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Dopamine Neurons of the Monkey Midbrain: Contingencies of Responses to Stimuli Eliciting Immediate Behavioral Reactions

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SUMMARY AND CONCLUSIONS

1. This study investigates the behavioral conditions in which dopamine (DA) neurons of substantia nigra and adjoining areas A8 and A10 respond with impulses to visual and auditory trigger stimuli eliciting immediate arm- and eye-movement reactions.

2. In a formal task, the rapid opening of the door of a small, food-containing box located at eye level ahead of the animal served as visible and audible trigger stimulus. Most DA neurons on the contralateral side responded to this stimulus with a short burst of impulses with median onset latency of 50 ms and duration of 90 ms (75% of 164 neurons). Similar responses were seen in a comparable fraction of DA neurons during ipsilateral task performance, suggesting that responses were not specific for the limb being used.

3. When the sensory components of the door opening stimulus were separated, DA neurons typically responded in a similar manner to the moving visual stimulus of the opening door, the low-intensity sliding noise of the opening door, and the 1-kHz sound of 90–92 dB intensity emitted from a distant source at the onset of door opening. Responses to each component alone were lower in magnitude than to all three together.

4. In a variation of the task, a neighboring, identical food box opened in random alternation with the other box but without permitting animals to reach out (asymmetric, direct-reaction go/no-go task). With each sensory component, DA neurons typically responded both to opening of go and no-go boxes. Responses were enhanced when stimuli elicited limb movements in go trials.

5. Monkeys reacted to door opening with target-directed saccadic eye movements in the majority of both go and no-go trials. Neuronal responses were equally present during the occasional absence of eye movements. Thus responses were not specific for the initiation of individual arm or eye movements.

6. Neuronal responses were absent when the same stimuli occurred outside of the behavioral task with target-direct arm and eye movements lacking. This shows that responses were not of purely sensory nature but were related to the capacity of the stimulus for eliciting behavioral reactions.

7. In a variation of the go/no-go task, an instruction light illuminated 2–3 s before door opening prepared the animal to perform the reaching movement on door opening or to refrain from moving (asymmetric, instruction-dependent go/no-go task). Phasic neuronal responses to both instruction lights occurred in a limited number of DA neurons in one monkey when the task was used infrequently, largely disappearing with more regular testing. Responses to instructions resembled those to door opening in terms of latency, duration, and magnitude. This suggests that DA neurons may also respond to novel stimuli with properties uncertain to the animal.

8. In a different reaching task, the offset of a distant sound stimulus was used for eliciting arm and eye movements toward the food box. None of the 16 DA neurons tested in one monkey showed responses to this trigger signal, although most of them responded to door opening in separate sessions. Thus responses were related to the appearance of a stimulus and not only to its capacity to elicit behavioral reactions.

9. These data suggest that the large majority of DA neurons respond in a similar and stereotyped manner to salient visual and auditory stimuli with both appetitive properties and the capacity for eliciting immediate behavioral reactions. A common factor contributing to these responses appears to be motivational arousal. As stimuli effective for driving DA neurons induce an expectancy for obtaining an object of high interest, DA neurons would be able to participate in the setting of a state during which behavioral reactions occur. In this way, they would be engaged in the initiation process without triggering each individual reaction.

INTRODUCTION

In the preceding study, we recorded the impulse activity of dopamine (DA) neurons in monkeys during self-initiated arm movements (Romo and Schultz 1990). Although we were particularly interested to study neuronal activity in the absence of phasic external stimuli, we found that changes predominantly occurred when the animal's hand touched a morsel of food during the reaching movement. Responses were absent when other objects were touched. This demonstrated that DA neurons were activated by somatosensory stimuli of particular behavioral significance. In the present study, we extended the investigation of behavioral contingencies to responses to visual and auditory trigger stimuli (Schultz 1986b). Neuronal activity was studied in the presence and absence of arm and eye movements by the use of a go/no-go paradigm. In a variation of this task, the effects of preparatory instruction signals presented several seconds before overt behavioral reactions were compared with stimuli eliciting immediate behavioral reactions. The physical onset of a stimulus was separated from its abstract triggering function in another task by the use of the offset of a sound stimulus for eliciting arm and eye movements. Some of the data have been presented before as abstract (Schultz and Romo 1986).

METHODS

With the exception of the behavioral tasks, the same experimental procedures were employed as in the companion study, in which they are described in detail (Romo and Schultz 1990). The same two *Macaca fascicularis* monkeys (*A* and *B*) were used.

After a training period of 5–6 mo, animals were implanted under anesthesia with cylinders for head fixation, a microelectrode base, electrooculographic (EOG) electrodes in the canthi of the orbitas, and electromyographic (EMG) wires in the extensor digitorum communis and biceps of the arm. The extracellular

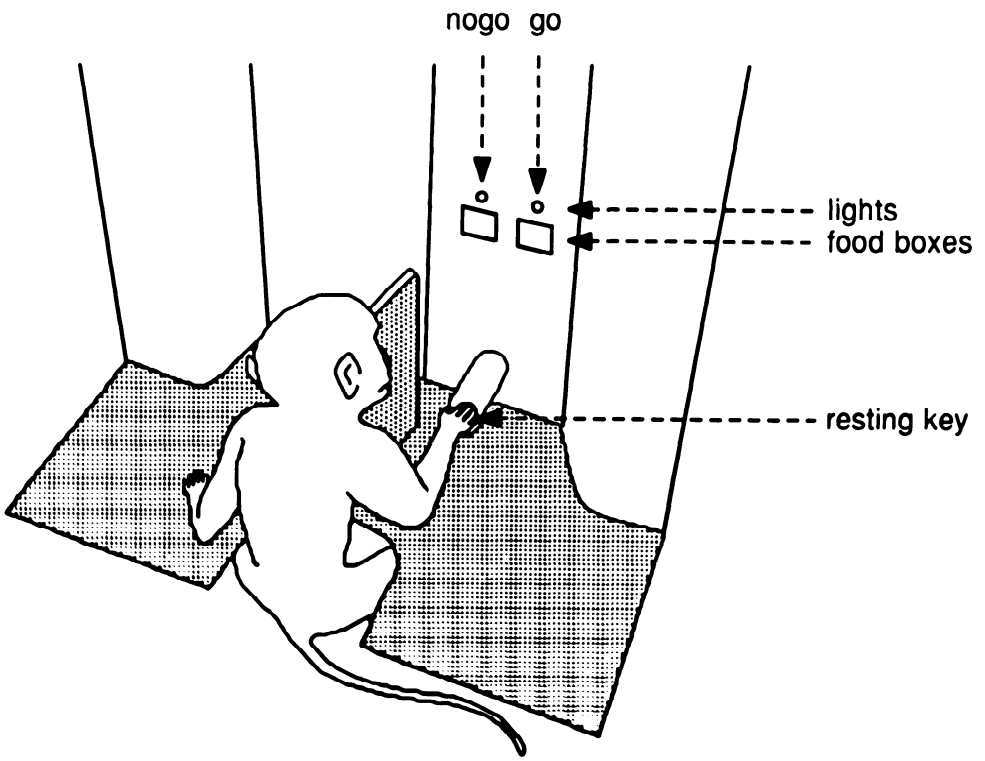

FIG. 1. Description of behavioral apparatus and tasks. Monkey faced a panel with 2 food boxes mounted on each side at eye level and at 15 and 27° lateral to the midsagittal plane, respectively. Only food boxes of the right hemifield are shown. Food boxes had a frontal opening of 40 × 40 mm. Their doors opened vertically upward behind the panel. Door opening consisted of a rapidly moving visual stimulus, a sliding noise of low intensity, and a 1-kHz sound of rectangular waveform and 100-ms duration triggered with onset of door opening. A cover could be mounted in front of each food box to prevent vision of the opening door while permitting access from below (not shown). In the food box task, opening of the lateral box invariably required the animal to release the immovable resting key, reach into the lateral food box (go), and collect a small morsel of food. In contrast, opening of the medial food box (no-go) required the animal to remain motionless on the resting key for at least 3 s. For the go/no-go task, opening of lateral and medial food boxes was alternated at random. When using instructions, a light above 1 of the food boxes was illuminated 2–3 s before opening of the covered food box. In the sound offset task, the lateral food box was used with the cover mounted in front of it. Its door was kept open, and the animal reached into the box for a food morsel after offset of a 100-Hz distant sound of rectangular waveform and 3-s duration. Figure digitized from a hand drawing by P. Apicella.

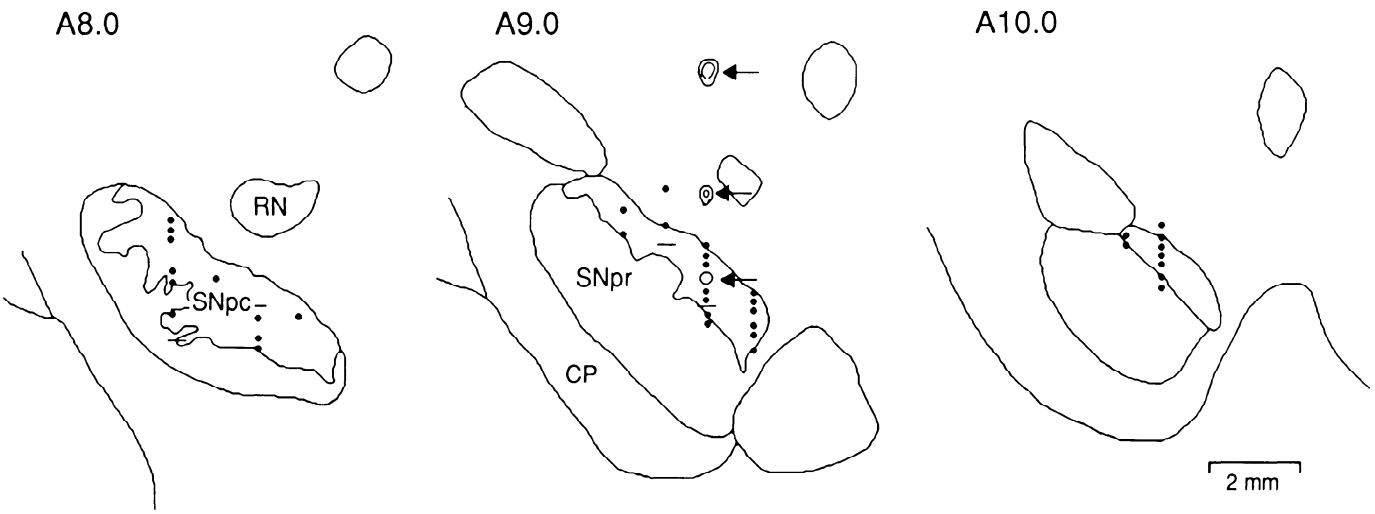

FIG. 2. Histological reconstruction of recording positions of dopamine neurons on 3 representative coronal sections from 1 brain. Approximate anteroposterior levels are shown in millimeters according to an atlas (Shanta et al. 1968). Filled circles, dopamine neurons activated by the visual trigger stimulus; horizontal lines, dopamine neurons not responding to this stimulus. Arrows point to lesions that were placed immediately after recording from a neuron at this position and above for track identification. SNpc, pars compacta of substantia nigra; SNpr, pars reticulata of substantia nigra; RN, red nucleus; CP, cerebral peduncle.

activity of single neurons was recorded with movable tungsten microelectrodes during task performance. A laboratory computer served to collect and display data obtained simultaneously from stimuli and behavioral events, neuronal impulses, EMGs, and horizontal and vertical EOGs. Only neurons tested with at least 10 and up to 50 repetitions in a given task situation were considered for this report. Recording positions were reconstructed after the experiment from histological sections of the brain.

Relationships of impulse activity to behavioral events were statistically evaluated by the use of a specially programmed implementation of the two-tailed Wilcoxon test. Only changes in activity substantiated by a significant difference at $P < 0.01$ in this test were considered as responses. Response magnitudes were assessed by counting neuronal impulses between onset and end of responses and expressed as percentage above or below background activity measured before the stimulus. The differences in pairs of response parameters of neurons tested in two different behavioral situations were assessed by the use of a conventional two-tailed Wilcoxon test.

Electromyographic and saccadic latencies were determined off-line by single-trial analysis with the use of a movable cursor on a computer screen (Schultz et al. 1989a–c). The median (50th percentile) was determined as single numerical value for each distribution. Differences in behavioral performance were assessed with the two-tailed Wilcoxon test on pairs of session medians while recording from the same neuron. Relationships between data pairs from single trials were assessed with the empirical linear correlation coefficient (Schultz et al. 1989c).

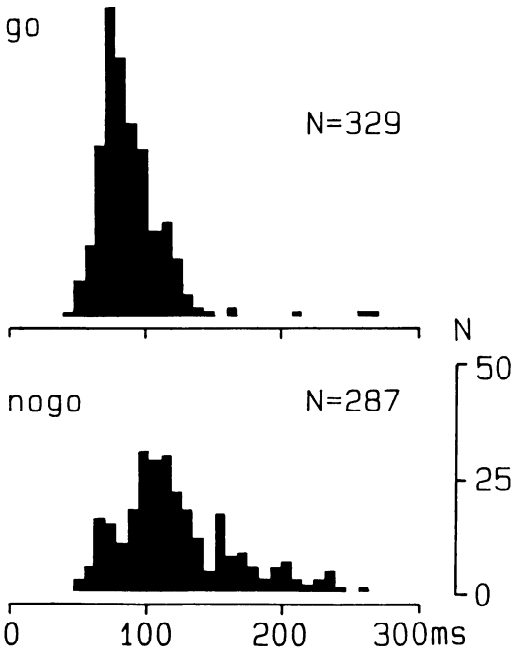

FIG. 3. Latencies of horizontal saccadic eye movements toward food boxes in response to the visual component of the door opening trigger stimulus. Trials were separated off-line according to go and no-go situations. 0 ms indicates time of door opening. Medians for go trials, 80 ms; for no-go trials, 116 ms. N = number of saccades.

Food box task

This task employed opening of the door of a food box as trigger stimulus for arm and eye movements (Fig. 1). Food- and fluid-deprived animals were required to keep one hand relaxed on an immovable, touch-sensitive key until the door of one of the food boxes opened. When the lateral box opened, they were invariably required to release the key; reach into the box; collect a small morsel of apple, cookie, or raisin; and bring it to the mouth. When the medial box opened, animals remained on the resting key for at least another 3 s and received no reward (asymmetric, direct-reaction go/no-go task). Thus opening of the lateral door

TABLE 1. *Major types of responses of midbrain dopamine neurons*

	Responding	Tested	%
Food box task			
Composite trigger stimulus			
Contralateral (go)	123	165	75
Ipsilateral (go)	39	45	87
Visual trigger stimulus			
Go	57	64	89
No-go	35	44	80
No task	0	38	0
Door noise trigger stimulus			
Go	62	78	79
No-go	32	40	80
No task	3	36	8
1-kHz sound trigger stimulus			
Go	29	31	94
No-go	18	20	90
No task	3	44	7
Instruction task			
Go light	14	61	23
No-go light	15	61	25
Go door noise trigger	50	61	82
No-go door noise trigger	23	61	38
Sound offset task			
Trigger stimulus	0	16	0

Composite trigger stimulus refers to door opening consisting of the visual, door noise, and 1-kHz components together. Only responses showing statistically significant increases in activity are included.

TABLE 2. *Parameters of behavioral reactions to the door opening trigger stimulus*

	Saccadic Latency, ms	Reaction Time, ms	Saccadic Frequency, %
Monkey A			
Composite (go)	112 (571)	319 (689)	83
Visual go	144 (165)	451 (191)	86
Visual no-go			
Door noise go	152 (250)	426 (273)	92
Door noise no-go	180 (86)		85
1-kHz go	252 (70)	672 (90)	78
1-kHz no-go			
Monkey B			
Composite (go)	68 (349)	260 (504)	69
Visual go	80 (329)	295 (592)	56
Visual no-go	116 (287)		84
Door noise go	76 (673)	232 (844)	80
Door noise no-go	68 (258)		52
1-kHz go	116 (368)	289 (444)	83
1-kHz no-go	108 (200)		51

Arm movement reaction times (from door opening to key release) and saccadic latencies were measured in the same trials and are given as medians (50th percentile). Numbers in parentheses are numbers of measures. Frequencies denote the occurrence of saccades in percentage of trials. Only data from saccades toward the right food box (contralateral to the side of neuronal recording) are shown. Composite trigger stimulus refers to door opening consisting of the visual, door noise, and 1-kHz components together.

constituted the trigger stimulus for an immediate arm movement in the go situation, whereas the animal refrained from moving in the no-go situation after opening of the medial door. The food box was closed 800–1,000 ms after opening and, after a go trial, was simultaneously refilled with a morsel of apple. Intervals between door closing and opening in the following trial varied between 4 and 8 s. Animals performed the task contralateral and ipsilateral to the side of neuronal recordings in separate sessions, respectively. The side of stimulus presentation corresponded without exception to the side of arm movement.

Food boxes had a frontal opening of 40 × 40 mm (9 × 9°). Door opening required 20–22 ms, was visible to the animal, and produced a sliding noise of low intensity. In addition, a 1-kHz sound of rectangular waveform, 100-ms duration, and 90–92 dB intensity emitted from a distant source was triggered with onset of door opening. A cover could be mounted in front of each food box to prevent vision of the opening door and the interior of the box while providing a 40 × 50 mm access from below. Food reward was not given, and data recording was aborted, whenever untimely muscle activity or premature movements were detected.

Behavior was electronically monitored from standard pulses generated by the different events of the task. Onset of door opening activated an infrared photocoupler. Key release was detected by a frequency-sensing circuit, which reacted to a change in electrical capacity induced by the touch of the animal's hand. Phototransistors sensitive to an infrared light beam across the entrance of each food box served to detect the time at which the animal's hand entered and left the box.

After performance of the go/no-go food box task was established, animals were trained in a number of task variations. These concerned separation of the door opening stimulus into its three sensory components, as well as the illumination of an instruction

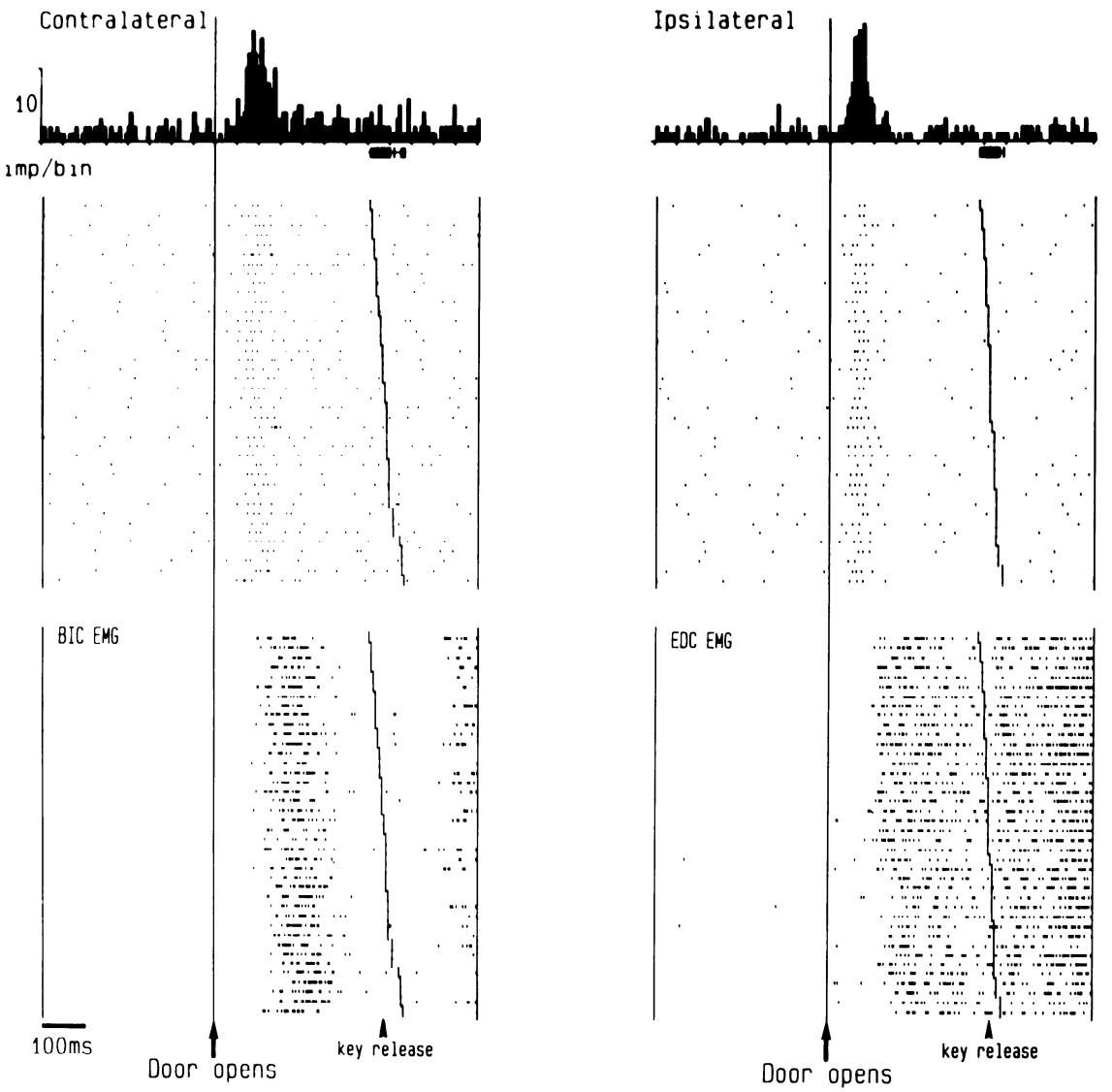

FIG. 4. Responses of 1 dopamine neuron to door opening on the contralateral and ipsilateral side, respectively (composite trigger stimulus). *Top* to *bottom*: perievent time histogram of neuronal impulses; dot display of neuronal impulses; and dot display of EMG activity in the biceps brachii (BIC) or extensor digitorum (EDC) muscle, recorded simultaneously with neuronal impulses. In the dot displays of this and the following figures, each dot represents the time of a neuronal impulse or rectified EMG activity above a preset level. 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. Sequence of trials is rearranged according to the length of time intervals between door opening and key release (reaction time). Histograms are composed of neuronal impulses shown as dots below them. Small bars below right parts of histograms and in dot displays represent the time of key release. Binwidth is 5 ms; small markers below histograms indicate 10 bins.

TABLE 3. *Latencies, durations, and magnitudes of neuronal responses to the composite trigger stimulus*

	Onset Latency, ms		Peak Latency, ms		Duration, ms		Magnitude, %		
	Median	Range	Median	Range	Median	Range	Median	Range	*n*
Contralateral	50	25–130	90	45–165	90	50–200	585	95–3,300	123
Ipsilateral	45	30–120	95	60–160	90	45–300	530	120–2,033	39

Composite trigger stimulus refers to door opening consisting of the visual, door noise, and 1-kHz components together. "Contralateral" and "ipsilateral" refer to the side of both stimulus presentation and arm movement (go situation only). The majority of neurons tested on the ipsilateral side were also studied and responded during contralateral task performance. Only data from responses consisting of statistically significant increases are included. Median = 50th percentile. Magnitudes are indicated as increases in percentage above activity immediately preceding the trigger stimulus. *n*, number of responding neurons.

light 2–3 s before door opening. During performance in the go/no-go task, go and no-go situations alternated randomly between trials in each session. In separate sessions, the door opening stimulus for each of the three components was applied in the absence of any behavioral task ("no-task" situation). In these sessions, which lasted 3–5 min, the medial box was used, whereas the resting key was absent and one-half of the frontal enclosure of the primate chair was kept open. Animals were fully awake during no-task sessions, as evidenced by the presence of spontaneous eye movements (Figs. 6, 7, and 10).

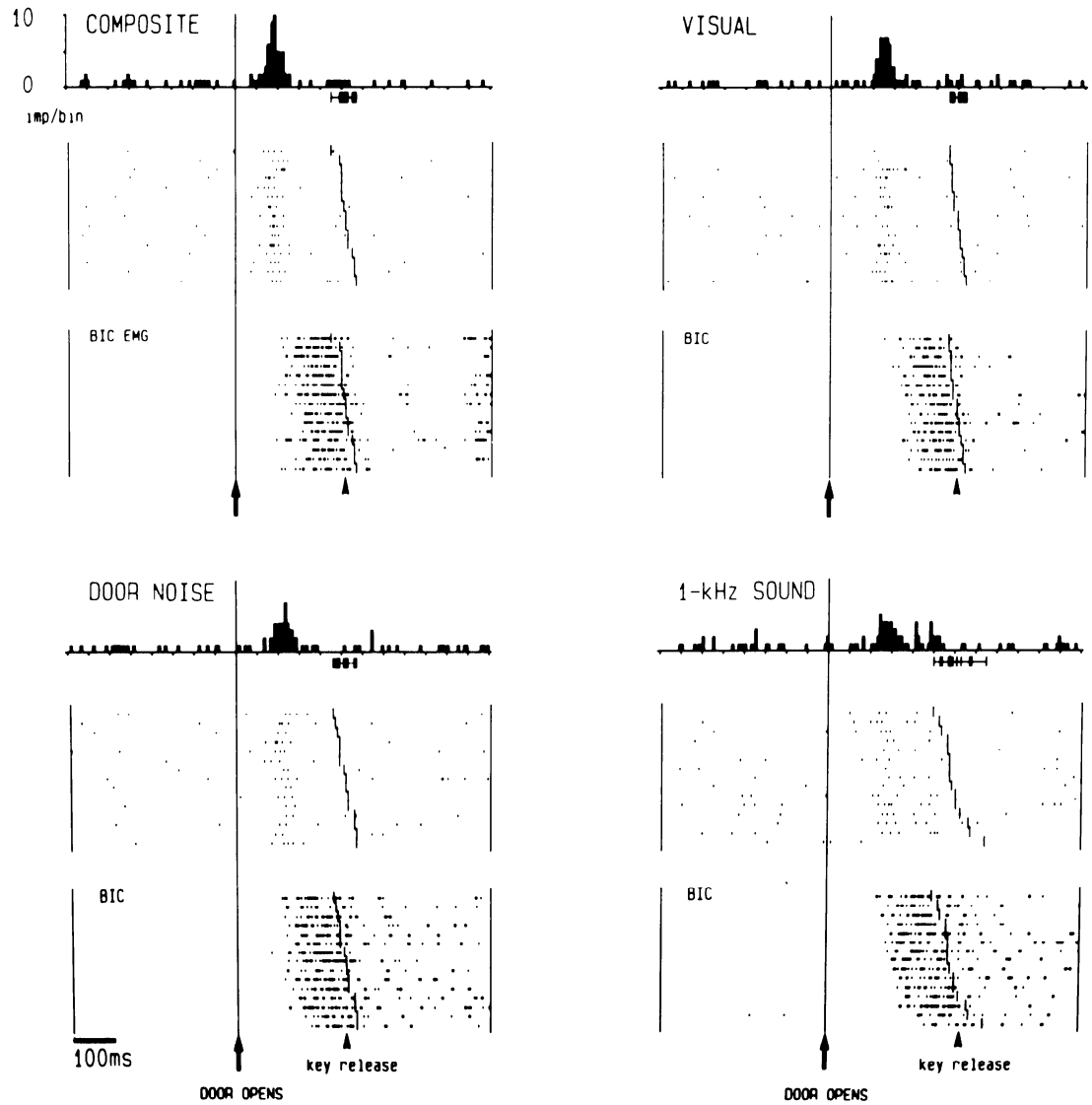

FIG. 5. Responses of 1 dopamine neuron to the different sensory components of door opening. Perievent time histograms and dot displays of neuronal impulses are shown above dot displays of simultaneously recorded biceps EMG activity (BIC). Sequence of trials is rearranged according to reaction time. Small bars below right parts of histograms and in dot displays represent the time of key release. Binwidth is 5 ms; small markers below histograms indicate 10 bins.

COMPOSITE TRIGGER STIMULUS. Used in the go situation only, door opening consisting of all three sensory components constituted the stimulus eliciting arm and eye movements. This situation is identical to the basic task of an earlier study (Schultz 1986b) and was often employed as reference for comparisons with different stimuli.

VISUAL TRIGGER STIMULUS. Only the visual component of the door opening stimulus was employed when both the 1-kHz sound was omitted and a masking noise of 91 dB intensity, which completely abolished the noise of the sliding door, was applied close to the animal's head. During recording of each neuron thus tested, effective masking of the door noise was ascertained by the absence of all behavioral reactions to door opening when, in addition, the cover was mounted in front of the food box.

DOOR NOISE TRIGGER STIMULUS. With the cover mounted in front of the box and the 1-kHz sound omitted, door opening became invisible to the animal, and the sliding noise alone served as trigger stimulus. Because the sliding noise did not indicate which box had opened, only one of the two boxes was covered in each session. For testing a given neuron in both go and no-go situations, alternate boxes were covered in two consecutive sessions while maintaining the random alternation between go and no-go trials.

1-kHz SOUND TRIGGER STIMULUS. With the cover mounted in front of the box and the masking noise of 91 dB applied, door opening was only recognized by the 1-kHz sound. The efficacy of the masking noise was controlled during the recording of each neuron by deleting the 1-kHz sound, which abolished all behavioral reactions. Similar to the door noise trigger stimulus, only one box at a time was covered in go/no-go trials, and complete testing included two consecutive sessions with alternate boxes being covered.

Each of the three stimulus components was employed separately for contralateral task performance, whereas only the composite trigger stimulus was employed for ipsilateral testing.

Instruction task

In the task variations described so far, door opening served both for discriminating between go and no-go situations and for triggering the behavioral reaction. In this variation of the task, instruction lights were used for separating these two informations in time. One of the green light-emitting diodes located directly above the lateral and medial boxes was illuminated in each trial for indicating the go or no-go situation, respectively (Fig. 1). After a variable period of 2–3 s, the respective box opened. With covers mounted in front of both boxes and the 1-kHz sound deleted, door opening was only recognized by the sliding noise and did not indicate which box had opened. Thus it served as trigger stimulus without providing information about the expected behavioral reaction. The instruction light was extinguished on key release in the go situation and ~5–6 s after door opening in the no-go situation. Thus instruction lights were the exclusive indicators of go and no-go situations and served as preparatory signals for the upcoming reaction to door opening (asymmetric, instruction-dependent go/no-go task).

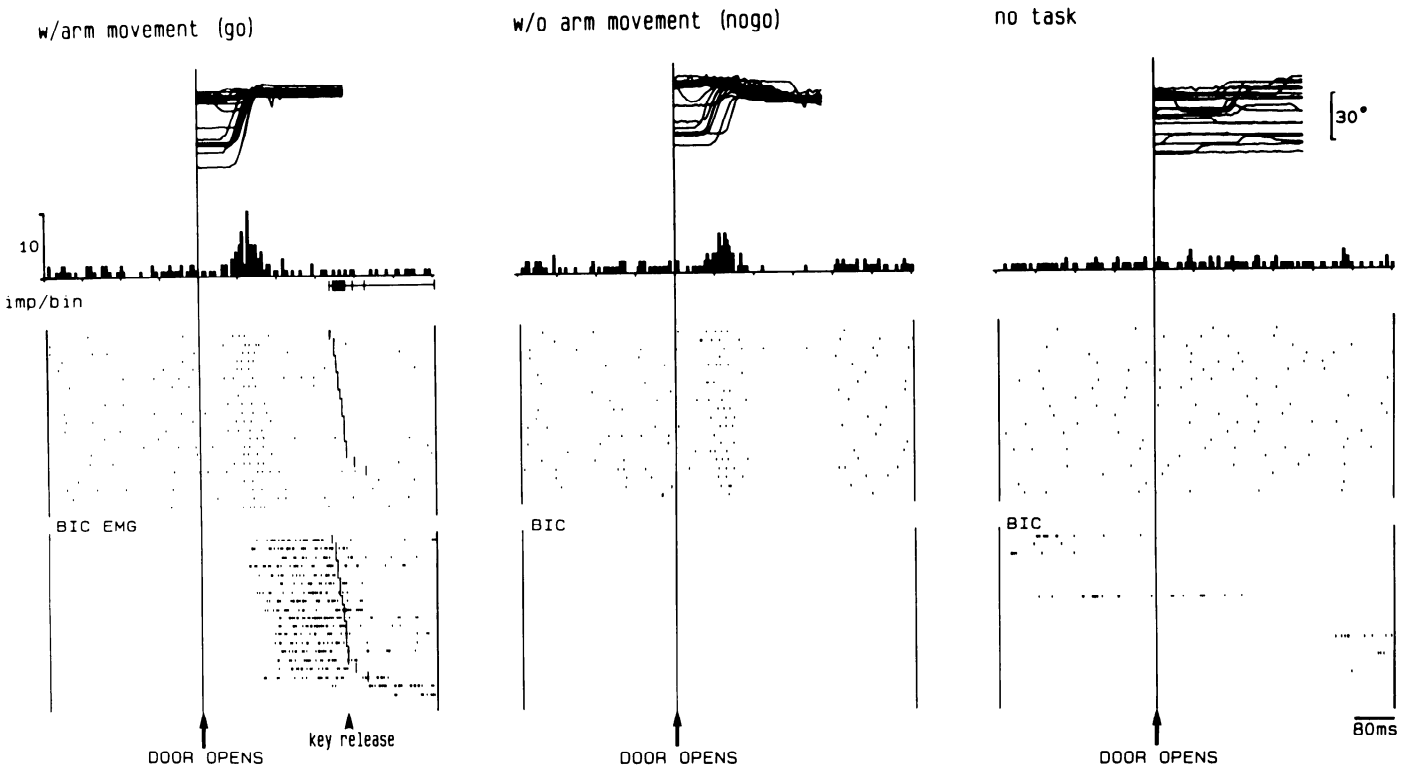

FIG. 6. Responses of 1 dopamine neuron to the visual trigger stimulus. *Left* and *middle*: performance of the go/no-go task; trials were separated off-line according to go and no-go situations (w/arm movement and w/o arm movement, respectively). *Right*: no-task session, with the use of the visual component of medial door opening in the absence of any behavioral task. *Top* to *bottom* in each of the 3 parts: superposed horizontal electrooculograms, perievent time histogram of neuronal impulses, dot display of neuronal impulses, and dot display of EMG activity in the biceps brachii muscle (BIC). Eye movements, neuronal impulses, and EMGs were recorded simultaneously in the same trials. Saccades toward the right are shown by upward deflections. Sequence of trials w/arm movements is rearranged according to reaction time, whereas otherwise the temporal sequence is preserved downward. Binwidth is 4 ms; small markers below histograms indicate 20 bins.

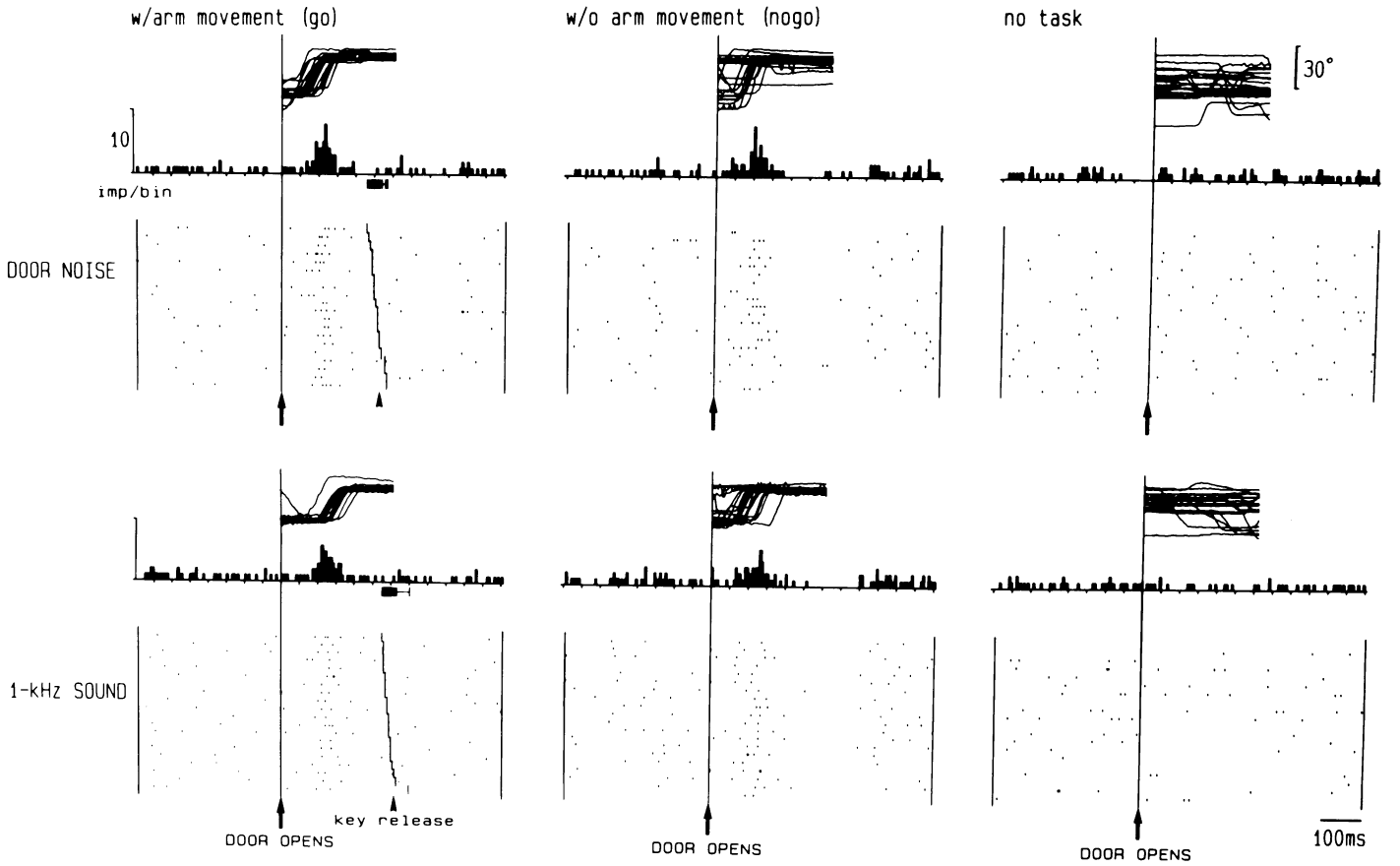

FIG. 7. Responses of 2 dopamine neurons to the 2 auditory trigger stimulus components, respectively. *Left* and *middle*: go/no-go task. *Right*: no-task sessions, with the use of the same door noise and 1-kHz components of medial door opening, respectively. Superposed horizontal electrooculograms are shown above simultaneously recorded perievent time histograms and dot displays of neuronal impulses. Saccades toward the right are shown by upward deflections. Sequence of trials w/arm movements is rearranged according to reaction time, whereas otherwise the temporal sequence is preserved downward. Binwidth is 5 ms; small markers below histograms indicate 10 bins.

Sound offset task

One of the monkeys was also trained to release the resting key in response to the offset of a sound stimulus of 100 Hz rectangular waveform, 3 s fixed duration, and 68 dB intensity. The animal subsequently reached into the food box placed at 27° lateral to the midline. The box was always kept open, but vision of its interior was prevented by the cover mounted in front of it. Whereas offset of the auditory stimulus served as trigger stimulus for the movement reaction, sound onset represented an instruction signal preparing for the upcoming movement reaction.

RESULTS

A total of 272 DA neurons, the electrophysiological characteristics of which are described in the accompanying report (Romo and Schultz 1990), were recorded during performance of the behavioral tasks. The frequencies of responses encountered in the different situations are given in Table 1. The majority of DA neurons were histologically located in the catecholamine cell group A9 of pars compacta of substantia nigra (237 neurons), whereas 30 and 5

TABLE 4. *Latencies and durations of contralateral responses to the 3 different components of the door opening trigger stimulus*

	Onset Latency, ms		Peak Latency, ms		Duration, ms		
	Median	Range	Median	Range	Median	Range	*n*
Visual go	70	30–110	110	75–155	90	55–170	57
Visual no-go	70	45–105	110	75–180	85	50–150	35
Door noise go	55	25–95	95	70–150	90	50–150	62
Door noise no-go	55	25–120	95	75–150	80	55–125	32
1-kHz sound go	75	40–105	135	90–175	115	70–190	29
1-kHz sound no-go	70	50–105	130	80–155	115	75–160	18

Only data from responses consisting of statistically significant increases are included. *n*, number of responding neurons.

neurons adhered to neighboring groups A8 and A10, respectively. An example of the positions of DA neurons tested with the visual trigger stimulus is given in Fig. 2.

Door opening in the food box task

BEHAVIORAL PARAMETERS. The behavioral response to door opening in the go situation comprised a horizontal saccadic eye movement directed toward the box, followed by activation of arm muscles and an arm movement. Only a saccadic eye movement occurred in no-go trials (Figs. 3, 6, and 7). Because of the absence of a visual fixation spot, saccades began from varying positions at the time of door opening. They occurred in 51–92% of trials with different stimulus components (Table 2). In the remaining trials, eye positions were already on the target at the time of door opening. Latencies of eye and arm movement onsets are shown in Table 2. Both movements differed insignificantly between the two sides of task performance ($P > 0.05$; Wilcoxon test). Onsets of saccades occurred independently from those of arm movements in all situations, as demonstrated by correlation coefficients of −0.10–0.64 in both animals. With food boxes mounted at the level of the eyes, vertical components of target-directed saccades were of less appreciable extent.

The short saccadic latencies, found in all monkeys performing the food box task (Schultz et al. 1989a,b), were probably due to intersensory facilitation (Raab 1962) provided by the combined auditory and visual trigger signal, the rapidly moving visual stimulus component, the spatial constancy of the stimulus, and the prolonged training. When we used a purely visual, stationary trigger stimulus in a similar task, saccadic latencies were increased to 160–180 ms (Ljungberg, Apicella, and Schultz, unpublished observations). In contrast, saccades in response to purely auditory stimuli have latencies of 115–140 ms (Whittington et al. 1981). Latencies of 70–120 ms are seen with "express saccades," which, different from presently reported saccades, occur with a bimodal distribution when a target light appears shortly after offset of an ocular fixation spot (Fischer and Boch 1983). Similarly short latencies may occur with skeletal responses in particular situations. Limb EMG activity began as early as 50–90 ms after combined somatosensory and visual target displacement in cats (Ghez and Vicario 1978) and 100 and 125 ms after auditory and visual stimuli, respectively, in monkeys reinforced for rapid responding (Luschei et al. 1967).

In agreement with results from previous experiments (Schultz 1986a, 1989c), prime mover muscles of the arm were the extensor digitorum communis and biceps. Their activity began at median latencies of 236–278 ms and 162–180 ms after door opening in *animals A* and *B*, respectively, this being 104–141 ms and 141–155 ms before key release. Onset of arm movement correlated well with EMG onset, as shown by correlation coefficients of 0.93–0.94 and 0.72–0.78 in the two animals, respectively. Equally early but less consistent activity was seen in the anterior and lateral deltoid, the upper and lower trapezius, and in thoracic paraspinal muscles. Later during the movement, the triceps, latissimus dorsi, and cervical paraspinal muscles became active. Task-related activity was absent downward of lumbar muscles. Only cervical and thoracic paraspinal muscles were activated bilaterally during movements.

CONTRA- AND IPSILATERAL COMPOSITE TRIGGER STIMULUS. A total of 123 of 165 DA neurons (75%) responded with a statistically significant, phasic activation of ~90-ms duration to opening of the contralateral food box (Fig. 4; Tables 1 and 3). Responses occurred at median onset and peak latencies of 50 and 90 ms, respectively, and amounted to a 2- to >30-fold increase of instantaneous impulse frequency (Table 3). Responses were time-locked to the stim-

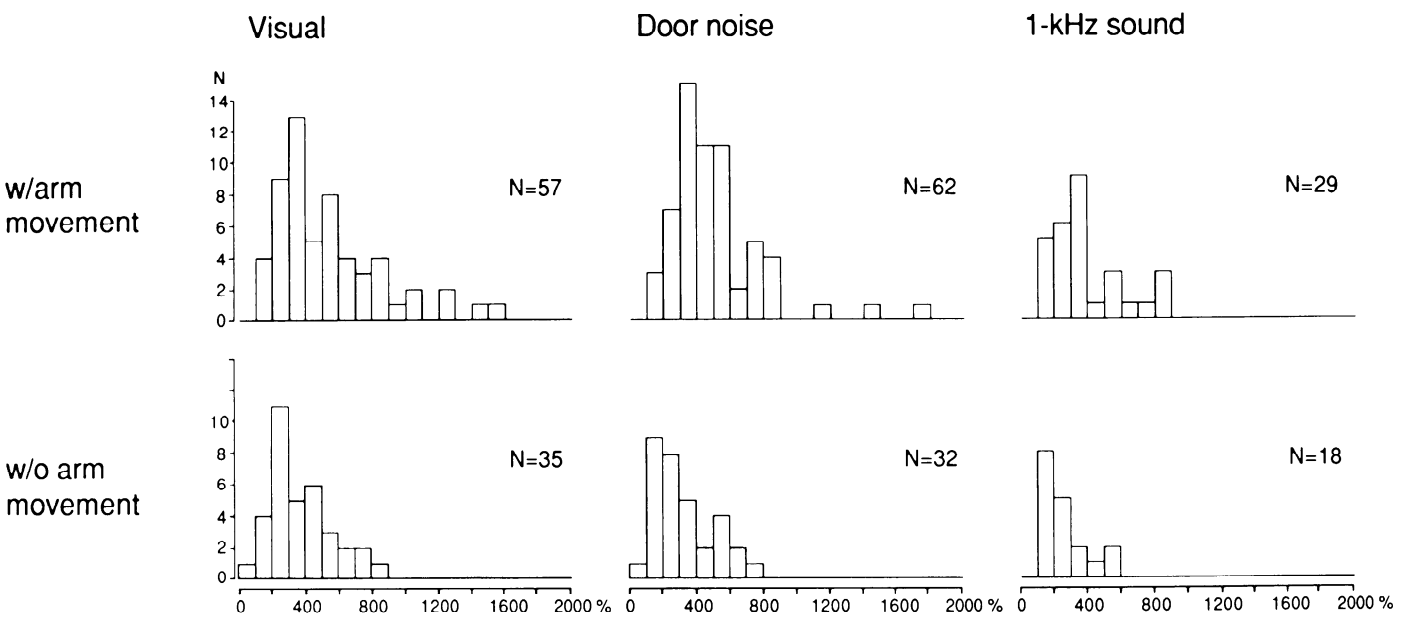

FIG. 8. Magnitudes of neuronal responses to the 3 sensory components of the door opening trigger stimulus. Values are given as increases in percent above base-line activity recorded before door opening. "w/arm movement" and "w/o arm movement" refer to trials grouped off-line within sessions according to go and no-go situations, respectively. The following median increases were obtained: w/arm movement: visual 410%, door noise 450%, 1-kHz sound 320%; w/o arm movement: visual 310%, door noise 260%, 1-kHz sound 210%. N = number of responding neurons.

ulus and not to the following arm movement or onset of EMG activity (Fig. 4). Eight DA neurons (5%) were depressed by door opening. Modest yet statistically significant activations lasting during the total duration of arm movement were seen in 25 DA neurons (15%), with median increases of activity amounting to 110% (range 78–245%). Sixteen of these neurons also responded to door opening. These results agree with data reported earlier (Schultz 1986b).

Of 45 DA neurons tested during ipsilateral task performance, 39 (87%) were significantly activated by door opening, whereas 2 (4%) were depressed in their activity

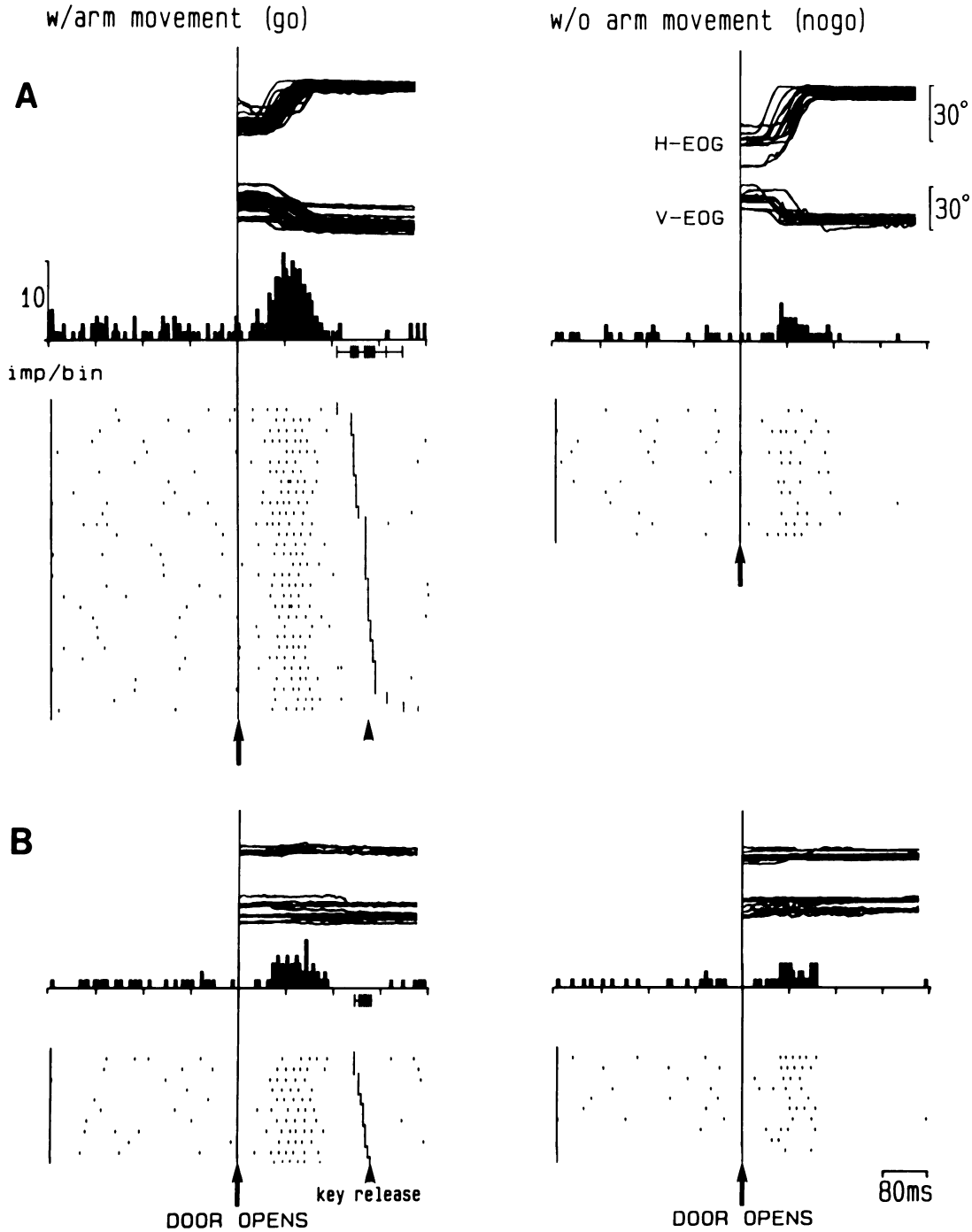

FIG. 9. Independence of door opening response from individual saccadic eye movements. Data were collected from 1 dopamine neuron during performance of the go/no-go task with the use of the door noise trigger stimulus. Data were separated off-line into go and no-go trials (w/ and w/o arm movement, respectively) and according to the presence or absence of target-directed saccades (*A* and *B*, respectively). Horizontal and vertical electrooculograms (H-EOG, V-EOG) are shown above perievent time histograms and dot displays of neuronal impulses recorded in the same trials. Sequence of trials w/arm movements is rearranged according to reaction time, whereas otherwise the temporal sequence is preserved downward. Varying numbers of trials should be taken into account when comparing response magnitudes between different histograms. Binwidth is 4 ms; small markers below histograms indicate 20 bins.

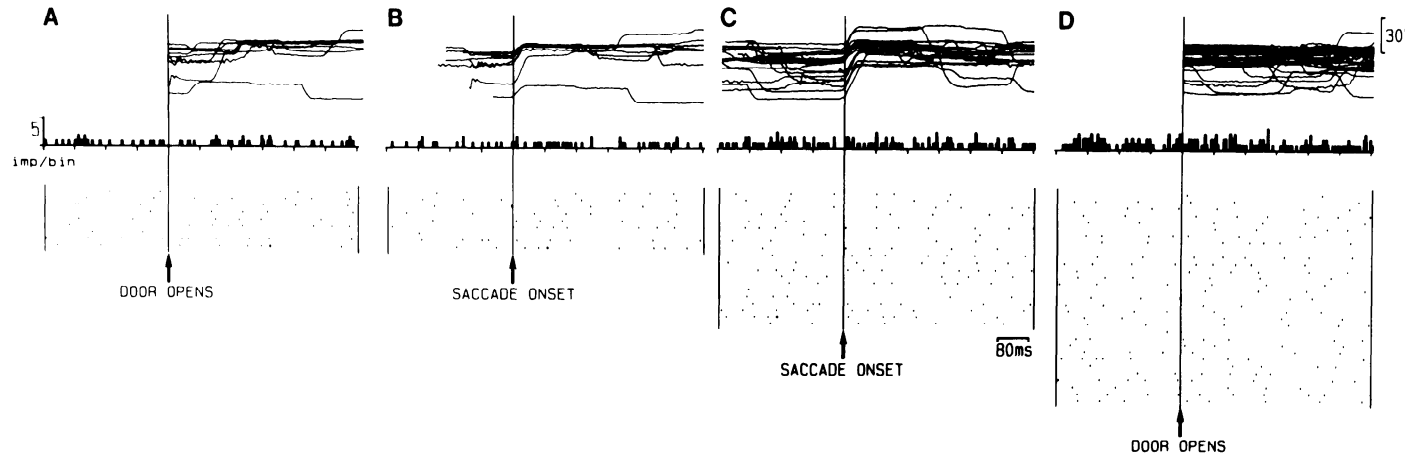

FIG. 10. Lack of neuronal relationships to saccadic eye movements in the absence of any behavioral task (no-task session). *A*: neuronal activity in trials selected for the presence of horizontal saccadic eye movements toward the right side within 300 ms after door opening. *B*: same data as in *A*, but referenced to saccade onset. *C*: neuronal activity in trials with horizontal saccades of similar amplitudes and same direction as in response to door opening in the go/no-go task. Only saccades occurring >300 ms after door opening are plotted. *D*: neuronal activity in trials lacking horizontal saccades within 300 ms after door opening. All data were recorded from a dopamine neuron during one no-task session, the trials being separated off-line into parts *A–D*. Responses of the same neuron to trigger stimuli in a separate session are shown in Fig. 9. Horizontal electrooculograms are shown above all perievent time histograms and dot displays of neuronal impulses recorded in the same trials. Temporal sequence of trials is preserved downward. Binwidth is 4 ms; small markers below histograms indicate 20 bins.

(Fig. 4; Tables 1 and 3). Of 34 DA neurons tested on both sides in separate sessions, 32 were bilaterally activated and 2 bilaterally depressed. Ipsilateral responses were insignificantly different from those on the contralateral side in terms of onset latency, peak latency, duration, and magnitude (Table 3) ($P > 0.05$). Five DA neurons were activated

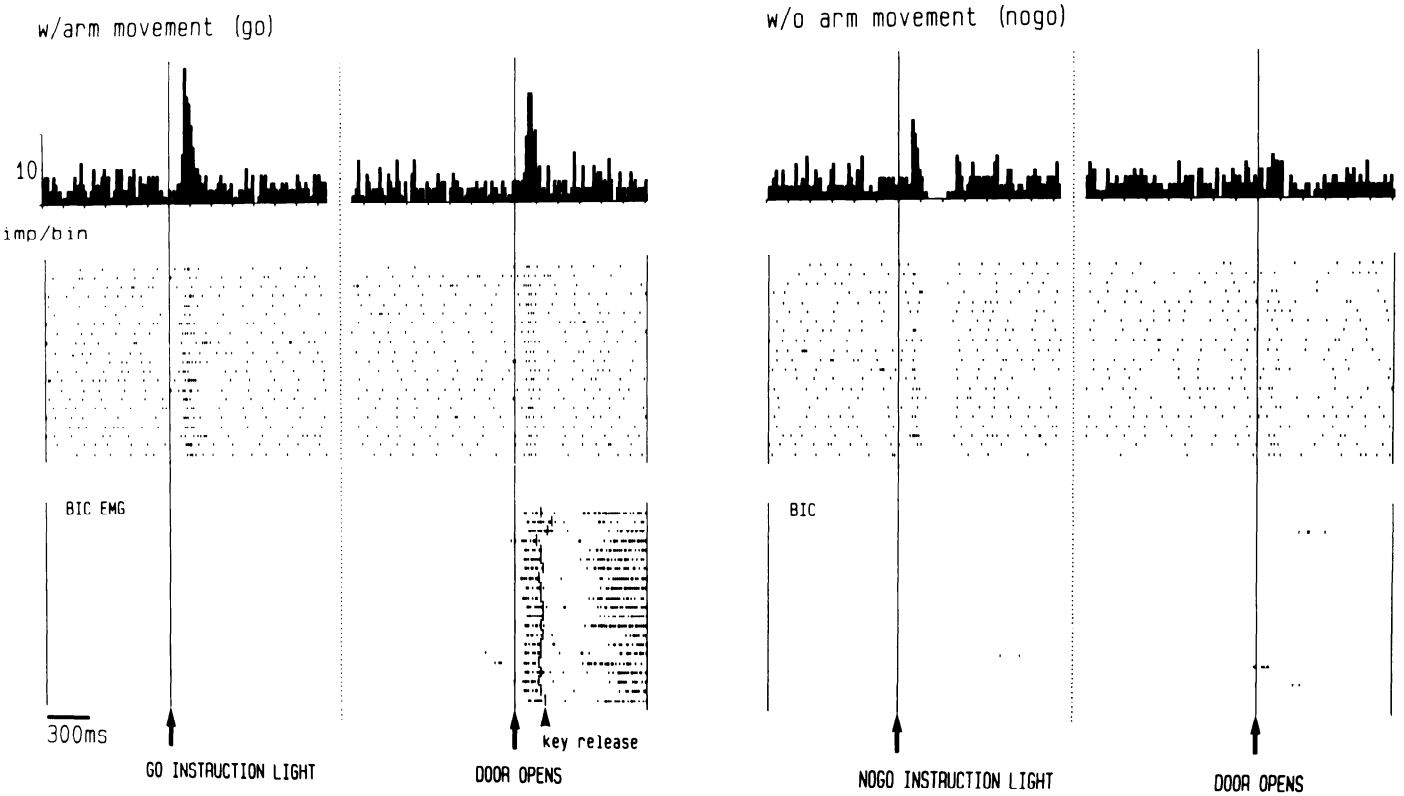

FIG. 11. Responses of a dopamine neuron to instruction lights in the go/no-go task. Trials from 1 session were separated off-line according to go and no-go situations (w/arm movement and w/o arm movement, respectively). Dot displays of biceps EMG activity are shown below perievent time histograms and dot displays of neuronal impulses recorded in the same trials. Temporal sequence of trials is preserved downward. Binwidth is 15 ms; small markers below histograms indicate 10 bins.

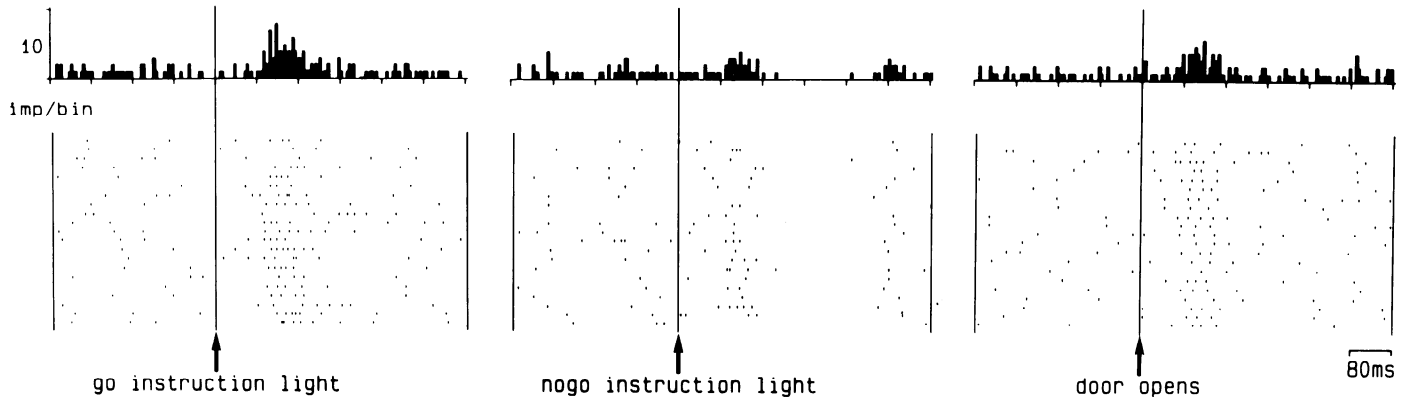

FIG. 12. Comparison of neuronal responses to instruction lights and door opening trigger stimulus in 1 dopamine neuron. Data were collected in the same session of the go/no-go task. Only trials with arm movements (go situation) were used for the right part. Binwidth is 4 ms; small markers below histograms indicate 20 bins.

during the arm movement on the ipsilateral side (11%), all of which also showed increases during contralateral movements. These data show symmetric responses of DA neurons to door opening on both sides.

INDIVIDUAL VISUAL AND AUDITORY STIMULUS COMPONENTS. When the visual, door noise, or 1-kHz components of door opening were used separately, latencies of arm and eye movements were significantly prolonged, as compared with the composite stimulus ($P < 0.01$, except arm movements with the door noise component, $P > 0.05$) (Table 2). Between 79 and 94% of DA neurons were activated by the separate sensory components of door opening in the go situation (Table 1; Fig. 5). With the exception of one neuron failing to respond to the 1-kHz sound component, all neurons responding to the composite trigger stimulus were also activated by the individual components tested in separate sessions (24, 18, and 19 neurons, respectively). Compared with the composite stimulus, response magnitudes were significantly decreased by 37, 22, and 48% when the visual, door noise, or 1-kHz sound components, respectively, were used in the go situation, whereas response latencies were increased for the visual (30% and 28% for onset and peak, respectively) and 1-kHz components (50% for onset and peak) ($P < 0.01$). Only insignificant increases by 0–22% were found in response duration ($P > 0.05$). These data show a slightly reduced responsiveness of DA neurons to separate sensory components in parallel with a slowed initiation of arm and eye movements, as compared with the composite trigger stimulus.

BEHAVIORAL CONTINGENCIES OF RESPONSES. In go trials of the go/no-go task, animals reacted with an eye and arm movement to opening of the lateral food box. In no-go trials, which randomly alternated with go trials in each session, animals reacted with an eye movement to opening of the medial box but refrained from moving the arm and received no reward. Saccades were directed to the lateral and medial food box in visual go and no-go situations, respectively, and were aimed at the box that was visible when using an auditory component. Only insignificant differences in saccadic latency were seen between go and no-go trials ($P > 0.05$) (Table 2; Fig. 3). Target-directed eye movements were absent when a food box opened outside of behavioral tasks in separate sessions (see Figs. 6 and 7).

Dopamine neurons were activated by door opening when animals reached to the food box (go situation) and when they refrained from moving the arm (no-go situation). However, the same door opening stimulus was largely ineffective outside the task (Table 1). Examples from tests with the three sensory components are shown in Figs. 6 and 7. The superposed oculograms demonstrate the presence of saccadic eye movements directed toward the food boxes in go and no-go situations, whereas comparable saccades were absent outside the task. Only six neurons responded in no-task sessions, all of which were recorded while animals performed regular target-directed saccades toward the food box, indicating erroneous behavioral reactions.

The activation in response to door opening was in several instances followed by a statistically significant pause of discharges lasting 50–200 ms. This occurred rarely in the go situation (7, 11, and 17% of activated neurons when using the visual, door noise, and 1-kHz components, respectively), whereas it was often observed in the no-go situation (46, 59, and 33% for the 3 components, respectively) (Figs. 6 and 7, *middle*).

TABLE 5. *Latencies, durations, and magnitudes of responses to instruction lights*

	Onset Latency, ms		Peak Latency, ms		Duration, ms		Magnitude, %		
	Median	Range	Median	Range	Median	Range	Median	Range	*n*
Go instruction	85	70–130	130	110–180	115	75–200	267	125–609	14
No-go instruction	95	65–220	140	100–380	85	50–290	221	108–800	15

Magnitudes are indicated as increases in percentage above activity immediately preceding the instruction light. Only data from responses consisting of statistically significant increases are included. *n*, number of responding neurons.

Response parameters were compared between go and no-go situations in neurons tested with the same sensory components. When the visual, door noise, and 1-kHz trigger stimuli were used separately, 33 of 36, 20 of 23, and 14 of 15 neurons responding in the go situation, respectively, were also activated when the no-go door opened and the animal refrained from moving the arm. Onset latencies, peak latencies, and durations of neuronal responses showed insignificant differences between go and no-go situations ($P > 0.05$). However, response magnitudes in no-go situations were significantly decreased by 34, 47, and 43% with the visual, door noise, and 1-kHz sound components, respectively, as compared with go situations with the same stimulus components ($P < 0.01$). Response latencies, durations, and magnitudes from all neurons tested with any of the three components in go or no-go situations are shown in Table 4 and Fig. 8.

Whereas DA neurons responded to stimuli capable of eliciting saccadic eye movements, their activity was not related to individual saccades. Neurons responded to door opening in the presence of target-directed saccades (Fig. 9*A*) as well as in their absence when eye positions were on the target already at the time of door opening (Fig. 9*B*), both in go and no-go situations. Thus, in individual no-go trials, DA neurons even responded to door opening when animals performed neither an arm nor an eye movement (Fig. 9*B*, w/o arm movement). The lack of relationship to individual saccades was observed in all DA neurons responding to the contra- or ipsilateral composite door opening stimulus or to each of the three sensory components.

The relationship to oculomotor behavior was further analyzed in no-task sessions. Neurons responding in the go/no-go task lacked responses even in those trials of no-task sessions in which spontaneous saccades of similar amplitude and direction as in go/no-go trials occurred within 300 ms after door opening (Fig. 10, *A* and *B*) or at a later period (Fig. 10*C*).

These data show that DA neurons responded to trigger stimuli that elicited immediate behavioral reactions. However, responses were not specific for individual arm or eye movements. Responses were absent when the same stimuli were presented outside of behavioral tasks.

Instruction task

In this task, an instruction light illuminated 2–3 s before door opening became the exclusive indicator of the behavioral situation when the door noise trigger stimulus was used in both go and no-go trials. Thus the light served to prepare the animal for the upcoming reaction to door opening.

NEURONAL RESPONSES TO INSTRUCTION LIGHTS. Of 61 DA neurons, 32 (52%) showed phasic activations or depressions of impulse activity after instruction-light onset. Activations were seen in 20 neurons (33%), which occurred with go instructions only ($n = 5$), no-go instructions only ($n = 6$), or both go and no-go instructions ($n = 9$). Typical phasic responses to both instruction lights are shown in Fig. 11. Responses to instruction lights resembled those to door opening in terms of latency, duration, and magnitude (Fig. 12; Table 5). Depressions in response to instruction lights were observed in 19 neurons (31%). These occurred only in the no-go situation. Of these 19 neurons, 6 were activated by the no-go instruction before the depression (Fig. 11), whereas 1 neuron was activated by the go instruction.

Responses to instruction lights were unequally distributed over the time of experimentation. Whereas responses were absent in all 8 neurons tested in *monkey A*, activations in *monkey B* were observed predominantly when instruc-

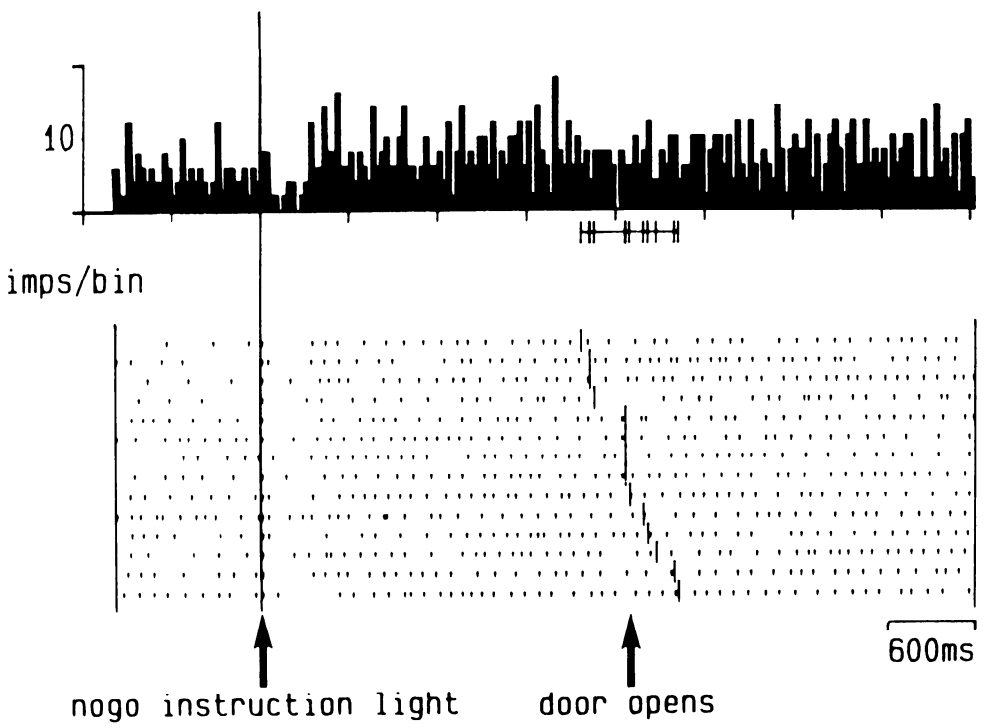

FIG. 13. Moderate tonic activation of a dopamine neuron during illumination of the no-go instruction light. Used in the go/no-go task with the door noise trigger stimulus, this signal prepared the animal to refrain from moving after door opening. Activation constituted an increase of 55% over background activity measured before light onset. It began ~250 ms after light onset after an insignificant depression ($P > 0.05$). Sequence of trials is rearranged according to the interval between light onset and door opening. Binwidth is 30 ms; small markers below histogram indicate 20 bins.

tion lights were employed infrequently but occurred less readily with regular testing. Thus 10 of 13 neurons (77%) responded with activations when instruction lights were used in fewer than three sessions per day, with the total of 13 sessions being studied over a period of 8 wk. When instruction lights were employed in three to eight sessions per day during the following 2 wk, only 10 of 40 neurons (25%) were activated. In contrast, all but one of the depressions after no-go instructions were seen during this last period (18 of 40 neurons = 45%).

Tonic responses to instruction lights were found in only 2 of the 61 DA neurons. Both responses consisted of moderate yet statistically significant increases in activity and were limited to the no-go situation. In one of the neurons, activity increased by 55% and lasted for >2 s beyond the trigger stimulus while the animal remained motionless (Fig. 13). The other neuron responded with a 56% increase of activity lasting ~1.3 s after light onset.

INFLUENCE OF INSTRUCTION LIGHTS ON RESPONSES TO DOOR OPENING. Of the 61 DA neurons tested in the instruction-dependent go/no-go task, 50 (82%) were activated by opening of the go box, whereas only 23 (38%) responded to opening of the no-go box. Thus a lower percentage of neurons responded to door opening in the no-go

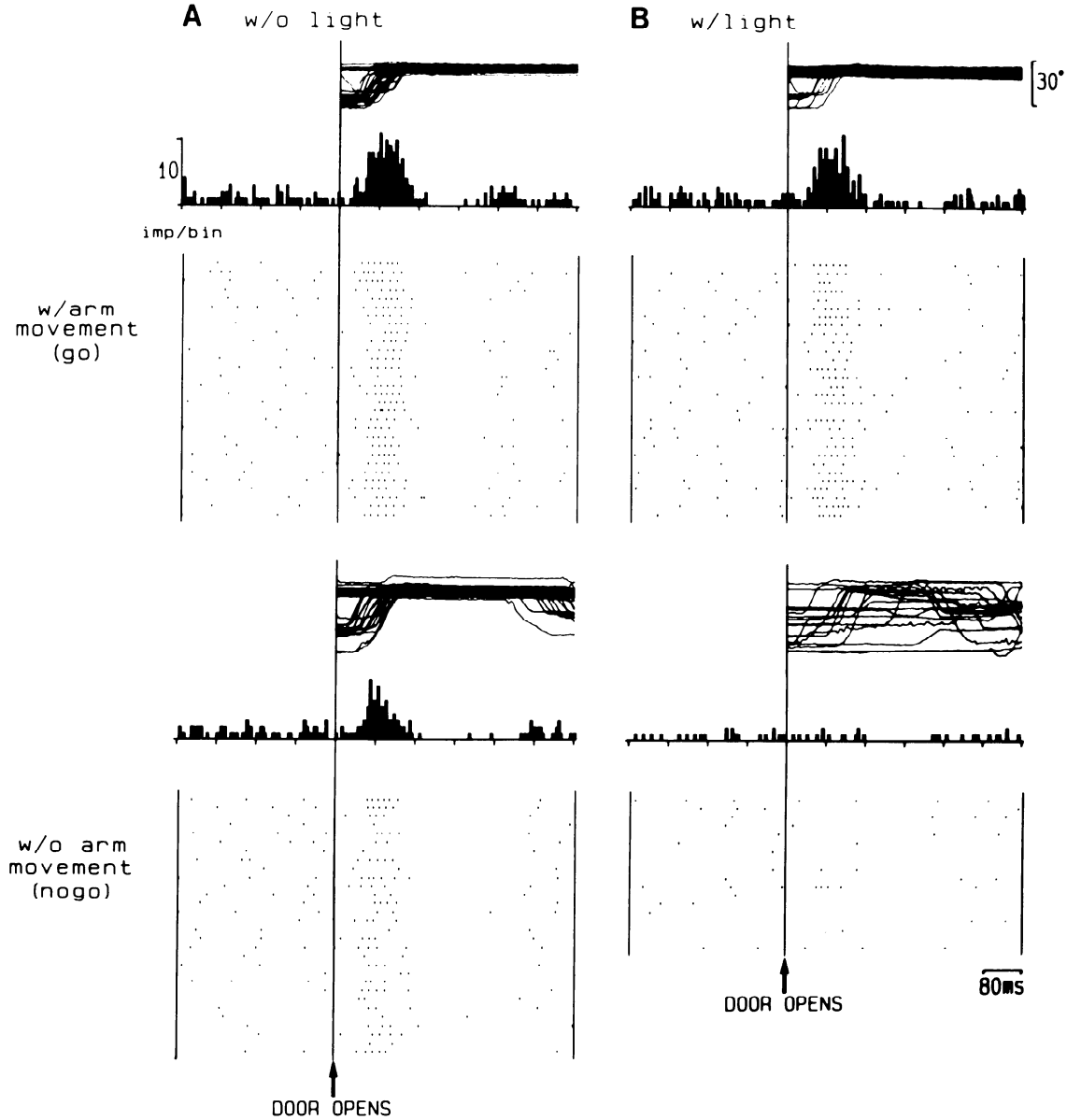

FIG. 14. Influence of preparatory instruction lights on responses to door opening in 1 dopamine neuron. *A*: responses to door opening in go and no-go situations without instruction lights. *B*: when instruction lights were used while testing the same neuron in a separate session, responses to door opening decreased by 12% in the go situation (*top*) while disappearing completely in no-go trials (*bottom*). In parallel, the eyes showed a higher tendency for fixating the food box at the time of door opening in go trials, whereas target-directed saccades were largely absent in no-go trials. Horizontal electrooculograms are shown above perievent time histograms and dot displays of neuronal impulses recorded in the same trials. Data were separated off-line into go and no-go trials (w/ and w/o arm movement, respectively). Door noise trigger stimulus was used in *A* and *B*. Binwidth is 4 ms; small markers below histograms indicate 20 bins.

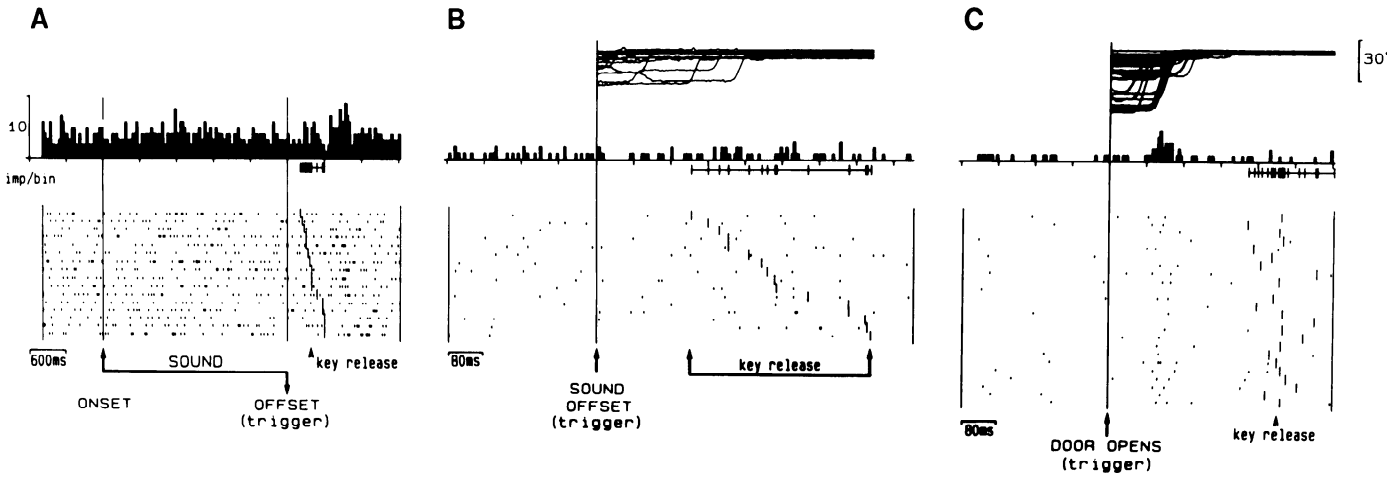

FIG. 15. *A* and *B*: activity of 1 dopamine neuron during the sound offset task. There is neither a change in activity after sound onset nor a phasic response to sound offset used for triggering the arm movement. Data in *A* and *B* are shown from the same trials by using different time bases, respectively. *C*: response of the same neuron to the composite trigger stimulus of the food box task tested in a separate session. In *B* and *C*, horizontal electrooculograms are shown above perievent time histograms and dot displays of neuronal impulses recorded in the same trials. Sequence of trials in *A* and *B* is rearranged according to reaction time, whereas in *C* the temporal sequence is preserved downward. Binwidth is 30 ms in *A* and 4 ms in *B* and *C*. Small markers below histograms indicate 20 bins.

situation when instruction lights were used as compared with the direct-reaction go/no-go task. This was further tested in neurons studied in both tasks.

In the absence of instruction lights, typical responses to door opening were seen in both go and no-go situations together with target-directed saccades (Fig. 14*A*). When the instruction light preceded door opening by ~2.5 s, the same neuron showed a slight reduction in neuronal responses in go trials, whereas the eyes showed an increased tendency for fixating the box at the time of opening (Fig. 14*B*, *top*). Altogether, 3 of 14 DA neurons completely lost their responses to door opening in go trials when instruction lights were used, whereas responses in all remaining neurons were reduced by 7–71% (median 42%). In no-go trials, 9 of 14 neurons entirely lost their responses to door opening when using instruction lights, and target-directed saccades were largely absent (Fig. 14*B*, *bottom*). No-go door opening responses in all remaining five neurons were reduced by 49–75% (median 58%), whereas target-directed saccades occurred occasionally during these recordings. This suggests that the animal often neglected door opening as trigger stimulus after the instruction light had indicated a no-go situation. The data shown in Fig. 14 illustrate how a stimulus became ineffective for activating DA neurons after losing its capacity for triggering a behavioral reaction.

Reductions of door opening responses in sessions employing instruction lights were independent of responses to these lights. Of the three neurons losing their responses in the go situation, two were activated by instruction lights. In the no-go situation, three of the nine neurons losing responses to door opening responded to instructions.

Sound offset as trigger signal

In this task, tested with 16 DA neurons in *monkey A*, the animal reached into the covered lateral box for food reward on termination of a distant sound stimulus of 3-s duration. Thus, instead of being triggered by onset of door opening, arm movements occurred in response to offset of the sound stimulus.

Behavioral reactions to this trigger signal were slower and more variable in latency as compared with door opening. Medians of arm reaction and movement times in 16 sessions were 699 and 318 ms, respectively (430 movements; range of session medians 408–1,644 ms and 190–452 ms, respectively). Activity in the biceps began at a median latency of 450 ms after sound offset (range 248–1,400 ms), this being 165 ms before key release (range 117–250 ms). Onset of arm movement was linearly related to onset of biceps EMG ($r = 0.76$ for pooled data; range of session r's 0.69–0.99). Saccadic eye movements were regularly directed toward the food box after sound offset (median latency 244 ms, 198 saccades; range 164–432 ms). Onset of individual saccades was unrelated to EMG or arm movement onset (r's of 0.41 and 0.58, respectively).

None of the 16 DA neurons studied in this task showed any response to sound offset as trigger signal, nor to the preceding onset of sound (Fig. 15, *A* and *B*). All 16 neurons were tested in separate sessions with the composite door opening stimulus. Of these, 14 responded with an increase of activity (Fig. 15*C*) and 1 with a decrease. Eight of the 16 neurons were also tested with the auditory door noise trigger stimulus, and 7 of them responded with an activation. These results suggest that the offset of a sound stimulus serving as trigger signal for target-directed arm and eye movements is ineffective for altering the discharge activity of DA neurons responding to door opening.

DISCUSSION

The present results demonstrate that a high percentage of midbrain DA neurons of substantia nigra and adjoining areas A8 and A10 in primates respond with a short burst of impulses to visual and auditory stimuli associated with immediate behavioral reactions. The data corroborate earlier

results (Schultz 1986b) and provide details on the nature of effective stimuli and the contingencies of neuronal responses to the behavioral meaning of the stimuli.

Responses to auditory and visual trigger stimuli occurred during performance of the go/no-go task while animals were prepared to react to them. Identical stimuli were ineffective when presented in behavioral contexts in which animals would not react, like the no-task situation or when a preceding light instructed the animal not to react in the unrewarded no-go situation. This shows that responses depended on the behavioral situation and were not of purely sensory character.

Responses to trigger stimuli occurred during contralateral as well as during ipsilateral task performance. Thus responses were not specific for the forelimb being used. Because the arm movement on both sides was mostly preceded by a target-directed saccade of the eyes, responses were equally not specific for the direction of the elicited eye movement. Thus the responses did not appear to be related to the parameters of an impending movement.

Neurons responded to trigger stimuli in both go and no-go situations. Thus responses were equally present in the absence of arm movements. Responses did not depend on saccadic reactions to trigger stimuli either, because they also occurred when saccadic eye movements were occasionally absent. This argues against a specific role of neuronal responses in the initiation of individual movements.

Although responses were neither of purely sensory character nor specifically related to the initiation of limb and eye movements, they should be involved in a more general mechanism subserving behavioral responses. DA neurons were activated in response to door opening in go trials that elicited arm and eye movements leading to the immediate acquisition of an object of high interest for the animal, a morsel of food. By signaling the availability of food and triggering rapid movement reactions, this stimulus had an appetitive character together with an arousing effect on the behavior of the animal, which may be termed "motivational arousal" (Bindra 1974; Wise 1982). Neurons equally responded in no-go trials, which alternated randomly with go trials. In this situation, animals refrained from the arm movement but usually performed a saccade toward the box that was visible, obviously for exploring the potential for acquiring a food morsel. Response generalization may have been an additional factor contributing to the response in no-go trials. Thus neuronal responses to opening of go and no-go boxes may be both related to motivational arousal provided by door opening. In contrast, opening of the no-go box after preparation by a preceding instruction light did not lead to eye movements and was probably neglected by the animal, and neurons lacked responses to this stimulus. Further arguments for a relationship of responses to arousal are provided by the uniformly short latencies and the similarities of latency, duration, and magnitude between the visual, auditory and somatosensory modalities (Romo and Schultz 1990).

Preparatory instruction stimuli were effective in activating DA neurons during a transitory period. Conceivably, the higher behavioral impact of infrequent or even novel stimuli rendered them more effective. Novel, unknown, or infrequent stimuli may arouse the animal through a potentially appetitive value. Interestingly, responses to instructions resemble responses to trigger stimuli and touch of food in terms of latency, duration, and magnitude. Responses of DA neurons to visual and auditory stimuli of high intensities outside of specific behavioral contexts have been found previously in cats. The responses faded away as soon as animals were being distracted (Strecker and Jacobs 1985). Dopamine neurons thus may respond to novel stimuli until their behavioral significance is better established through experience.

In the well-trained animal, instruction stimuli became largely ineffective for discharging DA neurons, in spite of their behavioral significance. Conceivably, they arouse the animal less than trigger stimuli by not signaling the immediate availability of an object of interest and by not calling for an immediate behavioral reaction. After the instruction, the animal still had to wait for an upcoming trigger stimulus to reach his target of interest. It remains to be established whether these properties explain the lack of response to instructions with increased testing.

The sound offset trigger signal was entirely ineffective in activating DA neurons, although it regularly elicited arm and eye movements. Obviously, the property of a signal to trigger movements toward reward alone is not a sufficient condition for activating DA neurons. This may be a further argument for a relationship of responses to arousal, because the offset of a stimulus, or the onset of silence after a sound of 3 s, would arouse an animal much less than the onset of an environmental trigger stimulus.

Many of the stimuli effective for driving DA neurons in this and a previous study (Schultz 1986b) clearly had incentive value for the behavior of the animal. According to current theories (Bindra 1968, 1974; Bolles 1972) and their application to dopaminergic functions (Fibiger and Phillips 1986), door opening in our experiments would predict through previous conditioning the availability of an object of high interest and thus serve as incentive stimulus, eliciting a goal-directed arm movement. However, relating the observed responses specifically to incentive stimulus properties may unduly narrow the behavioral role of DA neurons. For example, the presently suggested relationship to novel stimuli—as in the case of infrequently used instructions—the possible relationship to uncertainty with the touch of food during self-initiated movements (Romo and Schultz 1990), and the particular responsiveness to stimuli eliciting direct reactions—as opposed to preparatory instructions—would not be explained by a relationship to incentive stimulus properties alone. Conversely, the sound offset trigger signal, to which DA neurons did not respond, is probably an incentive stimulus for the animal. Future experimentation should reveal whether more general notions like motivational arousal would better explain the responses of DA neurons to environmental stimuli than purely incentive stimulus properties.

Comparison with behaviorally contingent responses in other structures

Neuronal responses dependent on the behavioral situation are also found in other structures of the brain, often in

relation to the initiation of movements. Similar to the presently observed responses of DA neurons, cells in the reticular formation of the monkey brain stem are activated by trigger stimuli independent of a following arm movement but are uninfluenced by the same stimuli outside a behavioral task (Ray et al. 1982).

A well-studied example of task-specific responses to visual stimuli is the enhancement effect observed in several cortical and subcortical structures. The responses of neurons in the parietal association cortex are increased when the animal directs its attention toward the stimulus without making an eye or arm movement (Bushnell et al. 1981; Mountcastle et al. 1981). The responses of other neurons are enhanced when the animal makes a saccadic eye movement toward the stimulus eliciting a response. These are found in the parietal association cortex (Bushnell et al. 1981; Robinson et al. 1978), the prelunate visual association cortex (Fischer and Boch 1981), the prefrontal cortex (Boch and Goldberg 1989), the frontal eye fields (Goldberg and Bushnell 1981; Wurtz and Mohler 1976), the caudate nucleus (Hikosaka et al. 1989), the pars reticulata of substantia nigra (Hikosaka and Wurtz 1983a), and the superior colliculus (Goldberg and Wurtz 1972). Visual responses in the parietal association cortex were equally enhanced when the stimulus served as target for a hand-reaching movement (Bushnell et al. 1981). In comparison with these results, DA neurons responded to behaviorally significant stimuli also in the absence of eye and arm movements in the no-go situation of the task, whereas their responses were stronger when the animal made an arm movement toward the food box in the go situation.

Neurons in other areas of the brain often show more pronounced differences in responding to stimuli that are used for triggering arm movements. In the supplementary motor area, many neurons only respond when a movement is elicited by the stimulus, while others are also activated in no-go trials of a go/no-go task (Kurata and Tanji 1985; Romo and Schultz 1987). In the motor cortex, responses to trigger stimuli are conditional on a following movement (Kurata and Tanji 1985; Martin and Ghez 1985). Movement-dependent and -independent responses to trigger stimuli are found in both parts of the striatum (Aldridge et al. 1980; Amalric et al. 1984; Rolls et al. 1983; Schultz and Romo 1988). Thus the responses of DA cells to trigger stimuli in both go and no-go situations differ from those of many neurons situated closer to motor output, particularly in the motor cortex.

Nature of information transmitted

Although DA neurons respond to behaviorally significant stimuli, they do not appear to transmit specific information about physical stimulus characteristics such as sensory modality or precise spatial position. The presence of responses in individual trials lacking arm or eye movements suggests that DA neurons themselves do not trigger the behavioral reaction. Rather, impulses of DA neurons would inform postsynaptic structures about the presence of a stimulus associated with the availability of an object of high interest. Dopamine neurons would equally not be involved in specifying the details of the emergent behavioral response, because they respond to stimuli eliciting a variety of behavioral acts and their movement-related changes are slow and of small magnitude. The analysis of stimulus parameters and the initiation and execution of appropriate behavioral responses need to be elaborated by other neurons. These neurons would be under the influence of DA, because thresholds for reactions to external stimuli are increased in subjects with striatal DA depletions (Carli et al. 1984; Ljungberg and Ungerstedt 1976; Marshall et al. 1971).

Because the observed bursts of impulses are suitable for releasing DA in the striatum (Gonon and Buda 1985), dopaminergic neurotransmission would be increased by an effective stimulus. This would allow postsynaptic neurons to process information related to appropriate behavioral responses. Besides stimulus-induced phasic changes in striatal DA transmission, a more tonic release of DA would allow the occurrence of neuronal processes related to other acts of behavior, such as the internal initiation of movements, or their execution. These acts are highly dependent on an intact striatal DA innervation but are not paralleled by major changes in impulse rate (Romo and Schultz 1990).

As far as stimuli predict the availability of reward, they induce a state of anticipation or expectancy during which goal-directed behavioral reactions are elicited and executed (Bindra 1968, 1974; Bolles 1972; Fibiger and Phillips 1986). In responding phasically to these stimuli, DA neurons may contribute to the setting of motivational states by providing an initial input to neuronal systems subserving reward-seeking or more general goal-directed functions. To be involved in these functions, neurons influenced by DA cells should show a tonically elevated discharge rate during the total duration of this anticipatory state. Increased activity over several seconds is found in the striatum during the preparation of movements (Alexander 1987; Schultz and Romo 1988) and in structures synaptically linked to DA and striatum neurons, such as the pars reticulata of substantia nigra (Hikosaka and Wurtz 1983b; Schultz 1986a), supplementary motor area (Romo and Schultz 1987; Tanji et al. 1980), prefrontal cortex (Fuster and Alexander 1971; Kubota and Niki 1971), and anterior cingulate gyrus (Niki and Watanabe 1976). It would be interesting to investigate whether similar continuous increases of activity occur when a stimulus signals the availability of reward.

Functional input to DA neurons

The area of DA neurons in substantia nigra and the adjoining midbrain receives afferents from striatum, frontal cortex, raphé, hypothalamus, amygdala, and nucleus pedunculopontinus (Jackson and Crossman 1983; Künzle 1978; Phillipson 1978; Swanson 1976; Yoshida and Precht 1971). Neurons of the striatum exert a predominantly inhibitory influence on substantia nigra (Yoshida and Precht 1971) and respond to trigger stimuli in a similar manner but often with longer latencies and smaller magnitudes than DA neurons (Rolls et al. 1983; Schultz and Romo 1988). Neurons of the dorsal raphé respond to auditory and visual stimuli at similar latencies as DA neurons (Heym et

al. 1982). Their functional influence on DA neurons is difficult to estimate because their relationship to behavioral acts is unknown. Neurons of the lateral hypothalamus specifically respond to food objects, or to stimuli associated with food or reward, at latencies comparable with door opening responses of DA neurons (Mora et al. 1976; Nakamura and Ono 1986; Ono et al. 1981; Rolls et al. 1976). Neurons of the amygdala respond to auditory and visual trigger stimuli (Fuster and Uyeda 1971; O'Keefe and Bouma 1969) at slightly longer latencies than DA neurons (Sanghera et al. 1979). Responses of amygdala neurons unrelated to reward appear to be specific for the physical details of environmental stimuli (Jacobs and McGinty 1972). Thus context-dependent responses in these potential input structures do not closely resemble those of DA neurons. It may be speculated that either converging afferents from striatum, lateral hypothalamus and amygdala induce the response characteristics in DA neurons, or inputs from structures not considered so far may induce the specific responses of DA neurons.

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