, and was increased to 3.65 by dopamine. However, the discriminability of the signal from noise was reduced from 29.8/SD without dopamine to 21.2/SD with dopamine (i.e. the differences of the response and the spontaneous firing rates.) (The SDs of the firing rates, have been taken to be constant for this example.) This example clarifies the difference between these

two analyses. Which is more helpful and relevant to the nervous system will depend on whether the postsynaptic neuron responds according to the ratio of the response to the spontaneous firing rate or to the difference between the response and the spontaneous firing rates. Regardless of which is used, the above discussion indicates that two ways in which dopamine could act to influence transmission through the striatum are by influencing the magnitude of the responses relative to the spontaneous activity or by setting the threshold.

These findings of regional differences in the types of neuronal response found in the striatum, and of how dopamine influences the responses of striatal neurons, lead us to suggest that dopamine may not only be involved in setting the sensitivity of transmission of information received from the cortex through the striatum to output structures, but may also be involved in shaping the activity of different parts of the striatum and thus in the type of behavioral response selected. For example, if activity were high in the tail of the caudate nucleus as a result of a sudden change in the pattern of a visual stimulus, then this could, through differential effects on dopaminergic neurons projecting to this as compared to other parts of the striatum, set transmission in this part of the striatum to a high level and at the same time reduce the sensitivity of other parts of the striatum to a low level. This would result in the selection of behavioral orientation to the changed patterned visual stimulus, with the suppression of other competing less strong responses being processed in other parts of the striatum. It may be noted (in line with the discussion on discriminability and signal to noise ratio above) that this setting to a low level could be performed by a large release of dopamine which would reduce the activity of the striatal neurons so much that they would not only show a zero spontaneous firing rate, but would also have a small change of firing rate to their normal input; or it could be achieved by decreasing the release of dopamine, so that the spontaneous firing rate of the neurons and thus the signal to noise ratio detected by the next stage of processing decreased. It is possible that some of the changes of firing rate observed in neurons in the striatum during the performance of behavioral tasks could be related to this resetting of sensitivity of different parts of the striatum by dopamine which may be part of the mechanism of response selection. In this way, only one response would be emitted by the animal. It may also be noted that this selective setting of the sensitivity of transmission through different parts of the striatum could be achieved by differential influences on the firing rates of dopaminergic neurons by input from other systems, such as the basal forebrain.

Some of the disorders of striatal function may be related to alterations in the ability of dopamine to select and regulate transmission through the striatum. Thus the akinesia of Parkinson's disease may be considered to be due to reduced processing and transmission through the striatum of cortical information to output regions, resulting from a decreased level of dopamine in the striatum and thus a decreased signal to noise ratio of the transmission. In contrast, increased dopamine function, produced by for example too much release of dopamine or enhanced receptor sensitivity to dopamine, would increase the signal to noise ratio of all the different signals reaching the putamen. This would mean that the normal response selection function of the striatum, involving perhaps competition between the inputs and thresholding, could not be performed adequately, with consequent oversensitivity to environmental stimuli.

Although there is little previous evidence on how dopamine affects the sensitivity of neurons to their normal inputs, there is some evidence suggesting that noradrenaline can influence signal to noise ratios. For example, noradrenaline decreased the firing of Purkinje cells of the cerebellar cortex evoked by stimulation of the climbing or mossy fiber inputs less than it decreased their spontaneous activity, so that the ratio of evoked to spontaneous activity was increased.[5,6] Also, the responses of cerebellar cortical neurons to natural visual stimulation are enhanced by the iontophoretic application of noradrenaline[23] or by electrical stimulation of the locus coeruleus.[22,38] Similarly, electrical stimulation of the locus coeruleus has been reported to enhance the overall transmission of hippocampal pyramidal cells of excitatory and inhibitory responses evoked by behaviorally significant stimuli.[35] In the present study we have shown that the iontophoretic application of dopamine tends to reduce the normal responses and the spontaneous activity of striatal neurons by a similar amount, pointed out that this type of effect may have implications for transmission through the striatum and argued that this effect could be described using either signal to noise ratio analysis or signal detection theory.

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