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Responses of Midbrain Dopamine Neurons to Behavioral Trigger Stimuli in the Monkey

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SUMMARY AND CONCLUSIONS

1. Destruction of the midbrain dopamine (DA) system in Parkinsonian man and experimental animals leads to deficits in initiation of behavior, motor performance, and cognitive mechanisms. We have investigated the extracellular impulse activity of single midbrain DA neurons in unlesioned monkeys performing in a controlled behavioral task that was designed to paradigmatically test behavioral reactivity. Animals were trained to execute natural forelimb reaching movements for food reward in response to a trigger stimulus.

2. Presumptive DA neurons were histologically located in the pars compacta of substantia nigra and in neighboring areas A8 and A10. They spontaneously discharged polyphasic impulses of relatively long duration (1.4–3.6 ms) and at low frequencies (0.5–8.5/s). Systemic injections of low doses of the DA autoreceptor agonist apomorphine (0.05–0.2 mg/kg) depressed the activity of virtually all thus tested DA neurons. In following established criteria, these characteristics strongly suggest the DAergic nature of the recorded neurons.

3. The majority of midbrain DA neurons (70 of 128) responded to the behavioral trigger stimulus of the task with a short burst of impulses. Latencies ranged from 39 to 105 ms (median 65 ms) for onset and from 65 to 165 ms (median 95 ms) for peak of responses. Responses occurred before arm movement and at the time of or before onset of electromyographic (EMG) activity in prime mover muscles. Responses were time-locked to the stimulus and not to the onset of movement or EMG.

4. Responses remained present in most neurons but were reduced when vision of the behavioral trigger stimulus was prevented while maintaining the associated acoustic signals. In another variation of the task, most neurons also responded to a stimulus that was physically identical to the behavioral trigger but to which the animal made no movement.

5. The activity of a few DA neurons (11 of 128) was reduced following presentation of the behavioral trigger stimulus, with latencies comparable to those of activations.

6. The activity of many DA neurons was increased (40 of 128) or reduced (22 of 128) during execution of the forelimb reaching movement. These changes were of a slow and moderate nature, and were minor compared with responses to the behavioral trigger stimulus. About half of movement-related neurons also responded to the behavioral trigger.

7. The activity of a few DA neurons was increased (11 of 128) or reduced (1 of 128) when the food reward reached the mouth. These changes did not occur with spontaneous mouth movements. About half of these neurons also responded to the behavioral trigger.

8. The activity of a few DA neurons was increased (4 of 77) or reduced (1 of 77) during the total duration of each single trial of performance in the behavioral task, this lasting several seconds. Most of these neurons also responded to the behavioral trigger.

9. In conclusion, DA neurons discharge impulses in response to stimuli that are associated with a quick and direct behavioral reaction. They also show moderate changes during its execution. Dopamine neurons thus are neither purely sensory nor purely motor in nature, but rather appear to subserve a spe-

cific mechanism that is related to the behavioral reactivity of the organism.

INTRODUCTION

Dopamine (DA) neurons of the mammalian midbrain send axons to a variety of brain structures. By far the largest projections are directed toward the striatum (the nigrostriatal DA system), the nucleus accumbens and amygdala (the mesolimbic DA system), and the frontal cortex (the mesocortical DA system). Nigrostriatal DA neurons appear to be mainly involved in the initiation and execution of behavioral acts. Their destruction severely affects reactions of the organism to salient external stimuli, as well as the occurrence of more loosely timed, "spontaneous" movements in the absence of directly activating stimuli. This is seen in Parkinsonian man, in which the majority of midbrain DA neurons are destroyed (14, 23), and in experimentally lesioned animals (45, 56, 60). Destruction of the prefrontal cortical DA innervation results in profound deficits in delayed response tasks (4, 64), a cognitive dysfunction typically also seen with lesions of prefrontal neurons. Reductions of cortical DA levels in Parkinsonian patients (55) may be a main factor in the frequently occurring cognitive impairments in this disease (31, 44).

Despite its fundamental importance in behavior, details of the functions of the DA systems are rather poorly understood. Most knowledge is presently derived from the "negative image" assessed after lesions. Modern neurophysiological techniques may help to provide closer insights by studying the impulse activity of single neurons during various behavioral situations. Using this approach, it was found that DA neurons in the cat were devoid of phasic variations in discharge rate during ambulatory walking (67), although mean discharge frequency appeared to be higher during active compared with quiet waking (72). Otherwise, no changes were seen across different stages of the sleep-waking cycle (36, 67, 72). In the monkey, pars compacta neurons of substantia nigra (SN) showed a lack of phasic changes while performing in a controlled arm tracking task with visual feedback signals (12). However, DA deficiency in Parkinsonian man and in experimentally lesioned animals results in a more general reduction and slowing of behavioral reactions including movements, rather than specific impairments of detailed parameters of motor performance. It may thus be more appropriate to study the effects of sensory stimuli that are known to result in behavioral activation. Without a behavioral context, DA neurons were found to respond to stimuli of different sensory modalities in anesthetized rat and monkey (9, 51) and in awake cat (68). In haloperidol-treated rats a limited number of midbrain DA neurons responded to conditioned stimuli that lead to a licking response or forelimb movement (37).

In our laboratory, we investigated the responsiveness of DA neurons in monkeys performing in a complex behavioral task involving several preparatory auditory and visual stimuli for a later occurring arm movement (59). We found no responses to these stimuli but observed a slow and moderate increase of discharge rate during, and sometimes before, execution of the arm movement that appeared to be related to the concomitant behavioral activation rather than contractions of individual muscles or groups of muscles. Puzzled by the absence of responses to informative sensory stimuli, we then designed a behavioral task in which the monkey reacted directly and quickly with an arm reaching movement to a trigger stimulus without being prepared by a sequence of signals. While the animal performed in this task, we studied the activity of neurons whose DAergic nature was assessed according to established electrophysiological and pharmacological criteria. Some of the data have been presented in preliminary form (57).

METHODS

Two female *Macaca fascicularis* monkeys (*A*: 2.0 kg and *B*: 2.75 kg) were trained to perform in a behavioral task, implanted with intramuscular electrodes and an electrode base for daily single cell recordings in the midbrain in relation to contralateral behavioral acts, and, on completion of the experiment, killed for histological assessment of the recording area. Many techniques were similar to those previously reported (58, 59, 60).

Behavioral task

Each animal was trained to perform in a common basic behavioral task. Variations of this task were used in addition for investigating certain aspects in more detail. Animals were seated 3–6 h each weekday in a specially constructed, completely enclosed primate chair that allowed free movements of both

arms, limited excursions of the legs, and some postural adjustments. Temperature in the chair was maintained at 23–26°C, and a constant background noise of 71 dB intensity from a computer hard disk drive largely masked unrelated acoustic stimuli. Animals were released each day into their home cages. Training and data recording periods each lasted 3–4 mo. Behavior was reinforced by food rewards that consisted of ~1/100–1/150th parts of an apple. Animals were deprived of food and fluid on weekdays, their weight being controlled and maintained above 90% of the preexperimental level. Animals worked in discrete trial schedules. Their performance was assessed and controlled on-line by a digital computer.

The basic task for both monkeys was a direct reaction task that was designed to represent a natural situation typical for primates in which the subject performs a reaching movement following a trigger stimulus. Stimulus presentation, movement target, and contact with reward were all located at the same position (Fig. 1). Before the trial start, the animal had to keep its hand relaxed on a key (Fig. 1*A*). The key consisted of a nonmovable round metal knob connected to an electronic frequency-sensing circuit that detected the touch of the animal's hand as a change in electrical capacity. Each trial was initiated by the experimenter by closing the door of a food-containing box. Food boxes had a frontal opening of 40 × 40 mm and were placed at eye level, at 27° laterally, and at reaching distance of the forearm (250 mm from the animals' shoulders), one on each side. About 15–40 s after closing, the door was opened vertically upward, with complete opening being achieved within 20–22 ms (Fig. 1*B*). Door opening was visible to the animal and produced a low-intensity sound that was audible in the presence of the background noise. In addition, onset of door opening triggered a 1-kHz rectangular sound stimulus of 100-ms duration from a distant source with an intensity of 90–92 dB, measured at the head of the animal. Animals released the holding key after door opening (Fig. 1*C*), reached into the box, took the food (Fig. 1*D*), and brought it to the mouth. Premature key release cancelled the trial. Animals were unable to reach into the box of the opposite side. Phototransistors sensitive to an infrared light beam across the entrance of each food box served to determine the time at which the animal's hand entered and left the box (beginning and end of beam interruption). Behavior was electronically monitored from standard electronic pulses generated from door closing and opening, release of the holding key, and entering and leaving the food box (Fig. 1*E*). Although no time limits for reacting to door opening were imposed, trained animals responded quickly and reliably. Reaction times (latency of key release after door opening) were virtually always below 350 ms and movement times (from key release to entering the food box) below 210 ms. Animals reacted to the visual and auditory stimuli associated with door opening and not to the sight of food. The quick movement reaction remained present during occasional absence of food morsels in the box.

An additional task of *monkey A* differed from the basic task by the fact that sight of the food box was prevented by a cover in front of it, positioned to give an access of 40 × 50 mm to the box from below. Thus neither door opening nor food reward were visible to the animal, and the behavioral trigger stimulus was reduced to the low-intensity sound and the 1-kHz sound accompanying door opening.

In the additional task for *monkey B*, the door of another box opened ~2 s before the food box (Fig. 1*F*). This accessory box had the same physical properties as the food box, with the exception of a 5-mm-thick perfectly transparent Plexiglas plate mounted across its frontal opening, which maintained vision but prevented manual access to the interior. Opening of its door was identical to that of the main door, since it was composed of the visual stimulus, the low-intensity opening sound, and the 1-kHz sound. One accessory box on each side was positioned medially to the food box at the same eye level, this being at 15° laterally. It never contained any food morsels. The animal remained motionless after its opening.

Electrophysiological procedures

Animals underwent surgery once a correct and stable behavioral performance had been obtained. Under deep pentobarbital anesthesia and aseptic conditions, bolts for head fixation and a stereotaxically positioned, stainless steel chamber were fixed to the skull to permit vertical access with microelectrodes to both SN. The dura was left intact. Teflon-coated multistranded stainless steel wires (Cooner Wire, Chatsworth, CA) were implanted into the extensor digitorum and bicep muscles of both arms and led subcutaneously to the head. All metal components, including plugs for the muscle electrodes, were imbedded in several layers of dental cement and fixed to the skull with surgical grade stainless steel screws.

Lateral and transverse radiographs of the head were taken with a guide cannula installed on an *X-Y* moveable microstage at a known coordinate in each hemisphere. The distances of the guide cannula to the midline and bony structures were used to establish a reference system with the coordinates of the microstage. In addition to localizing the SN by radiography, the ventroposteromedial (VPM) thalamus above it was electrophysiologically explored for trigeminal input under pentobarbital anesthesia 1 wk after implantation. Recordings in VPM thalamus were repeated in all tracks in the awake situation before lowering the microelectrode into lateral and intermediate parts of SN.

Extracellular activity of single neurons was re-

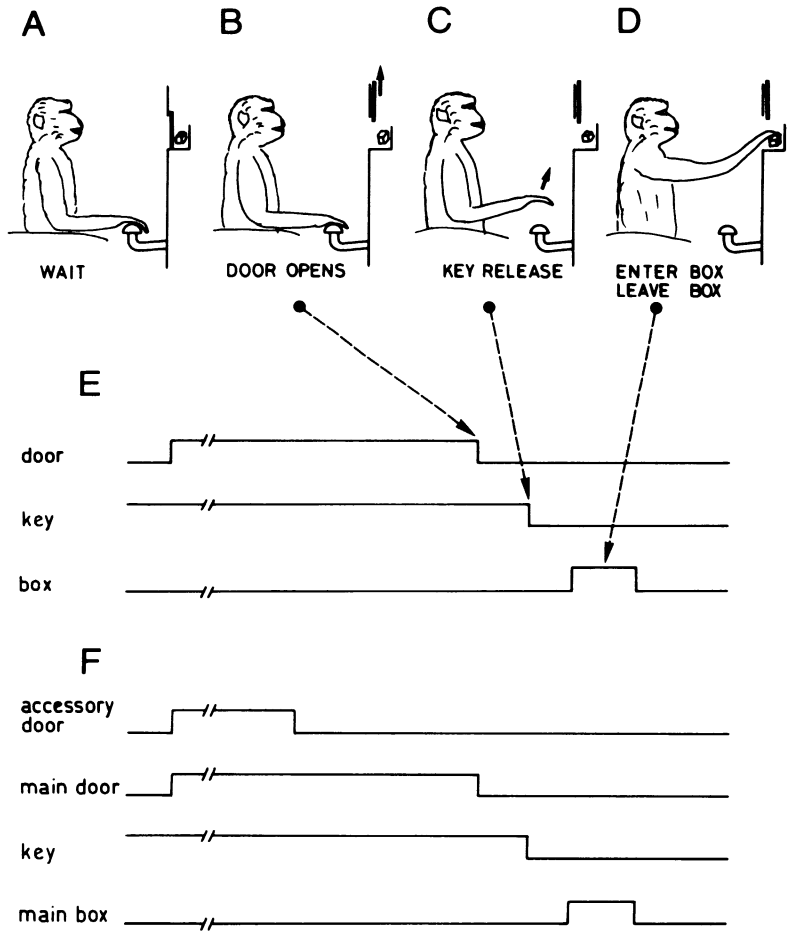

FIG. 1. Description of behavioral task. *A–D*: performance in the basic task. After the door of the food box was closed by the experimenter, the animal waits with his muscles relaxed for door opening (*A*). Then the door opens vertically upward, which is visible and audible to the animal (*B*). In direct reaction to this behavioral trigger stimulus, the animal quickly releases the key (*C*), moves his hand into the box (*D*) to collect the food reward ("enter box" and "leave box"), and brings it to the mouth. *E–F*: diagrams of standard electrical impulses generated with door closing and opening, key release, and entering and leaving the food box during performance in the basic task (*E*) and the double box task (*F*). Time axis is horizontal.

corded with glass-insulated, platinum-plated tungsten microelectrodes (exposed tips of 5–12 μm length and 1.8–3.0 μm diam, modified after Ref. 35), which were passed daily together with and inside a rigid guide cannula of 0.6 mm OD into the brain. Parallel electrode tracks were performed vertically, roughly in the stereotaxic plane, and conforming to a 1-mm grid. Signals from the microelectrode were conventionally amplified, filtered (100-Hz lower cutoff at −3 dB), and displayed in full waveform on a digital oscilloscope using the pretrigger facility. Responses to door opening were monitored on a conventional storage oscilloscope, the beam of which was triggered by this event. Discharges from all neurons included in this study were displayed in this way during at least five behavioral trials in the basic task and in the absence of variations of impulse height caused by pulsations or other local tissue movement. For digital sampling, neuronal impulses were converted into standard electronic pulses by an adjustable Schmitt-Trigger. Frequencies of spontaneously occurring impulses were assessed by an electronic counter in 10-s epochs while the animal sat quietly and without performing in any behavioral task. Sterile apomorphine (APO; Gattiker) was injected subcutaneously into the neck in volumes of less than 0.3 ml not more than once per week. Neuronal impulse rates were monitored in relation to APO administration while the animal was not performing in any task. They were displayed

on an analog plotter that was linked to the output of an electronic counter resetting at fixed time intervals.

Previous electromyographic (EMG) recordings from several flexor, extensor, pronator, and supinator muscles of the arm and from muscles of the shoulder, thorax, and dorsum in monkeys performing arm movements toward the visible or covered food box in the same testing apparatus have shown that the earliest active muscles for this movement were the extensor digitorum communis (EDC) and biceps (58, 59). Extensive comparisons between these two muscles revealed that, although both muscles were activated with about equal magnitudes, the EDC became active slightly before or together with the biceps, but usually not later (60). Therefore, EMG activity from chronically indwelling wire electrodes was routinely monitored from EDC during neuronal recording sessions and occasionally from biceps. EMG recordings were used to assess the earliest task-related motor activity and to cancel individual trials in sessions with repeated premature isometric contractions. Rectified and filtered (10–250 Hz band pass) EMG activity was transformed into standard digital pulses by an adjustable Schmitt-Trigger. Two closed-circuit video systems served to further supervise the behavior of the animal.

Data acquisition and analysis

All behavior-related electrical signals (see Fig. 1, *E* and *F*) and pulses from neuronal discharges and EMG activity were sampled as bits in parallel by a computer, this being performed on-line at a rate of 2 kHz (Ithaca Intersystems S-100 Z80 CPM system). The computer controlled the discrete trial schedule and cancelled trials in which premature key release occurred. Relationships of neuronal discharges and EMG activity to the behavioral events of the task were assessed in each trial on-line in the form of dot displays and perievent time histograms on the computer video screen, referenced to four of any of the behavioral events. All data were stored uncondensed on computer disks. Impulses from each neuron were sampled at a rate of 100 kHz in full waveform (100-Hz high-pass filter, −3 dB) by a digital oscilloscope (Tektronix) using the pretrigger facility and equally stored on computer disks.

Off-line computer programs permitted display and statistical evaluation of changes in neuronal discharge rate by using the two-tailed Wilcoxon matched-pairs signed-rank test (63) on single trial data (59). This was done on all neurons whose impulses were sampled by the computer with a minimum number of six repetitions of performance in the behavioral task, the usual numbers being 15–20, and maximally up to 50 trials. For this test, the series of single trial dot displays for a given neuron were visually inspected for apparent changes in relation to a behavioral event. Two time epochs of equal length were chosen that were constant in position and length for all trials of a given neuron. These epochs were immediately before the event, except when other events closely preceded, and after the event, respectively. The number of impulses in the time periods of each trial were considered as a pair and subjected to the test. Differences only become statistically significant when changes occur reproducibly in the same direction in virtually every trial. Onset latencies of neuronal responses were determined by measuring the time intervals between door opening and the first of three consecutive bins whose counts were above or below background (bin width 5 ms). All data and results from evaluations were stored and classed using a computer-based data base management system (dBaseII). Differences in distributions of frequencies among groups were statistically assessed by using the χ^2 test (63).

Histological reconstruction

During the last sessions with each animal several small electrolytic marking lesions were placed by passing a small negative current through the microelectrode (5–10 μA for 5–20 s). This was done in the SN immediately after recording from a neuron and at a few locations above it in the same tracks, thereby producing distinct patterns of vertically oriented histological marks in each hemisphere. Animals were deeply anesthetized with pentobarbital and conventionally perfused with formaldehyde through the heart. Guide cannulas were inserted into the brain at known coordinates of the implant system in order to delineate the general area of recording. The tissue was cut in 50-μm-thick serial coronal sections on a cryotome and stained with cresyl violet.

Recording positions in individual microelectrode tracks through the ventral midbrain were reconstructed by using marks from the electrolytic lesions. This was done by projecting all histological sections on paper and drawing the outlines of brain structures and marks from lesions and recent electrode tracks. Shrinkage factors of 5 and 10% were calculated for the two brains, respectively, by comparing the distances between lesions within each track with the original micrometer readings from the microelectrode manipulator. Recording positions in tracks marked by lesions were reconstructed by using the distances from micrometer readings, corrected by the shrinkage factor. Microelectrode positions were also reconstructed in parallel tracks that were 1 mm lateral or medial to tracks containing lesions by using the same vertical levels. Positions in tracks at 1 mm anterior or posterior to tracks marked by lesions were reconstructed at comparable vertical levels that were adjusted according to the depth of the aqueduct, this being the most reliable indicator of vertical position in this area of the midbrain (62).

RESULTS

General

DISCHARGE CHARACTERISTICS. This report describes the characteristics of discharges from perikarya of DA neurons in the pars compacta of SN and its close vicinity in three hemispheres of two behaving monkeys. The following criteria served to attribute a DAergic nature to these neurons: *1*) histological location, *2*) form and duration of impulses, *3*) spontaneous discharge rate, and *4*) reduction of discharge rate following systemic administration of low doses of the DA autoreceptor agonist apomorphine (15). Whereas criteria *1* to *3* needed to be fulfilled for every neuron, criterion *4* was only tested for a selected number of neurons whose recordings were still sufficiently stable following behavioral investigation. None of the four criteria alone was considered to be sufficient for postulating a DAergic nature for any given neuron.

Impulses of DA neurons were invariably of relatively long duration (1.4–3.6 ms at 100-Hz high-pass filtering) (Figs. 2 and 3). They were recorded in basically two forms according to the polarity of the predominating initial deflection: initially negative with a prominent late positivity (Fig. 2, *A, B, E,* and *F*), or initially positive with a following negativity and a variable, late positivity (Fig. 2, *C, D, E,* and *F*). An interruption of the ascending part of the initial positive deflection occurred with most initially positive impulses. On several occasions, both forms were seen while recording from the same neuron with a systematic transition occurring between them (Figs. 2, *E* and *F* and 11*C*); beginning with the initially

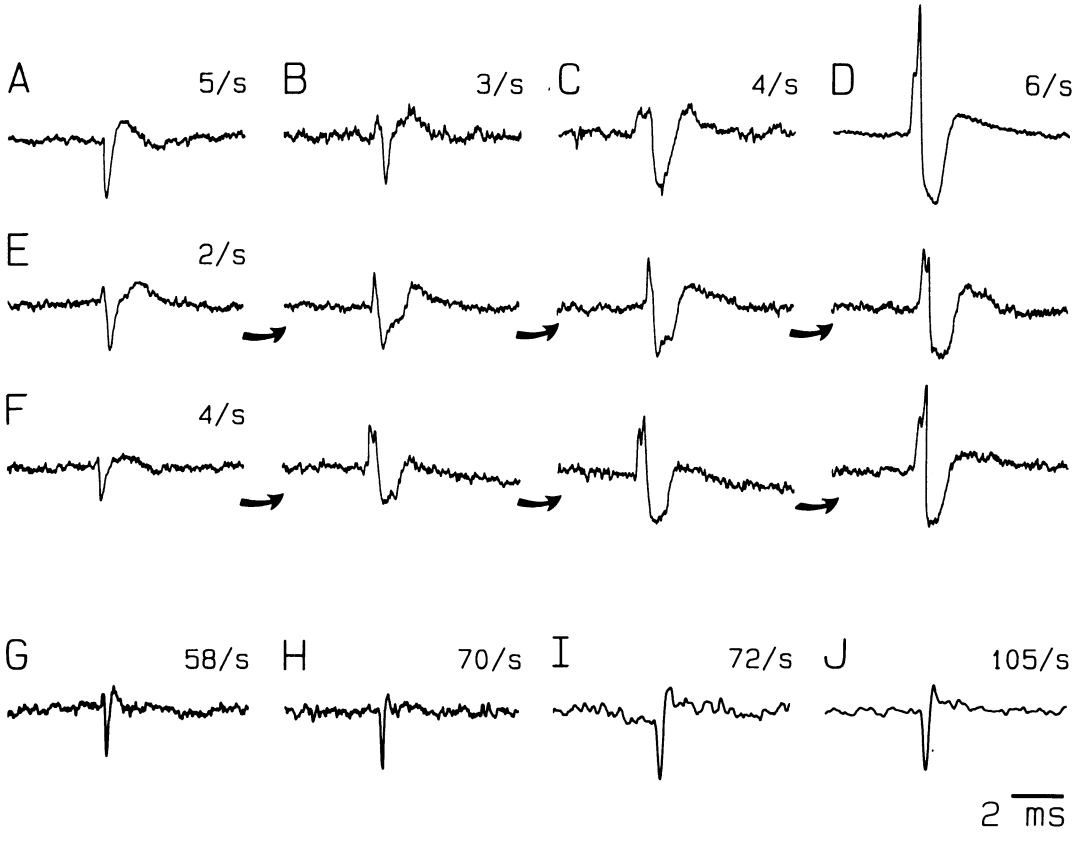

FIG. 2. Impulse forms of extracellularly recorded neurons of the monkey substantia nigra. *A–F* are derived from DA neurons, and *G–J* from non-DA pars reticulata neurons. *E* and *F* show transitions of impulse forms from predominating initial negativity to initial positivity in 2 DA neurons. Spontaneous discharge frequencies are indicated above impulse forms for each neuron. In this and all subsequent figures, positive deflection was upward and high-pass filtering was set at 100 Hz (−3 dB).

negative discharge form, the early part of the late positive deflection became increasingly negative while a positive deflection developed in front of the negativity. Transitions like these, which were probably caused by slight movements of the electrode and are not uncommon in extracellular electrophysiological recordings, suggest that the two forms of impulses were in fact recorded from the same population of DA cells. Initially negative discharges provided more stable recordings than initially positive ones and were used to collect the majority of the present data. However, all classes of behavioral relationships were also seen with neurons recorded with initially positive discharges. Neurons with these impulse forms discharged at rates of 0.1–8.5/s (median 3.3/s) when the animal sat quietly, not performing in any task (Fig. 3). Neurons with higher discharge rates of 25–150/s always showed shorter impulses of 0.5–1.1 ms (Fig. 2 *G–J*) and were considered to be nonDAergic pars reticulata cells (58). These elements, as well as slowly discharging neurons with shorter impulses (0.5–1.0 ms) and presumptive fibers having very narrow impulses (0.1–0.3 ms), are not the subject of the present report.

Apomorphine was injected subcutaneously in doses of 0.05–0.2 mg/kg while recording the spontaneous activity of a total of 11 DA cells. Ten of these neurons showed a reduction of activity of at least 50% within the first 5 min. A typical example is shown in Fig. 5*A*. Apomorphine-induced depressions lasted for 5–25 min. Discharge activity rarely recovered to full preinjection levels. Apomorphine injections did not depress the discharge activity of typical reticulata neurons (two cells tested). These data agree with our earlier findings (1).

TYPES OF RELATIONSHIPS TO BEHAVIOR. During performance in the basic behavioral task, DA neurons showed four types of changes in impulse activity (Table 1). The majority of neurons discharged in response to opening of the door of the food box, which constituted the behavioral trigger stimulus. A few DA neurons showed a reduction in discharge rate following this stimulus. Nearly half of all neurons were moderately activated or depressed during the execution of arm movements. The magnitude of response to door opening, as assessed from the instantaneous impulse rate and the number of reactive neurons, made this activation the major change of DA neuron activity in the present paradigm. Compared with this, changes during the reaching movement were much slower and quantitatively minor. Another type of change was seen in a small number of DA neurons that were activated in a late phase of the arm movement and afterward at a time when the animal had collected the reward. A few neurons were activated during the total duration of the task, between closing of the door by the experimenter and the final movement toward the reward. Many neurons showed more than one type of relationship (Table 1). In particular, more than half of the neurons with changes during the movement phase also responded to door opening. No comodulations existed between reward-related and task-related neurons.

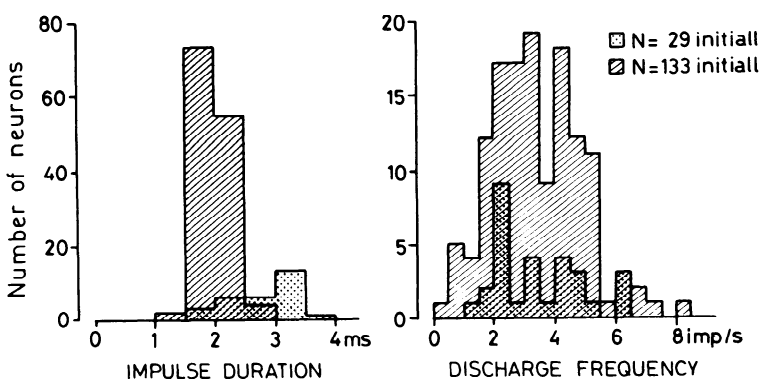

FIG. 3. Histograms of impulse durations and spontaneous discharge frequencies of DA neurons of the monkey midbrain. Data are shown separately for the 2 principal discharge forms.

TABLE 1. *Behavioral relationships of dopamine neurons in monkey midbrain*

	Tested	Modulated	Comodulated with Trigger Movement			
			Act	Depr	Act	Depr
Trigger stimulus						
Activated	128	70 (55%)				
Depressed	128	11 (9%)				
Movement execution						
Activated	128	40 (31%)	22	3		
Depressed	128	22 (17%)	8	4		
Reward phase						
Activated	128	11 (9%)	4	1	0	2
Depressed	128	1 (1%)	0	1	1	0
Task duration						
Activated	77	4 (5%)	3	0	2	0
Depressed	77	1 (1%)	1	0	0	0

Values are no. of neurons.

Histological reconstructions revealed that recording positions of most DA neurons were located within the SN, particularly in the cell-dense regions of pars compacta (area A9, Refs. 18, 46) (Fig. 4). Some neurons with the same electrophysiological characteristics were recorded in areas A8 and A10 above and medial to SN (Table 2), where DA perikarya are known to exist (18). Regional distributions differed for trigger stimulus- and movement-related neurons. When dividing the area of DA neurons into three equal mediolateral zones, trigger stimulus-related neurons prevailed in intermediate and medial parts, whereas movement-related neurons were found more often in the lateral third (left part of Table 2). These differences were statistically significant for both classes of neurons ($P < 0.01$; χ^2 test). A similar, but less clear and statistically insignificant, trend was seen when grouping neurons according to more anatomical criteria into areas A8, A9, and A10 (right part of Table 2).

Responses to the behavioral trigger stimulus

BASIC TASK. Seventy of 128 tested DA neurons discharged a short burst of impulses in response to door opening (29 of 58 neurons in *monkey A* and 41 of 70 neurons in *monkey*

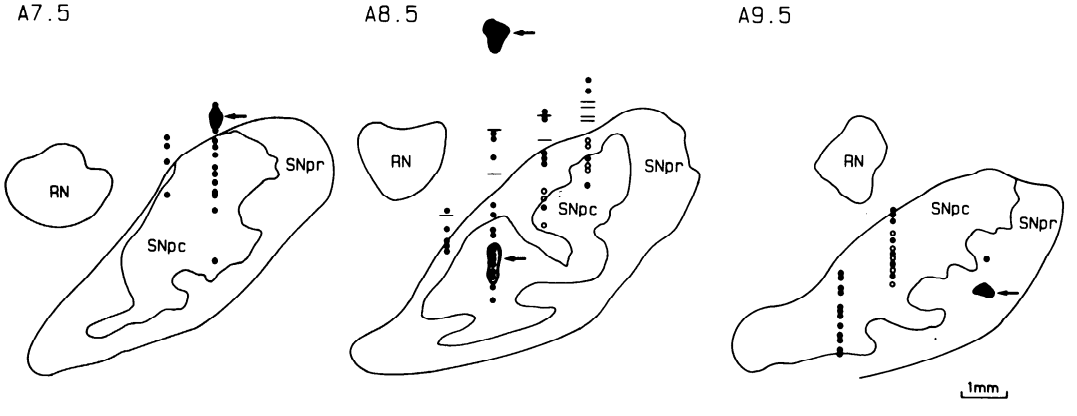

FIG. 4. Histological reconstructions of recording positions of neurons in the ventroanterior midbrain of 1 side in 1 monkey. Coronal sections are shown with their approximate anteroposterior levels (in millimeters) according to an atlas (62). *Closed circles*, DA neurons; *open circles*, non-DA neurons of pars reticulata type; *horizontal lines*, unclassified neurons not belonging to either of the 2 main groups. *Arrows* point to lesions that were placed immediately after recording from neurons at these positions. SNpc, pars compacta of substantia nigra; SNpr, pars reticulata of substantia nigra; RN, red nucleus.

TABLE 2. *Regional distributions of behavior-related dopamine neurons in monkey midbrain*

	Midbrain			Dopamine Cell Group		
	Medial (37)	Intermed (63)	Lateral (28)	A10 (12)	A9 (101)	A8 (15)
Trigger stimulus	65	73	39	75	63	53
Movement execution	30	51	68	33	50	47

Values are given as percentages of neurons recorded in the different regions. Behavior-related increases and decreases of activity are pooled. Nos. in parentheses are no. of neurons tested.

B). The increases of 46 neurons were statistically significant at $P < 0.01$, and of four more neurons at $P < 0.05$ (Wilcoxon test). Responses of the remaining 20 neurons were recorded with less than six trials on computer media, in which case the Wilcoxon test could not be applied. Figure 5 shows three typical examples. As with all neurons of this group

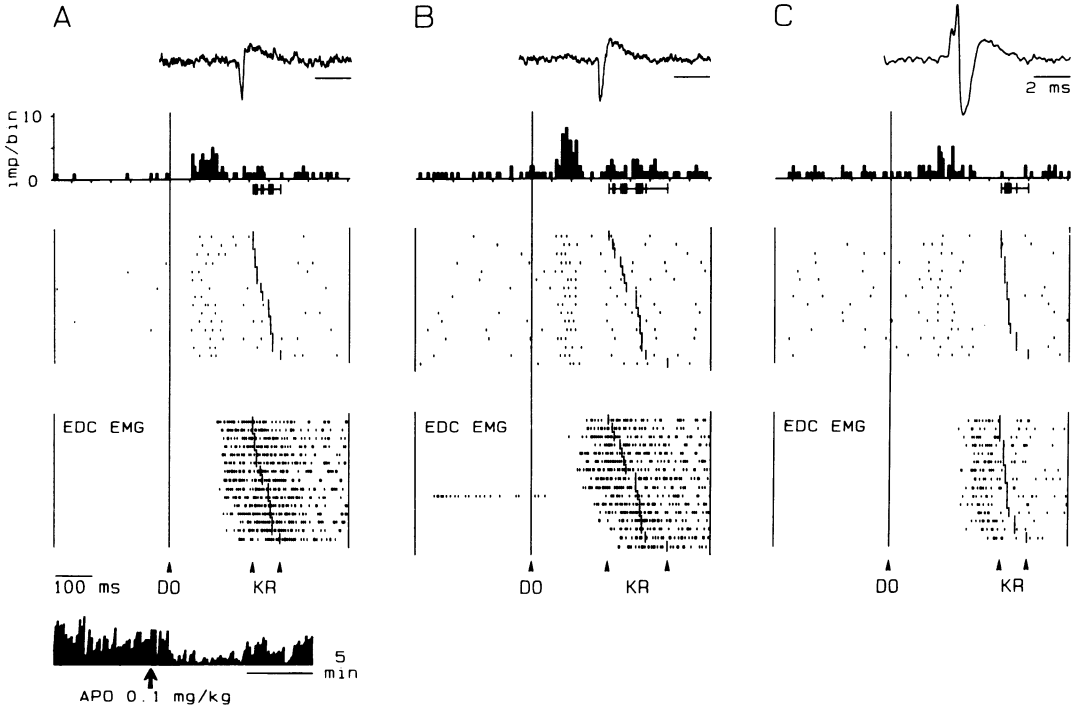

FIG. 5. Responses of 3 DA neurons (*A–C*) to the behavioral trigger door opening (DO). In parts, *A–C* are shown from above downward: impulse form of the neuron under study (positivity upward, 100 Hz −3 dB high-pass filter); perievent time histogram of neuronal impulses; *dot display* of neuronal impulses; *dot display* of EMG activity in the extensor digitorum communis muscle (EDC) recorded simultaneously with neuronal impulses; ratemeter recording of spontaneous discharge activity in the absence of behavioral performance before and after subcutaneous injection of apomorphine (APO) (only *neuron A*). In the *dot displays* of this and the following figures, each *dot* represents 1 impulse of the neuron under study or rectified EMG activity above a preset level. The distance of each *dot* to the behavioral event (in this figure door opening) corresponds to their real time interval. Each *line* of *dots* represents activity during performance in 1 trial. *Dot displays* of neuronal impulses and EMG activity are from the same trials. Histograms are composed of those neuronal impulses that are shown as *dots* below. In all *dot displays* of this figure, the sequence of trials is rearranged according to the length of time intervals between door opening and key release. *Lines* below *right parts* of histograms represent the moments of key release (KR), as in the *dot displays*. Separate time scales apply to impulses (2 ms) and to histograms and *dot displays* (100 ms). Bin width is 5 ms, *tickers* below histograms indicate 10 bins.

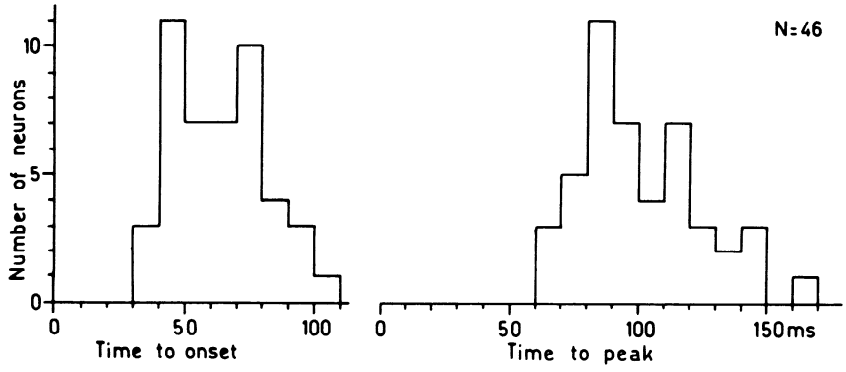

FIG. 6. Latency histograms of responses of DA neurons to the behavioral trigger stimulus door opening. Data are taken from statistically significant responses ($P < 0.01$, Wilcoxon test). *N*, no. of neurons.

the responses were time-locked to door opening. They occurred before onset of movement, as monitored by release of the holding key (upper three dot displays in Fig. 5), and together with or before activation of one of the earliest prime mover muscles (lower three dot displays in Fig. 5). However, responses were not directly related to onset of movement (longer lines in right half of all dot displays in Fig. 5) nor to onset of EMG activity. Neuronal responses to door opening remained present in occasional trials in which no food morsels were placed into the box. Responses were seen equally well with neurons discharging initially negative (Fig. 5, *A* and *B*) or initially positive impulses (Fig. 5*C*). A complete pause of discharges occurred immediately after the response in seven neurons, lasting for 100–400

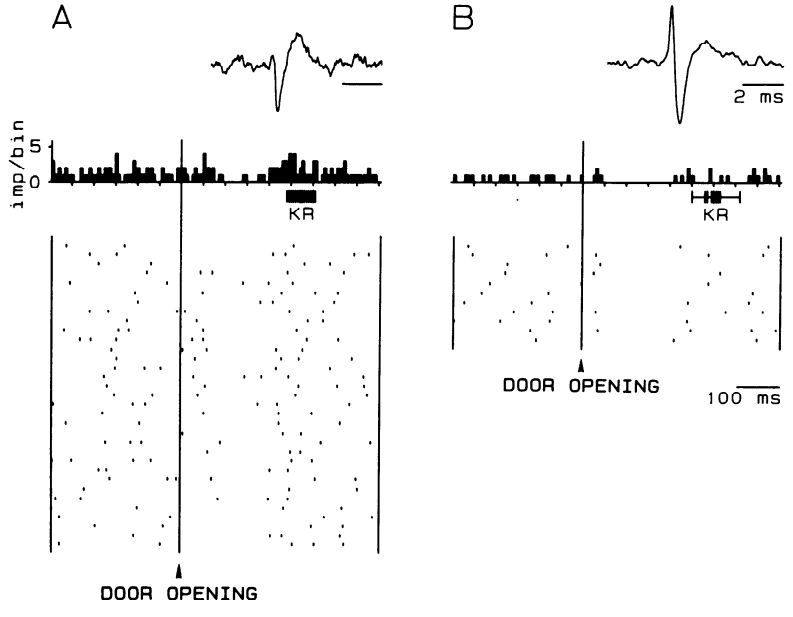

FIG. 7. Reduction in discharge activity of 2 DA neurons (*A* and *B*) in response to the behavioral trigger door opening. *Lines* below *right parts* of histograms represent the moments of key release (KR). The original sequence of trials is preserved downward. Impulse forms of the neurons under study are shown above histograms (positivity upward). Bin width is 5 ms; *tickers* below histograms indicate 10 bins.

ms. The spontaneous activity of the neuron shown in Fig. 5*A* was depressed following subcutaneous injection of apomorphine.

Response latencies varied within a narrow range between individual trials with each neuron (see upper dot displays in Fig. 5). Onset and peak times of responses ranged from 39 to 105 and 65 to 165 ms, respectively, with respective medians (50th percentile) of 65 and 95 ms (Fig. 6).

Eleven of 128 DA neurons decreased activity in response to door opening (3 of 58 neurons in *monkey A* and 8 of 70 neurons in *monkey B*). This was seen equally well with neurons discharging initially negative (Fig. 7*A*) or initially positive impulses (Fig. 7*B*). Changes were statistically significant at $P < 0.01$ in six and at $P < 0.05$ in four more of them. As with activations, the depressant responses appeared to be more related to door opening than to

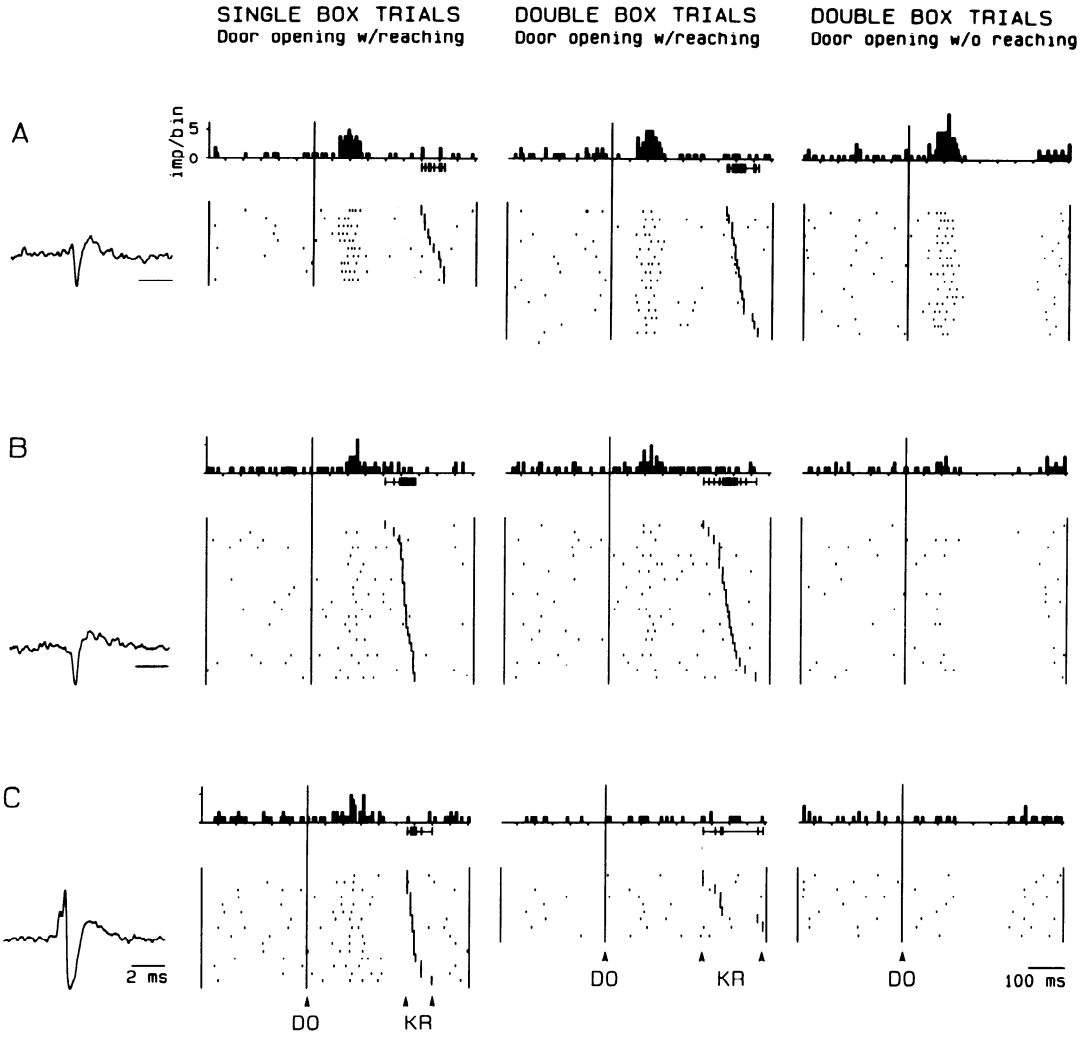

FIG. 8. Responses to the behavioral trigger stimulus in 3 DA neurons (*A–C*) during performance in the double box task compared with the basic behavioral task. Responses in the basic task are shown as controls in the *left column* ("single box trials"). In the double box task, the animal did not move in reaction to opening of the accessory box (*right column*), and only reached out for reward in response to opening of the main box (*middle column*). Trials are rearranged in sequence according to length of time intervals between door opening (DO) and key release (KR) in the *dot displays* of the 2 *left columns*, whereas their original sequence is preserved downward otherwise. Impulse forms of the neurons under study are shown at the *left* (positivity upward). Bin width is 5 ms; *tickers* below histograms indicate 10 bins.

the later occurring key release, although this was difficult to judge in view of the low levels of background activity. Onset times ranged from ~50 to 100 ms, their durations from ~100 to 200 ms.

It occurred during a few trials that an animal did not move in reaction to opening of the food box. In these cases, neuronal activations in response to door opening remained present in four neurons and became equivocal in two.

DOUBLE BOX TASK (*MONKEY B*). The responsiveness of DA neurons was tested independent of a movement reaction by opening an identical, accessory box about 2 s before the main box was operated. The trained monkey never made any limb movements toward the accessory box, and EMGs from extensor digitorum communis and biceps muscles remained at rest. The animal only moved in reaction to opening of the main box. Eleven DA neurons that were activated by door opening in the basic task ($P < 0.01$) were also tested in this situation.

Nine of the 11 neurons were also activated by opening of the accessory door. Responses

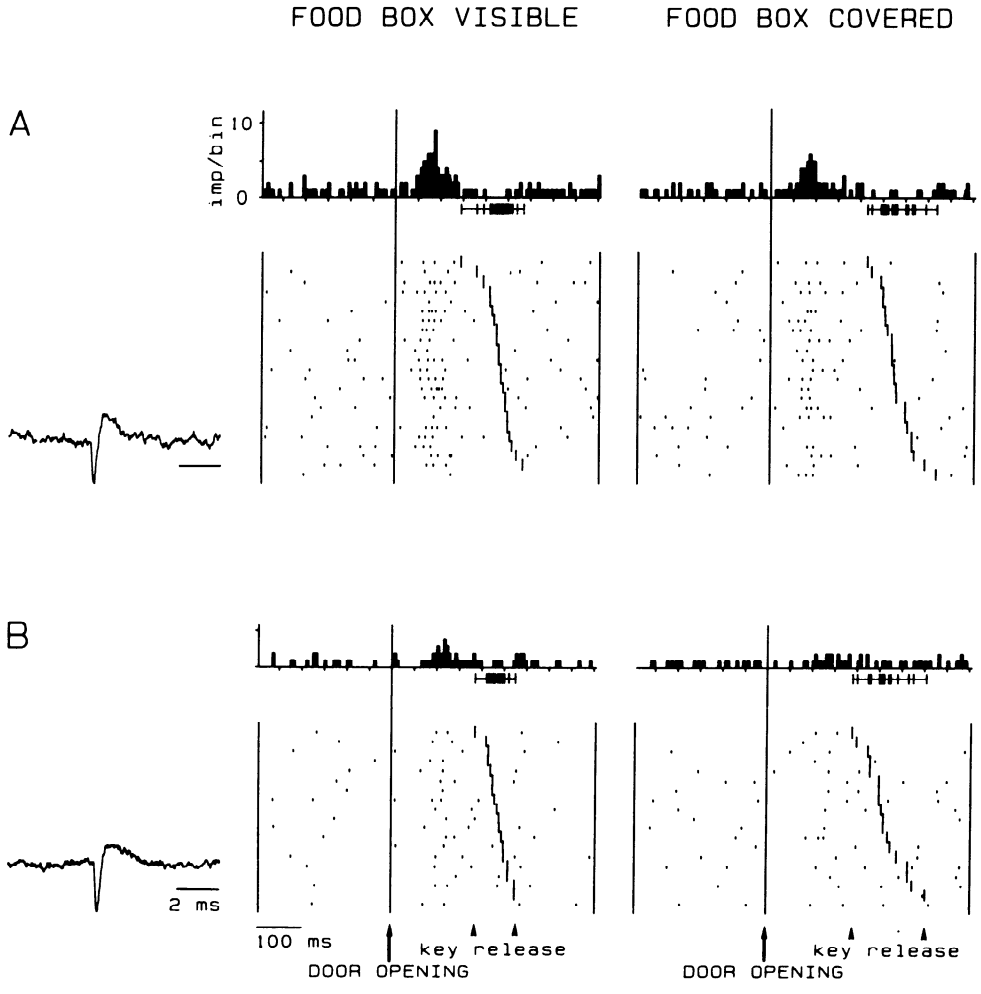

FIG. 9. Responses to the behavioral trigger stimulus in 2 DA neurons (*A* and *B*) during performance in the covered box task. In the basic behavioral task (*left column* of histograms and *dot displays* of neuronal impulses), the food box opened visibly and audibly. When the food box was covered by a shield, which still allowed manual access, door opening was only audible but not visible to the animal (*right column*). The sequence of trials is rearranged according to the lengths of time intervals between door opening and key release in all *dot displays*. Impulse forms of the neurons under study are shown to the *left* (positivity upward). Bin width is 5 ms; *tickers* below histograms indicate 10 bins.

were quantitatively equal as with door opening in the basic task in three of them (Fig. 8*A*) and were decreased by 21–69% in the other six (Fig. 8*B*). No responses were seen in the remaining two neurons (Fig. 8*C*). Four of the nine activated neurons showed a complete pause of discharge during the interval between 150 and 300–350 ms after opening of the accessory door (right column of Fig. 8), which was not present in these neurons when moving in reaction to opening of the main door in either task (left and middle columns in Fig. 8). Responses to opening of the main door in the double box task were equal (4 neurons, Fig. 8*A*), decreased by 21–36% (4 neurons, Fig. 8*B*), or totally absent (3 neurons, Fig. 8*C*), compared with door opening in the basic task.

These data, and those collected during the few errors the animals made, suggest that DA neurons also respond to a stimulus that is

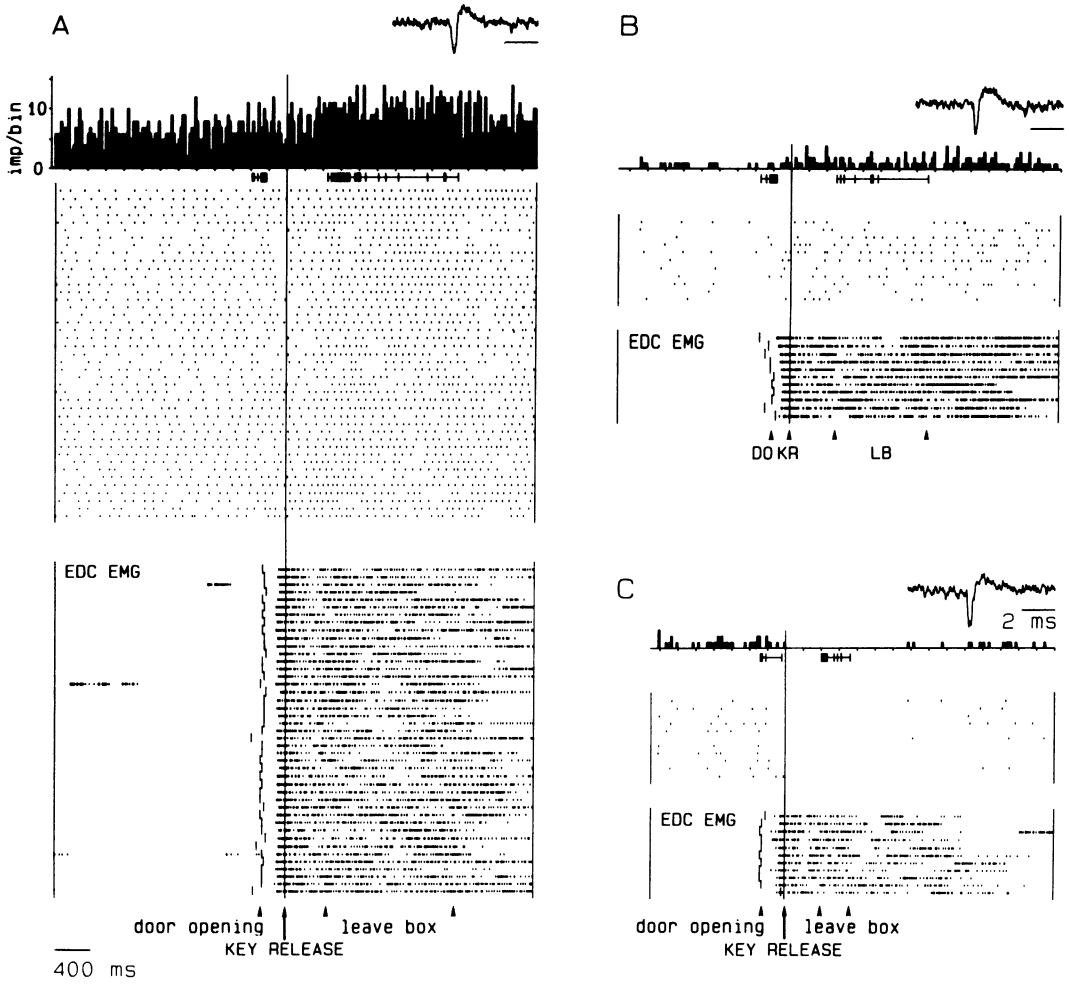

FIG. 10. Impulse activity of DA neurons is increased (*A* and *B*) or decreased (*C*) during execution of arm movement toward the food box. From above downward are shown in parts *A–C*: neuronal impulse form (positivity upward), perievent time histograms of neuronal impulses that are shown as *dot displays* below them, and *dot displays* from simultaneously recorded EMG activity in the extensor digitorum communis muscle (EDC). "Key release" (KR) indicates onset of movement, "leave box" (LB) indicates the moment at which the hand leaves the food box in order to bring the food reward to the mouth (*vertical bars* below histograms). Opening of the food box, "door opening" (DO), is marked by *vertical bars* below histograms and in *dot displays*. The original sequence of trials is preserved downward. Separate time scales apply to impulses (2 ms) and to histograms and *dot displays* (400 ms). Bin width is 20 ms; *tickers* below histograms indicate 10 bins.

physically identical to the behavioral trigger but to which the animal does not react with a movement.

COVERED BOX TASK (*MONKEY A*). In order to investigate whether responses were independent of the visual component of door opening, a cover was mounted in front of the food box. This completely prevented vision of the opening door and of food reward inside the box while maintaining manual access. Eight DA neurons that were activated by door opening in the basic task ($P < 0.01$) were also tested in this situation.

In seven of the eight neurons, responses to door opening remained present in the absence

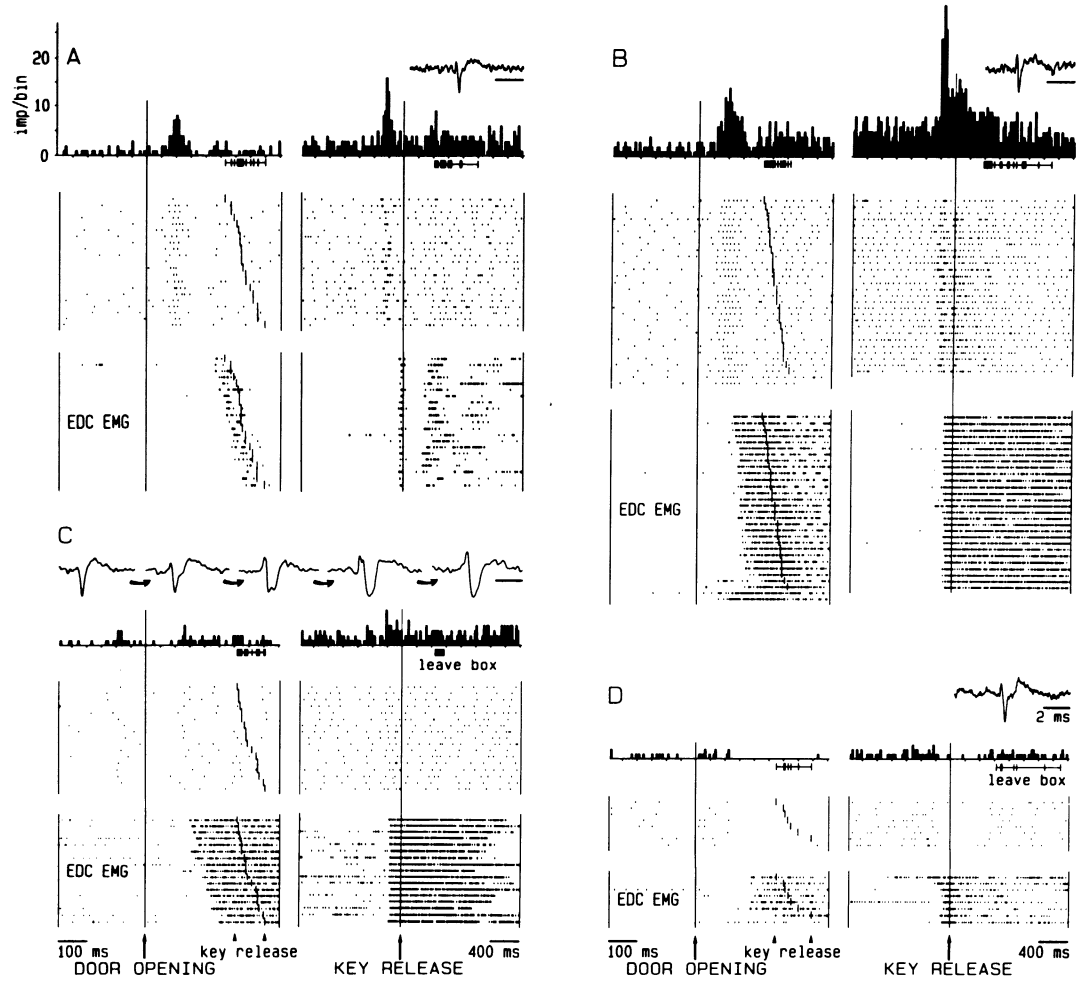

FIG. 11. Changes in impulse activity of 4 DA neurons (*A–D*) in relation to both behavioral trigger stimulus and arm movement. *Left columns* of histograms and *dot displays* in *A–D* show responses to door opening (bin width 5 ms, time scale 100 ms), whereas in *right columns* data from the same trials are shown referenced to movement onset ("key release") with a higher time base (bin width 20 ms, time scale 400 ms). Thus peaks in histograms of *right columns* in *A* and *B* represent responses to door opening before key release that are shown with greater temporal resolution in *left columns*. EMG activity from extensor digitorum communis muscle (EDC) is shown as *dot displays* below data from neuronal impulses. Trials are rearranged in sequence according to lengths of time intervals between door opening and key release in *left columns* of *A–D*, whereas their original sequence is being preserved downward in *right columns*. *Vertical bars* below right histograms in *A–D* indicate the moment at which the animal's hand leaves the food box. Different impulse forms in *C* show transitions from initially negative to initially positive recordings from this neuron (positivity upward). Same time scale (2 ms) applies to all impulse forms in *A–D*. *Tickers* below histograms indicate 10 bins.

of the visual component. However, responses were quantitatively inferior to those in the basic task, in which door opening constituted a visual and acoustic stimulus (Fig. 9). Decreases of responses ranged from 21 to 58% in the seven neurons, and amounted to a total disappearance of response in the remaining one. An increase of discharge rate occurred in four of these neurons during arm movement that was statistically significant at $P < 0.01$ and that was not present during performance in the basic task. These data suggest that the acoustic components of the trigger stimulus are effective for eliciting a response in DA neurons.

Changes during arm movements

Of 128 DA neurons, 40 increased their activity during execution of arm movement toward the food box in the basic task (26 of 58 neurons in *monkey A* and 14 of 70 neurons in *monkey B*) (Fig. 10, *A* and *B*). Increases in 23 of these neurons were statistically significant at $P < 0.01$, and in six more of them at $P < 0.05$ (Wilcoxon test). Data from the remaining 11 activated neurons were stored with less than six trials on computer media. In 22 of 128 neurons decreases were seen during arm movement (9 in *monkey A* and 13 in *monkey B*) (Fig. 10*C*). Decreases were statistically significant in 19 of these neurons ($P < 0.01$). Changes of activity during arm movements were seen equally well in neurons whose impulses were recorded with initially negative (Fig. 10, *A–C*) or positive (Fig. 11*C*) deflections.

Changes began with onset of muscle activity or key release. Increases of activity lasted between 300 ms and beyond the measuring period of 4.0 s after key release, mostly between 1.0 and 2.5 s (median 1.5 s). Decreases of activity were shorter, ranging from 300 ms to 2.4 s, mostly between 400 and 800 ms (median 600 ms). Statistically significant increases of activity ($P < 0.01$) amounted to augmentations of 25 to 238%, mostly between 70 and 120% (median 99%). Decreases ranged from 37 to 100%, mostly between 60 and 90% (median 73%).

About half of the DA neurons that were activated during the movement phase also responded with activation to door opening (Table 1). In these cases, the initial strong response to door opening was followed by a quantitatively minor but prolonged increase during the

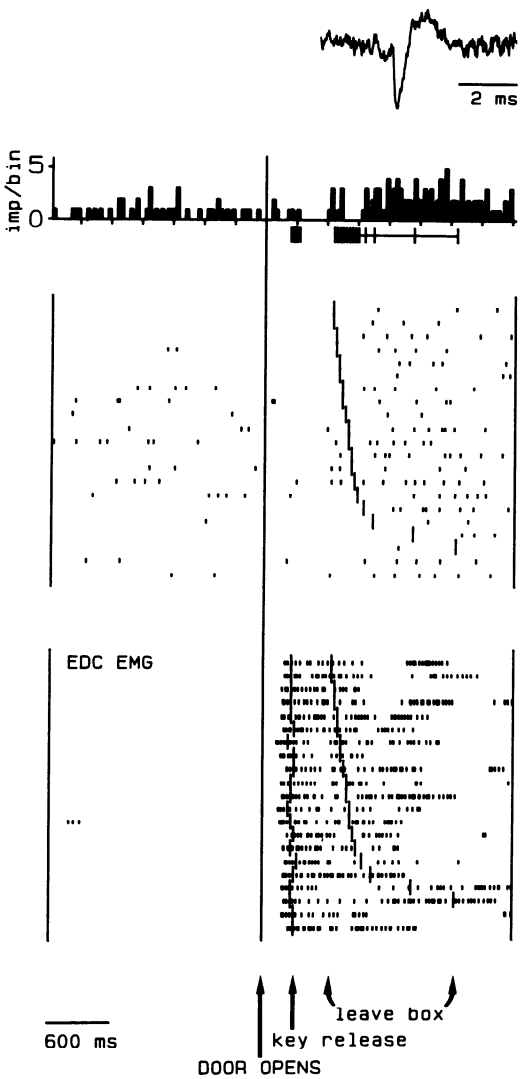

FIG. 12. Increased impulse activity of a DA neuron during the reward phase. After door opening, the animal's hand releases the key, moves into the food box, collects a small morsel of apple, and leaves the box in order to bring the food to its mouth. The time interval between leaving the box and reaching the mouth is ~300–400 ms. The histogram and *dot displays* are referenced to door opening. The 1st group of *vertical bars* after this event below the histogram and in the *lower dot display* represents the moment of key release. The later group of *vertical bars* below the histogram and in both *dot displays* represent the moment at which the hand leaves the food box, as detected by interruption of an infrared light barrier across its entrance. Trials showing *dot displays* from neuronal impulses (above) and simultaneous EMG activity in the extensor digitorum communis muscle (EDC, *below*) are rearranged in sequence according to the intervals between door opening and leaving the box. The impulse form of this neuron is shown *above* the histogram (positivity upward). Bin width is 30 ms; *tickers* below histogram indicate 10 bins.

movement (Fig. 11, *A* and *B*). In a few cases, only a small response to door opening was observed that continued into the activation during movement (Fig. 11*C*). This small activation occurred in response to door opening and not in temporal relation to the later occurring arm movement or onset of muscle activity (see left dot displays in Fig. 11*C*). With four neurons, decreases of activity in response to door opening were seen that continued into the beginning of arm movement (Fig. 11*D*).

Changes during reward phase

Clearly separated from modulations during arm movement existed a class of changes that occurred at a time when the animal received the food reward (Fig. 12). Of 128 DA neurons, 11 were activated and one reduced in their impulse rate during this phase (7 of 58 neurons in *monkey A* and 4 of 70 in *monkey B*; 1 reduction in *monkey B*). Activations were statistically significant at $P < 0.01$ in six and at $P < 0.02$ in two more of these neurons (Wilcoxon test). Changes began several hundreds of milliseconds after key release and mostly after the animal's hand had left the food box. However, the onset was not time-locked to the moment of leaving the food box (see upper dot display in Fig. 12). Quantitatively, increases of impulse activity amounted to 46–214%, with a median of 62%. No changes in activity were seen with any of these neurons during mouth movements outside of the behavioral task. Four neurons with changes during the reward phase were also activated and two depressed in response to door opening.

Changes during total task duration

Of 77 DA neurons, four were activated and one depressed in each trial during the whole period between closing of the door by the experimenter (left part of Fig. 13) and the final reaching movement for obtaining the food reward (right part of Fig. 13). Increases

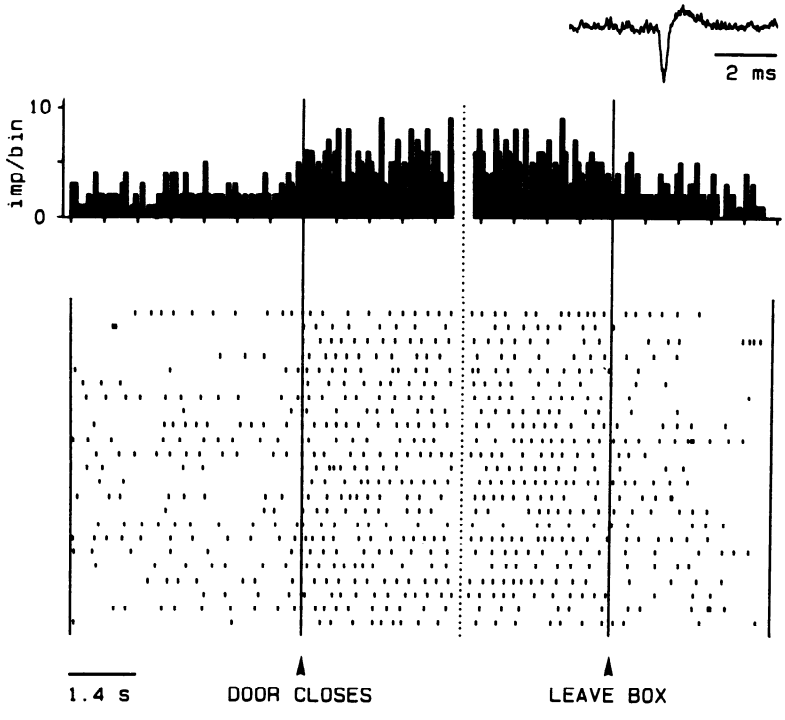

FIG. 13. Increased impulse activity of a DA neuron during total task duration. The increase begins when the experimenter closes the door of the food box visibly to the animal, and activity resumes control levels when the animal's hand has collected the food reward and leaves the food box. This neuron was not activated in response to door opening. Time axis is split in the *middle* of the figure because of variable intervals between the 2 behavioral events, while maintaining their mean interval. The impulse form of this neuron is shown *above* the histogram (positivity upward). Bin width is 70 ms; *tickers* below histograms indicate 10 bins.

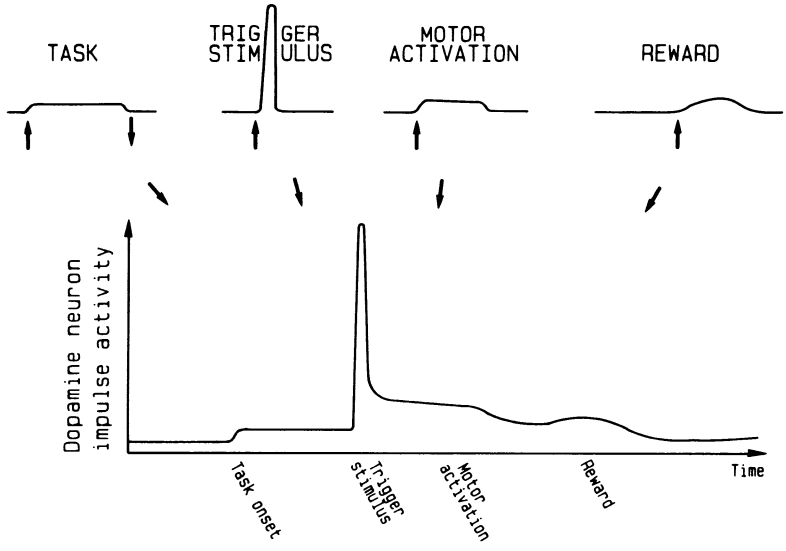

FIG. 14. A schematic diagram of impulse activity of DA neurons in relation to the direct reaction behavioral task of the present study. The 4 types of behavioral relationships shown above represent schematically approximate magnitudes and time courses. They are summed in the diagram below by taking into account their relative frequencies of occurrence. "Motor activation" denotes changes of neuronal activity accompanying arm movements.

amounted to about a doubling of background activity and were distributed to one of seven tested neurons in *monkey A* and three of 70 neurons in *monkey B*. One of the neurons virtually only discharged impulses while the door was closed during the trial. Four of the five task-related neurons were also activated in response to door opening.

DISCUSSION

Besides histological reconstructions, neurophysiological criteria were employed in the present study for postulating the DAergic nature of recorded neurons. We applied the most pertinent characteristics of identified rat DA neurons (6, 22, 52) to the monkey. These include the low spontaneous discharge rate and the relatively long duration and typical shape of the extracellularly recorded impulse. Discharges of DA neurons become particularly distinctive in this area of the brain when recorded with an initially positive waveform. The impulses of presently recorded DA neurons with this shape are very similar to those of antidromically and histochemically identified DA cells in anesthetized rats (22). Transitions were seen in several neurons between initially negative and initially positive forms of impulses. This suggests that elements recorded with either impulse form in fact belonged to the same population. Also, they showed the same behavioral relationships. This makes the initially negative form of the impulse a viable electrophysiological characteristic for DA neurons. The reduction of activity of these neurons by low doses of the DA receptor agonist apomorphine (15) replicates, as before (1), another parameter known from rat DA neurons (5). We were recently also able to antidromically activate monkey DA neurons with these characteristics from putamen (51). Although none of these characteristics alone is sufficient, their combination strongly suggests the DAergic nature of these cells and discriminates them against pars reticulata neurons and other elements in this area (58).

Nature of responses

The present findings show that more than half of the DA neurons in the monkey midbrain were activated by a teleceptive stimulus that triggered a direct behavioral reaction in the form of a movement. The magnitude of the response, as expressed in the high instantaneous impulse rate, exceeded the compara-

tively minor activation during the following movement. Taking also into account reductions in activity, only a mild total increase in impulse rate occurred during the execution phase of the movement. Besides these two major modulations, some DA neurons showed changes when reward was received, and some during the total length of task performance. A schematic summary diagram of the neuronal changes during performance in the present behavioral task is shown in Fig. 14.

Technical reasons in single cell behavioral neurophysiological experiments on primates only allow one to work with behavioral acts of relatively fast time course. This imposes limits on many studies that investigate neuronal activity in relation to movements and more complex behavioral events. The present study was not intended to only focus on neuronal mechanisms involved in forearm movements following sensory signals. The behavioral task was rather designed to represent rapid behavioral reactions to significant trigger stimuli. The observed responses of DA neurons should thus be regarded in a wider sense, as occurring when the subject reacts quickly to a directly activating behavioral stimulus.

Dopaminergic neurons also responded to the same door opening stimulus in the absence of a movement reaction. This was seen when animals failed to move after door opening in the basic task and in the situation with the accessory door. It seems likely that the effectiveness of these stimuli in spite of a lack of movement reaction is due to their close resemblance and association with the stimulus of the main door that normally triggers the movement. These responses do not appear to be of a purely sensory nature because we had found in an earlier study that acoustic and stationary visual stimuli not leading to a direct movement reaction were ineffective for activating DA neurons (59). Interpretation of the data obtained with the present double box task might be complicated by the fact that opening of the accessory box could also represent a warning stimulus to the animal for the later occurring opening of the main door. However, in on-going experiments (together with R. Romo) we find similar responses of DA neurons to opening of the accessory box in the absence of a movement reaction when opening of the two boxes is alternated at random and not done sequentially. This suggests that the close association with the movement-triggering stimulus is responsible for the neuronal response.

In order to obtain a better evaluation of the behavioral relationships of DA cells, it would be interesting to compare the present data with those from a previous study in which we studied DA cells in a situation that differed in several respects from the present one (59). In this task (59), a series of sensory signals preceded opening of the food box, including an acoustic warning stimulus and, 500 ms later, the illumination of one of two colored lights that instructed the animal to respond with an arm-reaching movement or to remain motionless when the door of the food box opened 1.0–4.5 s later. Opening of the box itself was only audible to the animal by the low-intensity sound from the opening door but lacked the associated intense 1-kHz stimulus and the visual component. The general lack of sensory responses in the earlier study (59) and the presently observed occurrence of responses to door opening suggests that only stimuli of particular behavioral significance are effective. A series of stimuli gradually preparing the animal for an impending movement and the conditional character of the door opening stimulus were of a less imminent nature than the presently used door opening that called for a quick movement reaction without a preparatory signal. The reduced sensory impact of the door opening stimulus (59) has probably also contributed to diminished responsiveness, as suggested by the results of the presently used additional task in which the box was covered by a shield. Taken together, it appears that effective stimuli for discharge responses of DA neurons should have a trigger or releasing function for immediate behavioral events that are important to the animal, or they should be closely associated with them. In a larger sense, effective stimuli may include all events leading to a rapid change in the level of behavioral activation or arousal.

These points may also be relevant when comparing studies of others. Pars compacta neurons in SN of probably DAergic nature were found to be unmodulated in a task where monkeys performed controlled forelimb flexion and extension movements to varying targets, with limb and target positions being displayed continuously from a series of light-emitting diodes (12). This task did not comprise the simple and quick reaction to the acute appearance of a triggering stimulus as the

present paradigm, and an explanation for the lack of responses should be sought in this difference. A similar behavioral task as the present one had been used on awake rats (37). A certain number of DA cells was found to be activated by conditioned stimuli in response to which animals performed licking or forelimb movements. Although most of these data (37) were recorded under the influence of the DA receptor antagonist haloperidol and were therefore more difficult to interpret, they are compatible with the present results in monkeys. In another study, slowly discharging neurons of the ventral tegmental area in monkeys were activated by sight of food following opening of a shutter, but only under the condition that the animal made a licking response (17). Although the DAergic nature of these neurons is uncertain, the data resemble to a certain extent the presently observed responses in DA neurons.

Implicated neuronal connections

Major afferences to SN and DA neurons of groups A8, A9, and A10 arise from caudate and putamen (38, 41, 42, 66, 74, 76), nucleus accumbens (39, 66), frontal cortex (27), hypothalamus (69), amygdala (43), raphe nuclei (2), and nucleus pedunculopontinus (25, 53). Nonhabituating responses to sensory stimuli at latencies comparable to those of DA neurons were seen in the dorsal raphe nucleus of awake cats (24) and may thus participate in mediating the presently observed responses. Responses occur in the caudate nucleus of monkeys in a similar behavioral context (48), but with considerably longer latencies than in DA neurons. However, caudate neurons may be involved in the pause of discharges in DA neurons following the response to the trigger stimulus through their inhibitory influence on SN (76). Changes during conductance of the movement were found preponderantly in DA neurons in lateral and intermediate parts of SN. These areas receive afferents from putamen (41) where many neurons are involved in the execution of movements (11).

Medially located DA neurons in SN and area A10 project to various regions of frontal cortex (47). Axons of DA neurons from medial areas of SN are largely directed to caudate nucleus and from lateral SN to putamen (70). Thus, midbrain DA neurons reacting to behavioral trigger stimuli, which preponderate in medial DAergic areas, may influence predominantly neurons in the caudate that are known to react to behaviorally relevant stimuli (48). More laterally located DA neurons with movement-related changes may mainly influence neurons in the putamen that are related to certain movement parameters (11).

Comparison with lesions

Destruction of the midbrain DA system results in sensory neglect (30, 33) and in deficits of initiating behavioral reactions. Rats with unilateral lesions show side preferences in using the forepaws (73) and in conditioned turning (13), and, in particular, they are impaired when initiating unilateral reactions to sensory stimuli independent of the side of stimulus presentation (7). Monkeys with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) -induced specific lesions of the nigrostriatal DA system show severe deficits in reactions to stimuli that go beyond a purely sensory neglect (60). Thus the presently observed responses of DA neurons to stimuli associated with a quick movement reaction may provide a basis for explaining the deficits in initiation of stimulus-triggered behavior after lesions of the nigrostriatal DA system. In fact, quantitative assessment in MPTP-lesioned monkeys performing in the same basic task as in the present study show a delayed onset of EMG activity and arm movement in reaction to the behavioral trigger door opening, as well as a prolonged movement time while reaching to the food box (60). These parameters of impairment match the different phases of normal activation of DA neurons in unlesioned monkeys seen in the present study. However, further comparisons show limits for associating the "negative image" of DAergic disfunctions with the "positive image" found in recordings of neuronal discharges. A notable example are the strong deficits in initiating "self-triggered" behavioral acts in the absence of a change of external stimuli that are found in Parkinsonian patients and in animals with striatal DA depletions. We know from work involving arm tracking (12) and performance in a more complex task (59) that DA neurons are not necessarily activated during initiation of every kind of movement, and they may thus not show increases before a "self-triggered" movement.

Strongly hypokinetic humans and animals with lesions of the nigrostriatal DA system are

able to perform a few movements when activated by intense behavioral stimuli (32, 60, 61, 75). This partial reversal of hypokinesia may well be mediated through extranigrostriatal mechanisms. However, from the present results it also appears possible that the few remaining DA neurons could be strongly activated by these behavioral stimuli, release DA for a short moment in the striatum, and thus influence striatal mechanisms that are implicated in these reactions. This hypothesis could be more closely evaluated by recording from DA neurons in an appropriate behavioral context in animals with a partly lesioned DA system.

Influences on striatal mechanisms

The continuous discharge activity of DA neurons rarely exceeds 10–15 impulses/s. This was shown when DA neurons were activated by pharmacological (28, 54, 65) or physiological (51, 59) means. However, the presently observed responses demonstrate that a few impulses may be discharged at much higher instantaneous frequencies. Impulse-dependent striatal DA release (10, 16) is exponentially related to the frequency of discharges (21). This suggests that the burst of impulses in DA neurons in response to a behavioral trigger stimulus may lead to an disproportionally stronger effect on DA release from striatal varicosities than a more general increase in discharge frequency with more widely spaced impulses would do. In this way, discharge activity of nigral DA neurons could very efficiently change striatal DA release at a fast time course. Although present methods do not allow study of striatal DA release at a comparable time course, indications exist that strong behavioral trigger stimuli may in fact lead to an increase of striatal DA release. Behavioral activation following external stimuli, particularly startle responses, augment DA-related electrochemical signals in rat and monkey striatum (26, 29). Although the action of DA on membranes of striatal neurons is not clearly understood, recent data suggest a focusing effect on striatal neurotransmission, through which only the strongest inputs to striatum would pass, whereas weaker activity would be suppressed (3, 71, 34). The DA system may in this way phasically control neurotransmission in the striatum according to the behavioral situation.

Release of DA in the striatum is not only controlled by neuronal discharges, but can also be influenced by local presynaptic interactions. Thus the neurotransmitters glutamate and acetylcholine, which are present in afferents to the striatum and in interneurons, increase DA release in striatal slice preparations (19, 20, 49) and in vivo independent of neuronal impulse flow (8). It is tempting to suggest that the two mechanisms for controlling striatal DA release may subserve different roles in behavioral processes. According to the present results, DA neurons respond phasically and at relatively short latencies to behavioral trigger stimuli. Increases in discharge frequency lead very rapidly to augmentations in striatal DA release (16, 21). This may suggest that responses with discharges play a role in those behavioral acts in which rapid changes of striatal DA release is needed. Modulations of striatal DA release mediated by presynaptic interactions appear to follow a slower time course (40, 50), although techniques allowing fast measurements of DA release have not yet been employed for investigating these phenomena. These results may imply that changes in striatal DA release mediated by presynaptic interactions could be predominantly operational in behavioral acts of less acute character, as for instance initiation of self-paced movements. Thus a number of behavioral acts requiring the presence or increase of striatal DA release may occur without a concomitant change in impulse flow of DA neurons. Only those events in the environment causing rapid alterations in the level of behavioral activation would lead to fast changes of impulse rate. In the present experimental situation, this may be a stimulus leading to an important movement response in a reaction time task, or the rapid conduction of a movement with a large trajectory toward a well-defined goal and starting from a resting position.

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