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ACTIVITY OF NEURONS IN THE VENTRAL TEGMENTAL REGION OF THE BEHAVING MONKEY

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SUMMARY

To investigate the functions of neurons in the ventral tegmental area, recordings were made of the activity of 257 single neurons in this area in the behaving monkey. Four main types of neuronal response were found in the ventral part of the tegmentum. First, neurons with activity phasically related to mouth or arm movements were found. Most of these were located relatively far lateral, close to the junction of the midbrain reticular formation with the zona incerta, or were in the substantia nigra, pars reticulata. Second, neurons were found which responded differentially in a visual discrimination task on trials on which the monkey had to initiate a licking response compared with trials on which he did not, and which also altered their firing rate tonically while mouth movements were being made in other situations (differential motor neurons). These were found mainly in the midbrain reticular formation, consistent with the view that populations of neurons in these regions are involved in the execution of movements. Third, neurons which also responded differentially in the visual discrimination task, but did not respond when the same movements were made in other situations, were found in the ventral tegmental area, in a region medial to and in some cases immediately dorsal to the substantia nigra pars compacta. Fourth, neurons which responded to cues such as a tone which enabled the monkey to prepare for performance on each trial of the visual discrimination task were found in the

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ventral tegmental area close to the midline. These third and fourth types of neurons were thus found in the region where neurons of the mesocortical and mesolimbic pathways are located. Their responses are similar to those of neurons found in the striatum, and it is suggested that they are important in enabling the animal to prepare for and then to engage in particular behavioral responses.

INTRODUCTION

The ventral tegmental area contains cell bodies of dopamine neurons in the monkey [9, 62] as well as in the rat [15, 65]. These neurons give rise to the mesolimbic dopamine pathway which projects to the nucleus accumbens and other structures in the ventral striatum, and to the mesocortical dopamine pathway which projects inter alia to the prefrontal and anterior cingulate cortex. In the monkey, neurons with these projections are found throughout a rather broad region bounded by the interpeduncular nucleus medially, and extending dorsally as far as the level of the red nucleus and laterally into and above the dorsal part of the substantia nigra, pars compacta [13, 37]. The non-nigroneostriatal dopamine systems have been implicated in a number of functions, including the initiation of locomotor [27] and exploratory responses to for example novel as opposed to familiar stimuli [10], and the integration and organization of complex behavior such as active and passive avoidance, visual discrimination performance, and delayed alternation [22, 58], as well as in the pathogenesis of schizophrenia [16, 25, 63]. However, although recordings have been made from single neurons in the substantia nigra of the behaving monkey, and neurons with movement-related activity have been found [7, 14, 29, 56], we do not know of previous recordings made from single neurons in the ventral tegmental area of the behaving animal. Therefore, in order to provide neurophysiological evidence on the functions of neurons in the ventral tegmental area, we investigated the activity of neurons in the ventral tegmental region of the behaving animal. In order to make the results as relevant as possible to understanding the functions and dysfunctions of this region in man, the recordings were made in a non-human primate, the macaque monkey.

Because this is the first study in which neuronal activity has been analyzed in the ventral tegmental area of the behaving monkey, the activity of neurons throughout this region was studied, and no attempt was made to record solely from putative dopamine neurons. Indeed, the activity of other neurons in this region was of interest, for not only may it influence or be influenced by the activity of dopamine neurons, but in addition these other neurons include neurons which are part of the midbrain tegmental reticular formation. This region has been implicated in a variety of functions, including the control of arousal and other behavioral states [2, 36]. A small number of studies have investigated reticular

formation activity in the behaving animal. Most have suggested motor functions, with neuronal activity related to for example movements of the limbs, head, eyes and tongue [5, 11, 38, 59, 60, 61].

The activity of neurons in this region was analyzed in behavioral tests of a type known to be disrupted by damage to the ventral tegmental area (VTA) or structures connected to it, and in situations in which neurons in structures connected to the VTA, are known to be responsive [42, 46, 47, 49, 50, 52, 53]. These tests included the initiation in response to tone and light cues, and the performance, of arm and hand movement and visual discrimination tasks. These tests are appropriate because this system including the dopamine pathways is implicated in the initiation, selection or switching of behavioral responses and movements [17, 22, 24, 28, 39, 58, 66], and because neurons in the striatum have been shown to respond both in relation to the initiation of movement and in relation to cues used to signal the initiation of movement [46, 52]. Particular attention was paid to whether neurons in the VTA responded differentially to a visual stimulus which indicated that a motor response could be made to obtain food, as opposed to a visual stimulus which indicated that no response should be made. Such differential activity would be of interest because the VTA receives projections from the preoptic area and lateral hypothalamus [30, 31, 55] in which neurons have been shown to respond to the sight of food [40–43, 45, 48] and because VTA neurons could be involved in switching behavioral responses on or off [28]. The behavioral tests also included the presentation of novel, aversive, and rewarding visual stimuli, and the elicitation of arousal, as these have been shown to activate separate populations of neurons in the ventral striatum of the monkey [50], with which the ventral tegmental region is reciprocally connected [12, 13, 35].

METHODS

The methods used were similar to those described previously [43–45, 52, 54, 64], and are presented here as briefly as possible, except where they differ.

Recording

Two male cynomolgous monkeys, *Macaca fascicularis*, 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. 26, but without the platinum plating). These etched electrodes had an exposed tip diameter and length of approximately 5 and 12 μm, respectively, and recorded from single neurons, as shown by the refractory period of the unit activity, shape of the waveform recorded, etc. The signal to noise ratios and action potential waveforms were similar to those illustrated previously [29]. 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. It was usually possible to investigate the activity of 20–25 neurons on each daily track, and to analyze the activity of particular responsive neurons for periods of up to 2 h.

Analysis of neuronal responses

(i) 'Clinical' tests. These tests provided a first screen for whether neuronal responses were related in any way to movements, to feeding, to the presentation of aversive objects, or to cues which enabled the monkey to prepare for the possible initiation of a movement. 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 neurons were taken in consecutive 2–3 sec 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 (prepresentation period 1); (3) as the experimenter's arm was gradually brought back into view (prepresentation period 2); (4) as the object was shown to the monkey at a distance of about 1 m; (5) as the object was gradually brought towards the monkey; (6) while the object was held close to the monkey's mouth so that mouth movements were made; (7) as the monkey was fed the object (if it was food or delivered saline); and finally (8) as the object was removed. The objects tested included foods such as banana, peanuts and a 2 ml syringe from which the monkey was fed fruit 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 cue or movement-related [43, 52, 64].

(ii) Shutter tests. This test situation was designed to determine whether neurons had visual responses, and to measure the latencies of the 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 (L.E.D.) 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. Visual stimuli were presented to the monkey in this computer-controlled task on a television screen mounted 2.3 m from the monkey. One of the stimuli, a white circle on a black background, 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, a white square of the same area and intensity as the circle, 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. The computer displayed the stimuli in a pseudo-random sequence. The stimuli subtended 2° at the retina. In order to ensure that the monkey was fixating the TV screen before the visual stimulus was turned on it was preceded by a 0.5 sec signal cue period during which a 450 Hz tone sounded and a small light mounted over the TV screen was illuminated. The monkeys' response latencies measured from time 0 when the positive discriminative stimulus was shown until the time of tongue contact with the lick tube were typically 300–400 msec.

(iv) Arm and hand movement task. In order to investigate the possible relation between the activity of the neurons and limb movements, the monkey was trained to perform a task involving a large arm movement followed by a repetitive hand movement. A trial of the task started when a light was switched on behind a reference button (RB) situated in front of the monkey level with his waist. The monkey then had to press the reference button for 300 msec. Next a light appeared behind a panel button (PB) situated on a vertical panel at eye level in front of the monkey, and the monkey then had to release the reference button, reach for the panel button, and press it 9 times in order to obtain fruit juice reward. A new trial started immediately, with the offset of the panel button light and the re-illumination of the reference button light. This task allowed neuronal firing to be measured in relation to the large arm movement involving mainly the proximal musculature as the monkey raised his arm from the reference button to reach the panel button, and in relation to small amplitude repetitive wrist and hand movements involving the distal musculature more.

Localization of recording sites

The locations of the neurons described in this paper were determained in two ways. First, at the end of every track, X-ray photographs were taken of the

frontal and lateral views of the head to determine (to within 0.5 mm) the position of the tip of the recording electrode relative to permanently implanted reference electrodes, whose positions were later determined histologically. Second, in the last 3 weeks of recording, lesions were made through the tip of the recording electrode to mark typical units. This was done by passing either cathodal current of 100 μA for 100 sec. Following tranquillization with ketamine and then a lethal i.p. dose of pentobarbitone sodium the animal was perfused with 0.9% saline followed by formol-saline. After equilibration in sucrose-formalin serial frozen 50 μm brain sections were cut and stained with thionin.

RESULTS

A total of 257 neurons was recorded in the ventral tegmental and adjoining region of the two monkeys. The following types of neuronal response were obtained.

Movement-related responses

Examples of the responses of a neuron in this region with movement-related activity are shown in Fig. 1. This neuron fired in relation to the presses of the panel button. It is shown in the upper part of Fig. 1 that the neuron fired at a high rate immediately before each press of the panel button (PPB). However no response was associated with either steady pressing (PRB) or release (RRB) of the reference button. The activity of the neuron in the same task displayed relative to the time of the panel button press (PPB) (time 0) is shown in the lower part of Fig. 1.

The activity of a neuron with responses phasically related to arm movements is shown in Fig. 2. The firing rate of the neuron (M571) was low while the monkey was repeatedly pressing the panel button with his arm elevated (PPB, left of Fig. 2), but increased to a high value while the monkey lowered his arm to the reference button, which was reached 500–600 ms after the last panel button press.

Of 23 neurons with movement-related activity, 8 had responses which were phasically related to mouth movements, whether these were made in the visual discrimination task, in clinical testing, or during continous licking to obtain fruit juice ad libitum. Fifteen neurons had activity related to movements of the contralateral forelimb, of which 13 responded phasically in relation to the large amplitude arm movement, one responded phasically in relation to the small amplitude hand movements made to press the panel button (e.g. Fig. 1), and one responded phasically during both the arm and hand movements. All 10 of these units tested failed to respond during ipsilateral arm movements, and 4 of 7 units tested showed a slight modulation in their activity during passive arm movements.

The locations of these neurons with movement-related activity are shown in Fig. 3 (see sections labeled A). The majority were found relatively lateral and

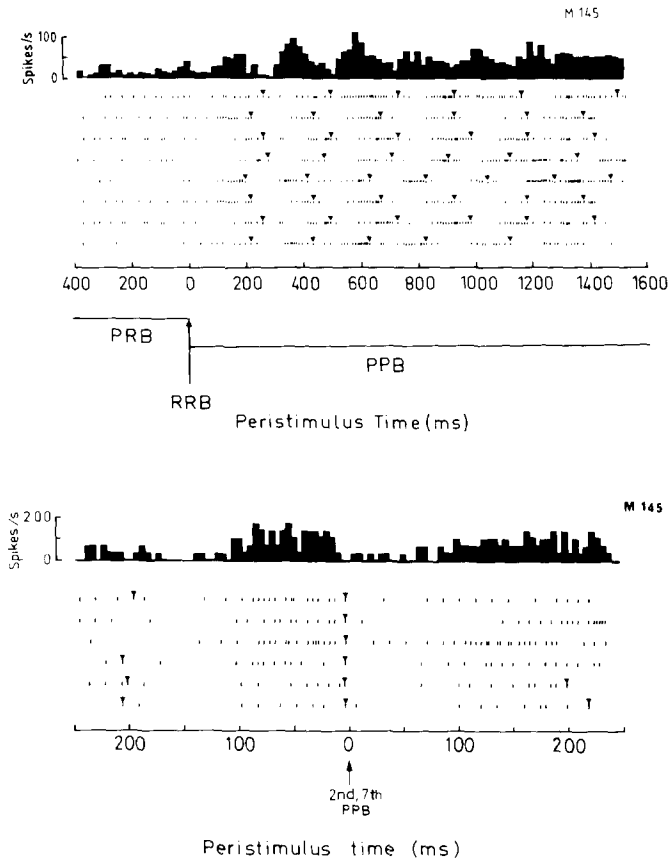


Fig. 1. A neuron with a movement-related response. The neuron fired phasically with every press of the panel button (PPB), the time of which is represented by an inverted triangle. The monkey pressed the reference button in the PRB period, at the end of which he released the reference button (RRB) and reached to press the panel button (PPB) repeatedly. Even horizontal line is one trial, and each spike from the neuron is represented by one vertical line. The filled histogram above shows the firing rate of the neuron calculated from the trials displayed. Bottom: the responses of the same neuron relative to the times of the panel press, to indicate the time locking of the neuronal response to the hand movement, are shown in the lower part.

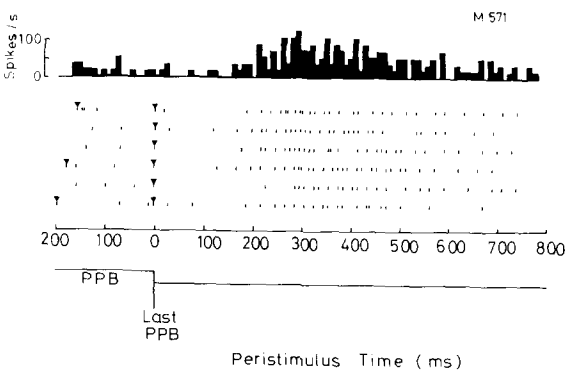


Fig. 2. A neuron with responses related to movement of the arm. The neuron fired when the monkey lowered his arm towards the reference button after the last press of the panel button (PPB). Conventions as in Fig. 1.

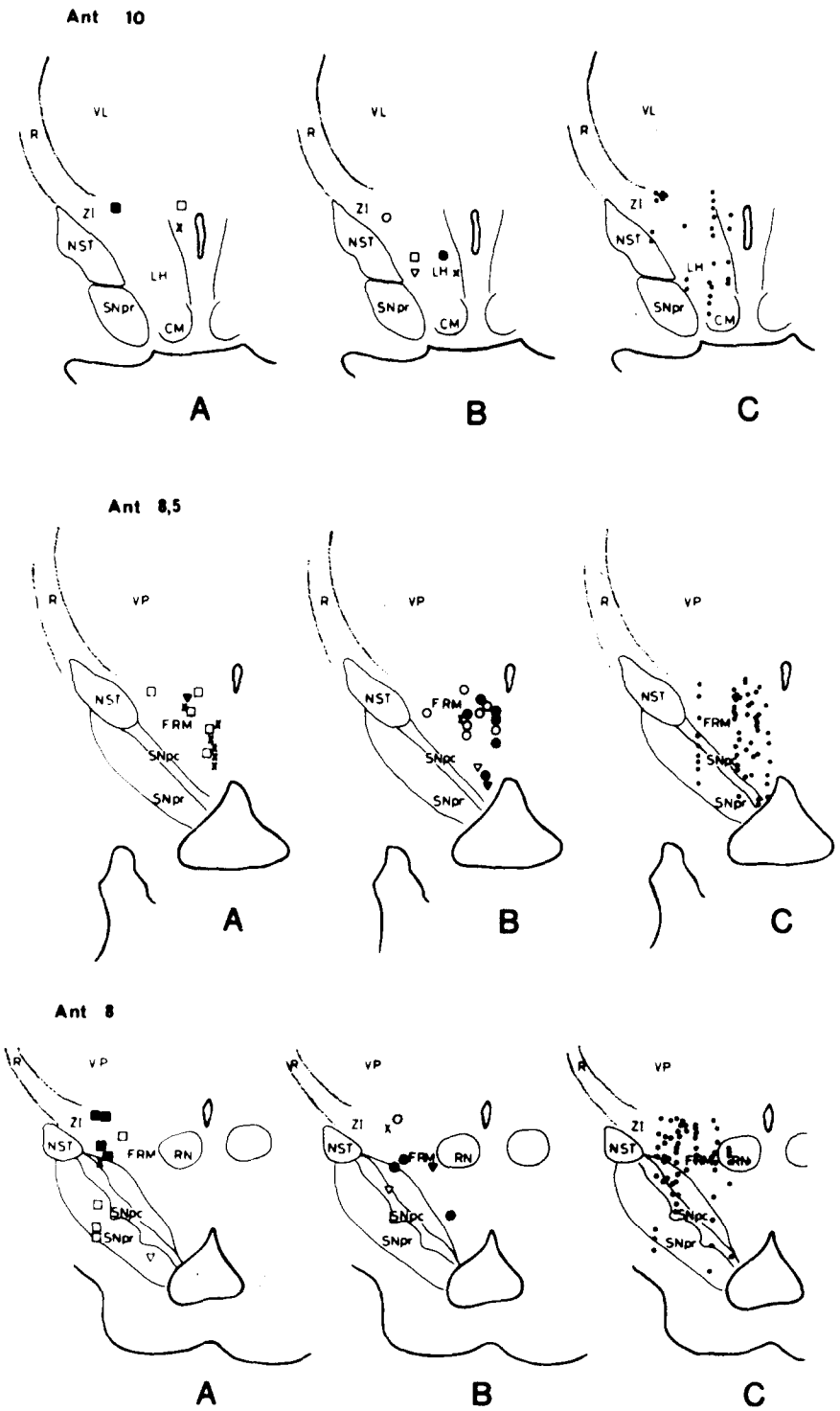
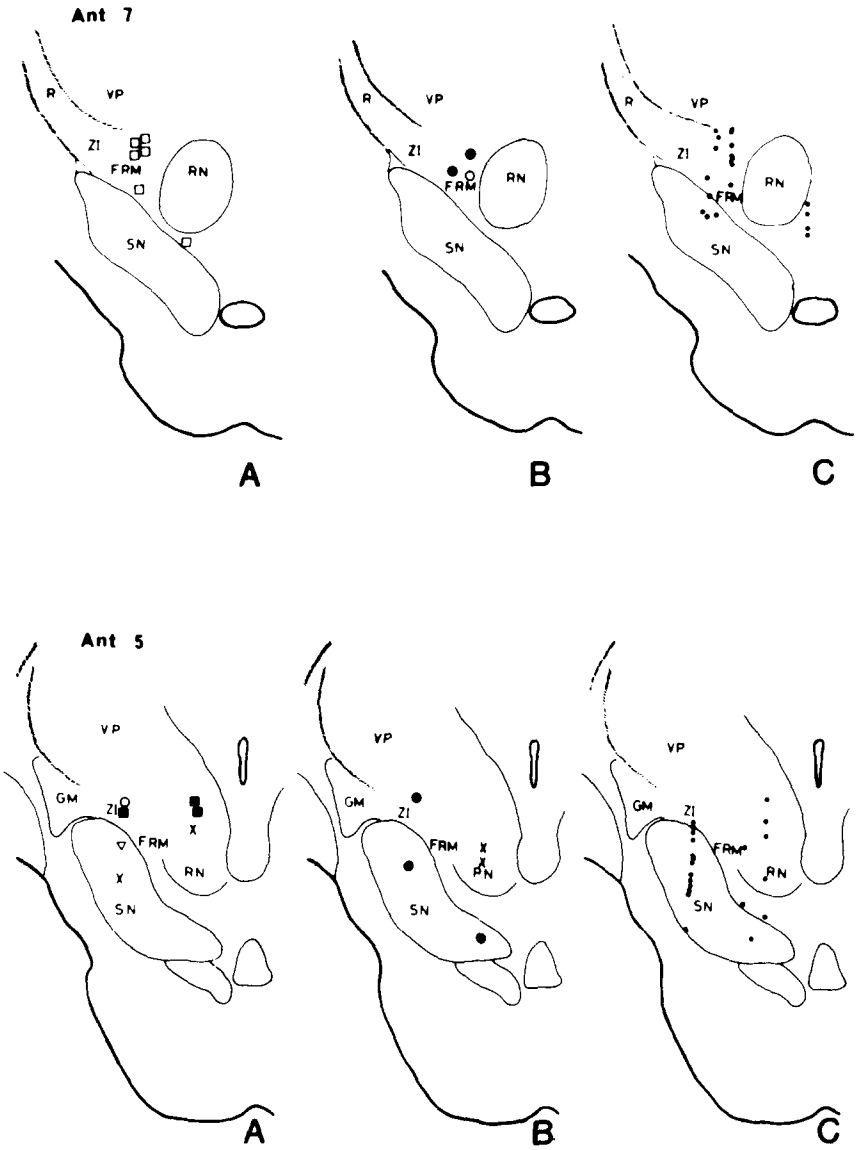


Fig. 3. The sites at which the different types of neuron were recorded, shown on coronal sections drawn from the histology. The planes are at the given number of mm anterior to the inter-aural plane. For each plane: Sections labeled A show cells related to limb (□) or to mouth (■) movements,



cue-related cells (x), and visual (▽), auditory (○), and eye movement related cells (▼). Sections labeled B show the different types of differential neuron; motor (○), task specific (●), arousal (▼), unconditional (□), unclassified (▽) and late differential (x). A novelty cell is shown by (⬢); because of its other response characteristics it is classified as task-specific differential in Table I. Sections labeled C show the locations of the unresponsive neurons. CM, mammillary body; GM, medial geniculate nucleus; FRM, midbrain reticular formation; LH, lateral hypothalamus; NST, subthalamic nucleus; R, reticular nucleus of the thalamus; RN, red nucleus; SNpc, substantia nigra, pars compacta; SNpr, substantia nigra, pars reticulata; VL, ventrolateral nucleus of the thalamus; VP, ventroposterior nucleus of the thalamus; ZI, zona incerta.

dorsal compared to the other neurons described below, in the zona incerta, the mesencephalic reticular formation, and the substantia nigra pars reticulata, although approximately one quarter of them were situated in the region of the ventral tegmental area within which dopaminergic neurons are located.

Neurons with cue-related activity

The activity of a neuron which responded during the cue period of the visual discrimination task is shown in Fig. 4 (M451). These neurons did not respond during mouth or arm movements made during the tasks, and did not fire in relation to body movements made in the experimental situation. Of 10 such neurons with cue-related activity, 5 responded with an increase of firing rate, and 5 with a decrease. The response latencies to the tone/light cue were typically between 100 and 220 msec, and ranged from 40–320 msec. Six of these neurons responded only during the cue period, and 4 continued their responding during the period in which the visual discriminanda were shown. The majority of these cue-related neurons were located close to the midline immediately rostral to the red nucleus, and were thus in the ventral tegmental area (see Fig. 3, sections labeled A). One other neuron in the VTA had activity which may be considered cue related, in that it responded whenever the panel for the arm movement task was placed in front of the monkey, and also responded in the clinical testing situation to the cues which signaled the presentation of a food or non-food object.

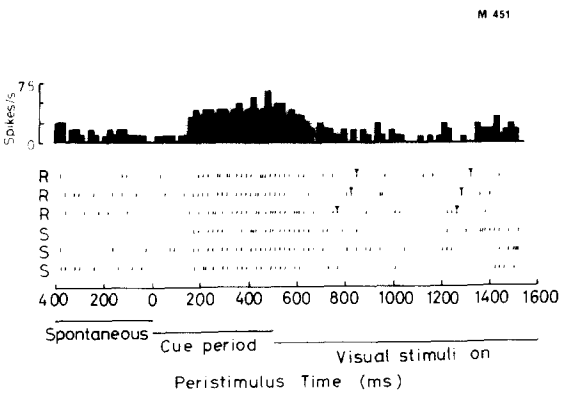


Fig. 4. The activity of a cue-related neuron. It responded in the 0.5 sec cue period in which a tone was sounded to indicate the start of a trial in the visual discrimination task. The visual discriminanda were shown at time 500 sec relative to the start of the tone cue. Licks, made to obtain fruit juice on the reward trials (R), are indicated by inverted triangles. Correctly, no licks were made on the trials on which aversive saline (S) would have been obtained. The trials are grouped together by type for this display, and were originally presented in random order. Other conventions as in Fig. 1.

Neurons with differential activity in the visual discrimination task

A considerable number of neurons was found which responded differently in the visual discrimination task on trials on which the reward-related visual stimulus was shown and the monkey initiated a lick response to obtain food, as compared to trials on which the visual stimulus associated with aversive saline was shown and the monkey did not initiate feeding. An example of such a neuron is shown in Fig. 5. This neuron started to respond by increasing its firing rate during the 500 msec cue period, and continued responding on reward trials (top traces), but stopped firing with a latency of approximately 130 msec relative to the onset of the visual stimuli on the trials on which the saline-aasociated visual stimuli were shown (lower traces). Of 36 neurons with differential responses in the visual discrimination task, 31 differentiated with short latencies which were for most neurons in the range 130–190 msec as shown in Fig. 6. These differential latencies were much shorter than the response latencies of the monkeys' licks, which were typically in the range 300–350 msec. The other 5 neurons had late differential responses in the range 220–390 msec.

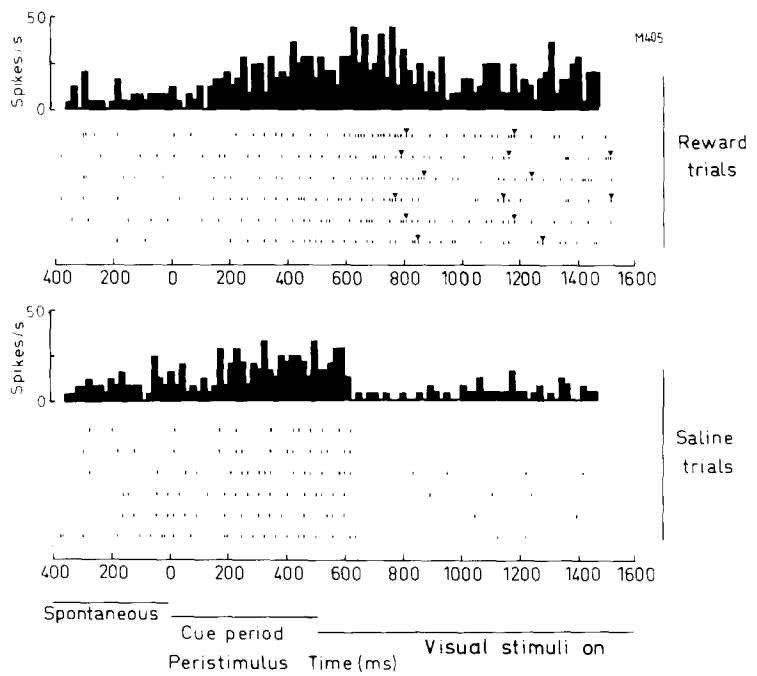


Fig. 5. The activity of a differential neuron in the visual discrimination task. The neuron responded more on reward than on saline trials, with a latency for the differential response of 120 msec relative to the onset of the visual discriminanda, which appeared at the end of the 0.5 sec cue period. The neuron showed a non-differential increase in firing rate in the cue period. Other conventions as in Fig. 4.

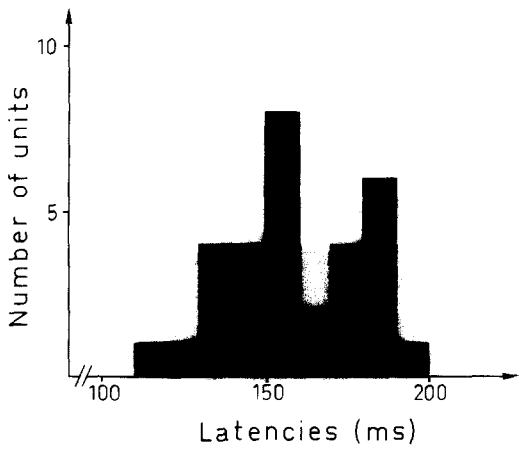


Fig. 6. The latencies at which neurons with differential responses in the visual discrimination task showed their differential response, relative to the onset of the visual discriminanda.

A group of 15 of these differential neurons was classified as showing task-specific differential responses, in that they had the following response properties. They had no response associated with lick or other mouth movements made outside the visual discrimination task, for example during clinical feeding or mouth movements (e.g. Fig. 7a), or during licking to obtain fruit juice ad libitum. Thus their responses in the visual discrimination task could not be ascribed simply to the mouth movements being made. Nor did these neurons respond to the sight of food when it was shown to the monkey in the shutter testing situation. In the clinical testing situation the majority (n = 10) did not respond (see e.g. Fig. 7a), but even if they did respond, they (n = 5) responded from the prepresentation cue throughout the period in which the monkey was engaged in feeding, so that their activity was more related to involvement in the testing situation that to the sight of food per se. Thus their responses did not occur to a range of different visual stimuli which were food or were associated with food, and were in this respect different from the responses of hypothalamic neurons associated with the sight of food (see refs. 43, 45). It is because the responses of these VTA neurons were differential in the visual discrimination task, but did not occur unconditionally to stimuli associated with food, that their responses are termed task-specific differential responses. It may also be noted that the responses of these task-specific differential neurons were not produced by arousing stimuli such as somatosensory stimulation, and were thus different from the arousal related differential responses described below. Eleven of these neurons responded by increasing their firing rate to the reward-related stimulus and decreasing it to the saline-related stimulus, and 4 responded in the opposite direction.

Eight (more than 50%) of these task-specific differential neurons responded not only in the period in which the visual discriminanda were shown, but also

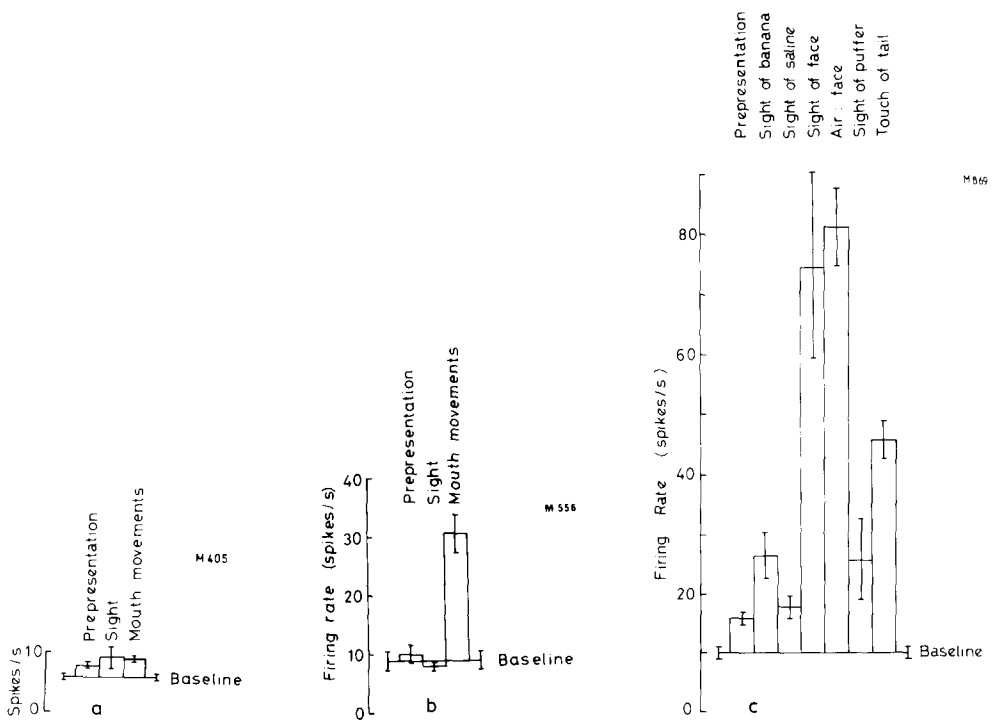


Fig. 7. a: firing rate of a neuron (spikes/sec) which did not respond in the clinical testing situation to cues which signaled the presentation of a food or non-food object ('prepresentation'), to the sight of food ('sight'), or in relation with mouth movements, but did have a differential response in the visual discrimination task (see Fig. 5), so that it was classified as task-specific differential. The response histograms are shown as changes from the baseline spontaneous firing rate, and the mean and the S.E.M. of 4 or more tests are shown for each condition. b: firing rate of a neuron in the clinical testing situation which responded during mouth movements. The same neuron had a differential response in the visual discrimination task, and because of its response in the clinical tests, was classified as motor differential. c: firing rate of a neuron in the clinical testing situation which responded to a number of stimuli which produced arousal. The same neuron had a differential response in the visual discrimination task, and because of its response in the clinical tests, was classified as differential arousal.

during the cue period, as illustrated in Fig. 5. These neurons thus responded for the whole period of each trial in which the monkey was engaged in the task, that is from the onset of the cue until the end of the reward availability period on reward trials, or until the saline-related visual stimulus had been shown on saline trials and the monkey has disengaged himself from the task. (These neurons were thus similar to some of the neurons in the head of the caudate nucleus with differential responses in the same task [52]). As noted above, 5 of these neurons also responded while the monkey was engaged in the clinical testing situation while he was prepraring for and receiving food.

The sites at which these neurons with task-specific differential responses in the visual discrimination task were recorded were mainly in the ventral tegmental

area, or in the region immediately dorsal to the substantia nigra pars compacta in which the cell bodies of the neurons which give rise to the mesocortical and mesolimbic pathways are found in the primate [4, 9, 37] (see Fig. 3, sections labeled B).

Ten of the 36 differential neurons were classified as differential motor because of the following properties. Like the task-specific neurons, they responded differentially in the visual discrimination task, but in contrast they also responded with a tonic change of firing rate when the monkey was making mouth movements in other situations, for example in the clinical testing situation (see e.g. Fig. 7b). Because these neurons had responses associated with mouth movements irrespective of the testing situation, it appeared likely that the differential responses of these neurons in the visual discrimination task were related to the generation of the mouth movements, and thus they were classified as differential motor. It should be noted that the responses of these neurons were not phasically related to each lick or mouth movement, as were the responses of the mouth movement related neurons described above. Instead, these neurons responded with a steady change of firing rate for the whole period in which the monkey was making mouth movements (see e.g. Fig. 7b). These neurons did not respond to the sight of food (e.g. Fig. 7b), but in 50% of cases did respond in the cue period which immediately preceded each trial of the visual discrimination task and which enabled the monkey to prepare to make the mouth movement response required. These neurons were mainly in the midbrain reticular formation (see Fig. 3, sections labeled B, e.g. Ant 8.5, and Table I).

A number of other types of neuron which responded differentially in the visual discrimination task were found (see Table I). First, two neurons which responded differentially responded in other situations to a wide range of stimuli which produced arousal. For example, the neuron shown in Fig. 7c (M869) responded to stimuli which produced arousal such as touch to the tail, air directed towards the face from a puffer, the sight of the puffer, etc, so that it was likely that the differential response of the neuron in the discrimination task was related to arousal, which may be maintained on reward trials. Second, 3 other neurons responded differentially in the visual discrimination task, but were not analyzed sufficiently in other situations to enable further classification. Third, another neuron responded differentially in the visual discrimination task to the stimulus associated with food, and also responded to the sight of food when this was shown to the monkey in clinical testing and through the shutter when testing for visual responsiveness. This neuron thus responded unconditionally, that is independently of the testing situation, to the sight of food. It was located rostral to the other neurons, at the posterior border of the lateral hypothalamus (Fig. 3, sections labeled B, Ant 10). (The responses and recording site of this neuron were thus similar to neurons in the lateral hypothalamus and substantia innominata which respond to the sight of food [43, 45, 48], and were distinct from those of the

TABLE I

Numbers of neurons recorded in different parts of the midbrain tegmentum

	Totals	*VTA**	*SN*	*FRM/ZI*	*Others*
Motor	23	4	3	15	1
Cue-related	10	5	2	2	1
Differential					
Motor	10	1	0	9	0
Arousal	2	2	0	0	0
Task-specific	15	7	2	5	1
Unconditional	1	0	0	0	1
Unclassified	3	1	1	0	1
Late differential	5	0	0	2	3
Other responses	5	1	2	2	0
Unresponsive	183	26	43	85	29
Total cells recorded	257				

* VTA column includes supra-nigral neurons.

differential neurons described above in the ventral tegmental area (see Discussion).

Five further neurons responded differentially on reward and saline trials in the visual discrimination task, but the latencies of the differential responses were relatively long, in the range 220–390 msec. These relatively long differential response latencies suggested that these neurons were involved in details of the performance of the motor responses being made, and although these neurons did not respond in relation to movements made in the clinical testing situation, the brain sites in which they were recorded were different from those of the neurons with task-specific differential responses described above. Their recording sites were in the red nucleus (2 neurons), in the midbrain reticular formation (2 neurons), or in the far caudal lateral hypothalamic region (see Fig. 3, sections labeled B).

Neurons with responses to novel stimuli

Examples of the responses of a neuron recorded in the VTA which responded much more to novel than to familiar visual stimuli are shown in Fig. 8. The responses of this neuron to novel 3 dimensional visual stimuli presented in the shutter situation, and to the same stimuli presented later in the testing situation when they were familiar, are illustrated (M478). The duration of the memory reflected in the responsiveness of this neuron was estimated by presenting series

of visual stimuli in which each stimulus was shown for a first time as novel and then after a variable number of intervening trials as familiar (see ref. 51). The responses of this neuron in this type of series are shown in Fig. 9. It is clear that the neuron responded more to a novel visual stimulus than to a familiar visual stimulus even when the visual stimulus had not been seen for 33 trials. Linear regression analysis indicated that the response to familiar stimuli intersected with that to novel stimuli only when the familiar stimuli had not been shown for 45 trials. In another type of memory test, it was shown that the response of this neuron to a novel stimulus (presented on trial 1) habituated over a series of repeated trials (see Fig. 10). The viewing time was 1.5 sec/trial. Some dishabituation occurred when there was a gap with other intervening stimuli after trial 4 (see Fig. 10). In addition to its memory-related response, this neuron responded in the visual discrimination task more on reward than on saline trials, with a differential latency of 110 msec. The recording site in the VTA of this neuron with responsiveness which represented a fairly durable memory spanning many trials is shown in Fig. 3 (Ant 8.0, sections labeled B).

Other neurons recorded in this study include two neurons with visual responses which occurred non-selectively to different stimuli. These neurons were in the substantia nigra, pars reticulata. In addition, one neuron with activity related

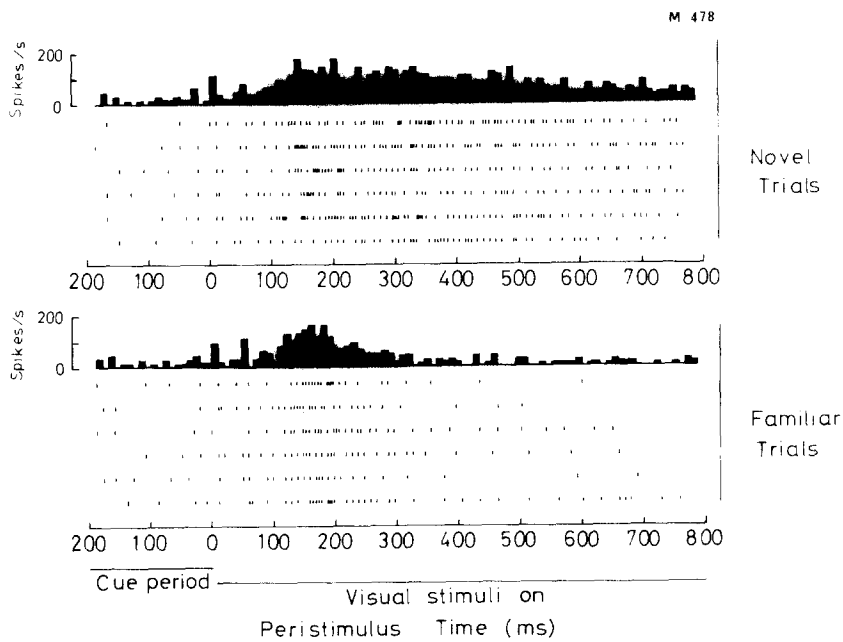


Fig. 8. Activity of a neuron which responded more to novel than to familiar visual stimuli. On each trial, the shutter opened after a 0.5 sec tone signal cue at time 0, to reveal either a novel 3-dimensional object, or one which had been seen before on a previous trial (Familiar). The trials were originally run in random order. For each condition the filled histogram above shows the firing rate calculated from the trials displayed.

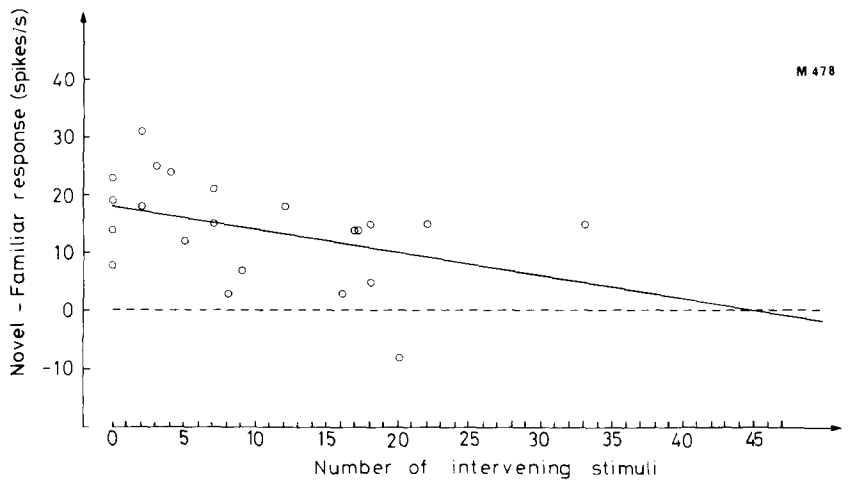


Fig. 9. Response of the neuron shown in Fig. 8 to visual stimuli as a function of the number of other stimuli intervening between the novel and the familiar presentation. The neuron responded more to the novel than to the familiar stimuli at most delays tested, and the response is expressed as the difference between the response to the novel and to the familiar presentation of the same stimulus, measured in a 0.5 sec period starting 0.1 sec after the shutter opened to show the stimulus. Each stimulus was shown for 1.5 sec. Each point represents the difference between the novel and familiar presentations of one stimulus. The linear regression line is shown.

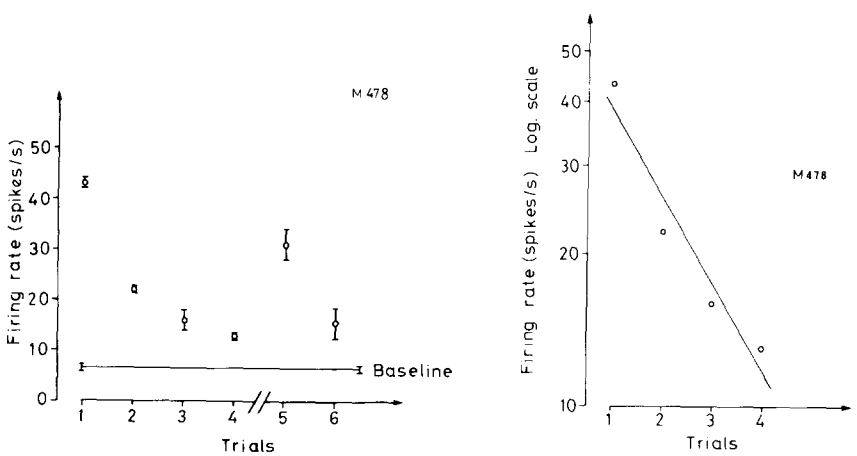


Fig. 10. Responses of the neuron shown in Fig. 8 and 9 to the same visual stimulus shown repeatedly. The same stimuli were repeated consecutively on trials 1–4, and were shown again on trials 5 and 6 after a period in which other stimuli were shown. The firing rate was measured in a 0.5 sec period starting 0.1 sec after the shutter opened to reveal the stimulus. Each point represents the mean (with the S.E.M.) of the first, second etc presentations of different stimuli. The graph on the right shows the firing rate plotted on a log scale, and the straight line is the calculated regression line for exponential decay.

to eye movements, and another with activity related to auditory stimuli, were noted in the midbrain reticular formation, consistent with other findings [5, 11, 18, 20].

DISCUSSION

Four main types of neuronal response were found in this investigation of neuronal activity in the ventral part of the tegmentum of the monkey. First, neurons with activity phasically related to mouth or arm movements were found (see Table I). These were usually located relatively far lateral, close to the junction of the midbrain reticular formation with the zona incerta (see Fig. 3, e.g. sections at Ant 7.0 and 8.0), or were in the substantia nigra, pars reticulata. Second, neurons which responded differentially in the visual discrimination task on trials on which the monkey had to initiate a motor response compared with trials on which he did not, but which also altered their firing rate tonically while mouth movements were being made (differential motor neurons), were found mainly in the midbrain reticular formation (see Fig. 3). These findings are consistent with the known anatomical inputs and outputs of these regions, and with the view that populations of neurons in these regions are involved in the execution of movements. For example, these regions receive inputs from motor structures such as the globus pallidus [32], the cerebellum, the tectum, and the motor cortex [18, 19, 23, 34]. In addition, the reticular formation sends axons towards the ventral spinal cord, so that neurons could have mono- or disynaptic connections with spinal cord motoneurons [1]. Neurons with mouth and arm movement-related activity in the substantia nigra, pars reticulata, have been described previously by Mora et al. [29] and Schultz [56]. Third, there were cue-related neurons, most of which were located in the ventral tegmental area close to the midline (see e.g. Fig. 3, Ant 8.5). This is the region where neurons of the mesocortical and mesolimbic dopamine pathway are located [4, 9, 13, 37], but in this study no attempt was made to determine the transmitter used by the neurons recorded. Fourth, neurons which had task-specific differential activity in the visual discrimination task but did not respond to the sight of food or during mouth movements, were found in the ventral tegmental area, in a region medial to and in some cases immediately dorsal to the substantia nigra pars compacta (see e.g. Fig. 3, Ant 8.0 and 8.5), that is they also were found in a region where neurons of the mesocortical and mesolimbic pathways are located [4, 9, 13, 37].

The neurons in the ventral tegmental area with cue-related responses had properties very similar to those of cue-related neurons in the head of the caudate nucleus [52] and ventral striatum [50] of the monkey. This similarity suggests a functional connection between the two regions, which could be mediated by the pathways which descend from the ventral striatum and perhaps the adjoining part of the head of the caudate nucleus to the ventral tegmental area [32, 33].The question of whether the responses of cue-related neurons are more closely related

to sensory input or motor output has been discussed in detail elsewhere [52]. It appears that in many cases they do not respond unconditionally to sensory stimuli in relation to any identifiable movement, but rather respond to environmental stimuli which are used as cues for the preparation for and initiation of movement. It is suggested that by responding to environmental stimuli which are used as cues for the preparation for and initiation of movement, these neurons may be part of a mechanism for the initiation of movements. The control of these cue-related neurons could be exerted by an influence on the striatum and frontal cortex, to which neurons in this region project [3, 13, 35, 37, 57]. Damage to the ventral tegmentum which results in disorders in locomotion [21] and in responsiveness to relevant environmental stimuli [22, 58] may be due to damage to the neuronal system described here.

The neurons with task-specific differential responses in the visual discrimination task, which were mainly in the VTA, had activity which implicated them in whether a response was generated on each trial. Although their responses were differential in the task, their responses did not reflect the sensory information required to perform the task, in that they did not respond to, for example, the sight of other reward-related visual stimuli such as the sight of food seen in clinical testing or through the shutter. Their responses were thus different from those of the neurons in the lateral hypothalamus and substantia innominata which respond to the sight of food in the hungry monkey [43,45, 48]. The distinction was emphasized in the present investigation when one neuron with responses to the sight of food, and differential responses in the visual discrimination task, was found rostral to the other neurons in this study close to the hypothalamus (see Fig. 3, Ant 10). Nor were the responses of the task-specific differential neurons related simply to the licking movement being performed in the task, in that they did not respond when the same movement was made outside the task in order to obtain fruit juice ad libitum. As the responses of these neurons continued for as long as the monkey was engaged in the task on each trial, that is until he had finished licking on reward trials or until he had aborted motor responses on saline trials, and in many cases started during the cue period of each trial, it is suggested that these neurons are important in enabling the monkey to remain locked into the performance of the task on each trial. This switching on or selection of behavior in the task could be at the expense of behavioral sensitivity to other inputs. This influence could be exerted by axons which ascend from this region to the striatum and frontal cortex. Consistent with this proposed function for these neurons is that lesions of the VTA alter the tendency of the animal to orient to stimuli and switch behaviors, and disrupt the performance of operant tasks [22, 39, 58]. Similarly, the observation of neuronal activity in the VTA related to the presentation of novel as compared to familiar stimuli may be related to the switching of behavior to explore new stimuli which occurs normally, but which is disrupted by destruction of dopaminergic terminals in a region to which VTA neurons project, the nucleus accumbens [10].

It is of interest that neurons in the VTA responded in situations in which VTA damage produces deficits, so that the neurons in this region may not mediate a purely sustaining function, but rather information related to changes in the environment to which a change of behavior is required may be transmitted along these neurons.

Although the recordings described here included recordings made from neurons in the ventral tegmental area, in the region in which dopamine-containing neurons are found and from which pathways ascend to the ventral striatum and prefrontal and cingulate cortices [13, 37], the recordings were not necessarily from dopaminergic neurons. The firing rates were often relatively low [19/31 differential neurons less than 20 spikes/sec), but in future studies tests for antidromic activation from the ventral striatum and prefrontal cortex would provide additional useful evidence on the identity of the neurons recorded. Nevertheless, the recordings described here give the first indication on the nature of neuronal responsiveness in the ventral tegmental area, and it is more than likely that even if these neurons are not themselves dopaminergic, they receive information from the striatum and frontal and cingulate cortex [32, 35], and may well influence the dopaminergic neurons. The frontal cortex, head of the caudate nucleus, and ventral striatum could, for example, provide a pathway through which task-specific differential and cue-related neurons in the VTA are driven, for neurons with these proporties are found in these regions [50, 52, 64].

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