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Dopamine Neurons of the Monkey Midbrain: Contingencies of Responses to Active Touch During Self-Initiated Arm Movements

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SUMMARY AND CONCLUSIONS

1. Previous studies have shown that midbrain dopamine (DA) neurons in monkeys respond to external stimuli that are used to initiate behavioral reactions. In the present study, we investigated to what extent changes in neuronal activity would occur when behavioral acts are generated internally or whether they would depend solely on external stimuli.

2. Monkeys performed self-initiated arm movements from a resting key into a covered, food-containing box at a self-chosen moment and without external preparatory or triggering signals. In a second task, the arm movement was triggered by rapid opening of the door of the food box. This stimulus was either audible and visible or only audible to the animal. Impulses of DA neurons were recorded with movable microelectrodes from the pars compacta of substantia nigra (area A9) and areas A8 and A10 and were discriminated from those of other neurons by their long duration (1.5–5.0 ms) and low spontaneous frequency (0.5–8.5 imp/s).

3. The activity of 12% of 104 DA neurons increased slowly and moderately up to 1,500 ms before the onset of individual self-initiated arm movements. Median increases amounted to 91% over background discharge rate. A further 16% of DA neurons were activated together with the onset of muscle activity and during the movement.

4. During self-initiated movements, a nonhabituating, phasic burst of impulses occurred when the monkey's hand touched a morsel of food inside the box. This response was seen in 84% of 154 neurons on the contralateral side, with median onset latency of 65 ms and duration of 160 ms. A comparable percentage of neurons responded to ipsilateral touch with similar latency and duration.

5. The touch response during self-initiated movements was absent, both on the contra- and ipsilateral sides, when the animal's hand touched the bare wire normally holding the food, when touching nonfood objects, or during tactile exploration of the empty interior of the food box. Thus responses appeared to be related to the appetitive properties of the object being touched rather than the object itself.

6. In the task employing stimulus-triggered movements, 77% of 86 DA neurons discharged a burst of impulses in response to door opening but entirely failed to respond to the touch of food in the box. The response to door opening in this task was similar to the touch response during self-initiated movements in the same neurons in terms of latency, duration, and magnitude. Apparently, the response was transferred from somatosensory touch to audible and visible door opening when passing from self-initiated movements to those elicited by an external trigger stimulus.

7. The experiments revealed minor changes of impulse activity during self-initiated movements. In view of the severe deficits after impaired DA transmission, these data suggest that DA neurons exert a predominantly enabling effect on neurons more directly involved in the internal generation of movements. In contrast, the large majority of DA neurons responded phasically and in a similar and stereotyped manner to various salient, environmental stimuli of different sensory modalities. The responses appeared to be related to motivational arousal elicited by stimuli with appetitive properties while not conveying specific information about the physical characteristics of stimuli nor the emergent behavioral reaction.

INTRODUCTION

Earlier investigations of impulse activity of presumptive dopamine (DA) neurons in the monkey midbrain revealed slow and modest changes during arm movements (Schultz et al. 1983) or virtually no modulations at all (DeLong et al. 1983). Although these results might suggest a tonic impulse activity of DA neurons unrelated to specific behavioral acts, other electrophysiological studies indicated that DA neurons could respond to external stimuli. Under anesthesia, impulse activity of midbrain DA neurons is mainly depressed by high-intensity, often noxious, somatosensory stimuli in rats (Chiodo et al. 1980; Maeda and Mogenson 1982; Tsai et al. 1980) and monkeys (Schultz and Romo 1987). Similar responses occur after electrical stimulation of peripheral nerves (Hommer and Bunney 1980; Tsai et al. 1980) and the anterior olfactory nucleus (Tulloch and Arbuthnott 1979). Although the more natural of these stimuli elicit strong behavioral reactions in awake subjects, a precise assessment of the relations to behavior would require experiments on behaving animals. In awake cats, DA neurons of substantia nigra are phasically activated by light flashes and intense auditory clicks in the absence of behavioral contexts (Steinfels et al. 1983). A relationship of these responses to ongoing behavior is suggested by their disappearance when the animal is being distracted (Strecker and Jacobs 1985). In a more formal task, DA neurons of groups A9 and A10 in haloperidol-treated rats show pronounced responses to visual stimuli eliciting licking or forelimb movements (Miller et al. 1981). In a recent investigation on monkeys in our laboratory, we identified DA neurons on the basis of histological location, electrophysiological parameters, and pharmacologic testing. The majority of these neurons were phasically activated by a combined auditory-visual stimulus, in response to which animals performed arm movements toward a food-containing box (Schultz 1986). These results suggested a particular relationship of discharges of DA neurons to stimuli eliciting immediate behavioral reactions.

The present experiments were conducted to answer two questions emerging from the cited data (Schultz 1985). *1)* Would the responses to external trigger stimuli imply that

DA neurons are primarily involved in the initiation of movements? This would relate to the deficits seen in Parkinsonian patients and in animals with experimental lesions of midbrain DA neurons. Because these subjects are particularly deficient in spontaneous arm and eye movements (Poirier 1960; Schultz et al. 1989,a,b), we aimed to test this hypothesis in unlesioned monkeys performing self-initiated movements. This report gives an account of the activity of DA neurons recorded in this task, together with a description of responses that were observed when animals touched certain objects during the course of the movement. Some of the data have been presented before as abstract (Romo and Schultz 1986). *2*) The second question refers to the nature of responses of DA neurons to external stimuli. Would they be of purely sensory nature, would they subserve the initiation of triggered movements, or could they be involved in more basic mechanisms mediating the activation of behavior? This question was addressed in the accompanying report (Schultz and Romo 1990) by investigating the behavioral contingencies of responses to external trigger stimuli in a modified version of a task used before (Schultz 1986).

METHODS

Two *Macaca fascicularis* monkeys (female, 3.0, and male, 3.5 kg body weight) were trained on both sides in behavioral tasks involving self-initiated and stimulus-triggered arm movements, respectively. Activity of single neurons was recorded during task performance with movable microelectrodes while monitoring electromyographic (EMG) activity and eye movements through chronically implanted electrodes. On termination of recording, animals were killed for histological reconstruction of electrode positions. The behavioral apparatus and most recording and evaluation techniques were similar to those previously reported (Schultz 1986).

Behavioral procedures

The behavioral apparatus was positioned in the frontal wall of the completely enclosed primate chair. Two food boxes were mounted on each side at reaching distance (250 mm from the animal's shoulder) and at eye level of the animal. Centers of medial and lateral boxes were located at 15° and 27° lateral to the midsagittal plane, respectively. Each food box had a frontal opening of 40 × 40 mm. A cover could be mounted in front of each box, which prevented sight of its interior while giving an access of 40 × 50 mm from below to the animal. Only the lateral box on each side was employed for the present investigation. A small morsel of apple (about a 100th to 150th part of an apple, 1 g) or, less frequently, a piece of cookie (1–2 g) or a raisin served as food rewards.

For the study of stimulus-triggered arm movements, the door of one food box opened vertically upward behind the frontal wall (20–22 ms time for complete opening). Without the cover mounted, the sensory stimulus emitted by the opening door was composed of the following components: *1*) a vertically moving visual stimulus with peak velocities of >400°/s, *2*) a low-intensity sliding noise, and *3*) a 1.0-kHz sound of rectangular waveform triggered by onset of door opening and emitted from a distant source with a duration of 100 ms and an intensity of 90–92 dB, measured at the head of the animal. Door opening in this configuration was termed the composite trigger stimulus. The stimulus emitted by the opening door was reduced to the sliding noise component by deleting the 1-kHz sound and mounting the cover in front of the food box (door noise trigger stimulus). The cover also prevented vision of the food after door opening.

For facilitating behavioral conditioning, both animals were first trained to perform stimulus-triggered arm movements in response to the composite or the door noise trigger stimulus . While the animal kept its hand relaxed on an immovable, touch-sensitive key, the door of the food box opened. The animal released the

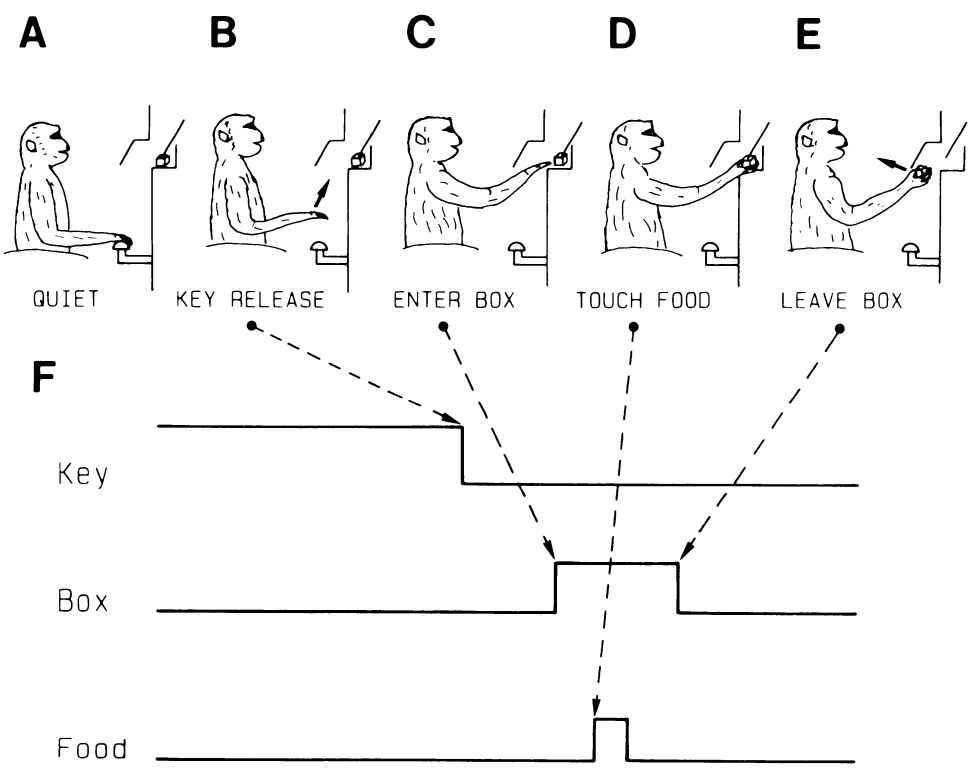

FIG. 1. Performance of self-initiated arm movements in a formal task. Animal sits with its muscles relaxed in a completely enclosed primate chair and faces a response panel with a touch-sensitive, immovable key and a food box containing a small morsel of apple or cookie stuck to the end of a touch-sensitive wire (*A*). Cover mounted in front of the box prevents vision into its interior while permitting manual access. At a self-chosen moment, the animal releases the key (*B*), enters the food box below the cover (*C*), touches the food (*D*), and leaves the box (*E*) to bring the food to its mouth. Electrical signals mark key release, interruption of an infrared lightbeam between entering and leaving the food box, and touching the food stuck to the wire (*F*). No phasic stimuli were presented to the animal in this task. Occasionally, the food was presented at the bottom of the box without a wire being present. In this case, the electrical signal closest to the touch of food was provided by interruption of the infrared light beam when the animal's hand entered the box.

key, reached into the box, collected a morsel of food, and brought it to the mouth. After proficiency in the task, and in particular after remaining relaxed for several tens of seconds with the hand on the resting key, both animals were conditioned to emit self-initiated arm movements toward the food box. The door was constantly kept open while the cover mounted in front of it prevented vision into the interior of the box. Food morsels, stuck to the end of a rigid wire, were entered into the box by an experimenter without giving auditory or visual cues. Animals released the key and reached into the box at a self-chosen moment and without receiving phasic external stimuli (Fig. 1, *A–C*). Their hand touched the morsel of apple at the end of the wire, took it, and brought it to the mouth (Fig. 1, *D* and *E*). Occasionally, the food morsel was placed at the bottom of the box and collected by the animal without touching a wire. Intervals between movements varied spontaneously between 5 and 30 s. Animals would occasionally not find food in the box should higher rates occur, a measure that was effective in preventing uncontrolled or repetitive motor acts. For this reason, and for testing the conditional nature of neuronal responses, food was present in the box during electrophysiological recordings in 40–90% of trials, mostly ~70%. Although highly practiced, self-initiated movements were at no time rhythmically paced and were devoid of automatic and involuntary character. After proficiency in this task, animals were conditioned to perform both tasks in alternating sessions. Food reward was not given, and data recording was aborted, whenever untimely EMG activity or premature movements were detected. In most sessions, animals performed the task contralateral to the side of neuronal recordings, in which case they reached with the contralateral arm toward the contralateral food box. When the task was performed on the same side as neuronal recordings, animals reached ipsilaterally toward the ipsilateral food box. With stimulus-triggered arm movements, the side of stimulus presentation corresponded without exception to the side of arm movement. Animals were deprived of food and fluids during weekdays. They were released after each daily experiment into their home cages and received monkey cubes and water for ~1 h.

Behavior was electronically monitored from standard digital pulses generated by the different events (Fig. 1*F*). 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. Interruption of an infrared light beam across the entrance of the food box detected the time at which the animal's hand entered and left the box (onset and end of beam interruption, respectively). The wire holding the food morsel was connected to an amplifier with high input impedance. Touching the food stuck to the other end of this wire produced an electric artifact, which was passed through an appropriately set Schmitt-trigger. During the study of stimulus-triggered arm movements, onset of door opening activated an infrared light beam switch.

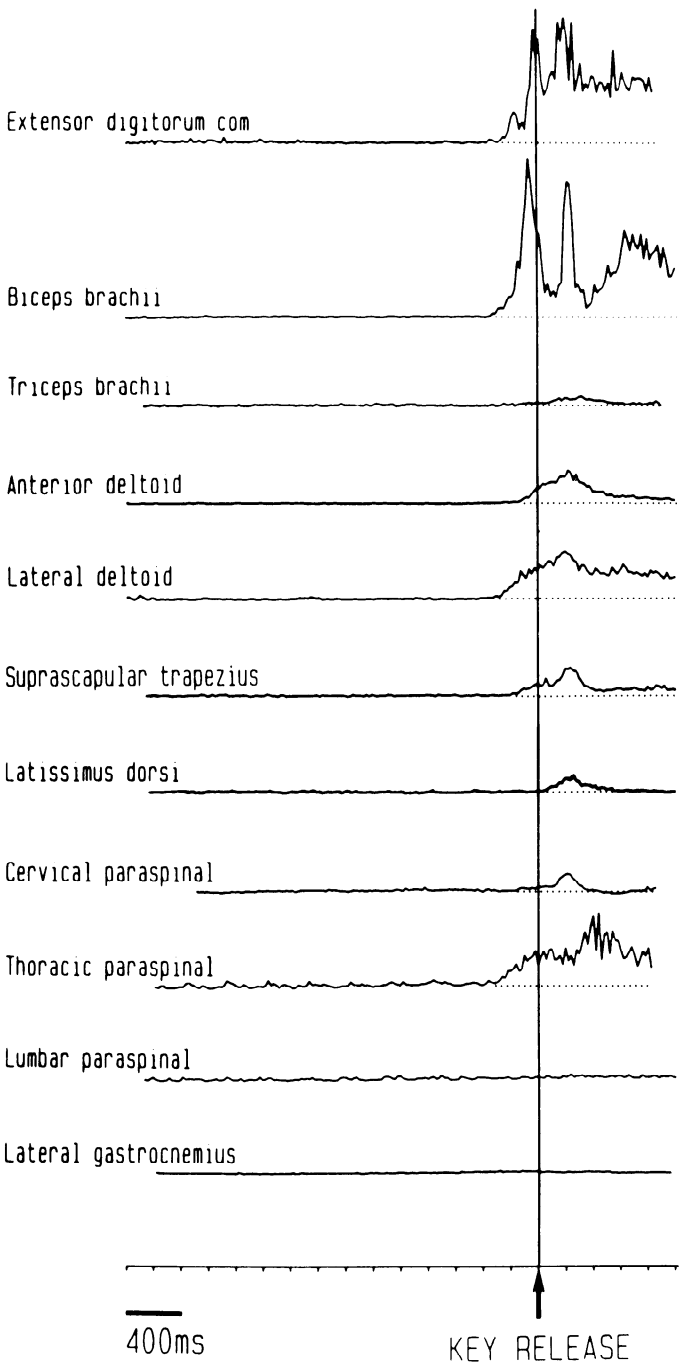

FIG. 2. Activity of different arm, shoulder, neck, dorsum, and leg muscles during self-initiated arm movements. Averages were obtained from rectified EMGs during 15–25 movements.

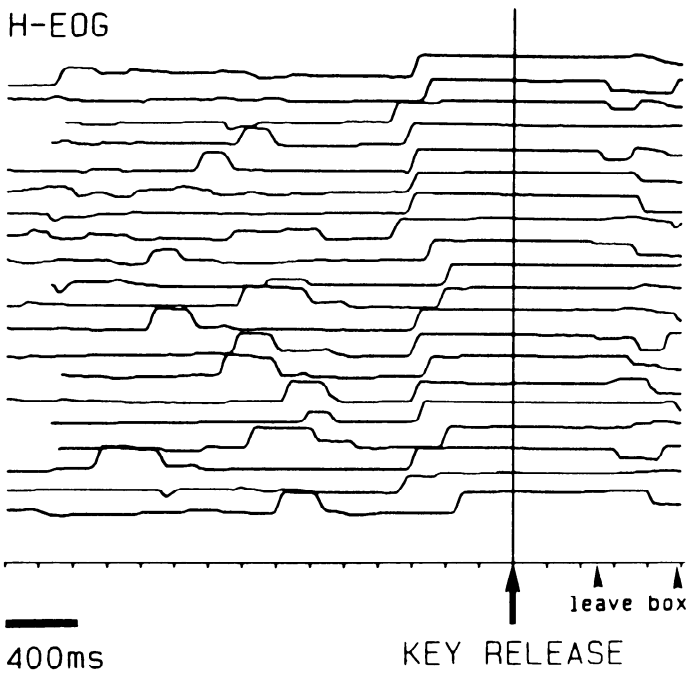

FIG. 3. Horizontal eye movements during performance of self-initiated arm movements. Data are shown from 20 consecutive trials. Key release, onset of arm movement.

Electrophysiological techniques

Animals underwent surgery once proficiency in both behavioral tasks had been obtained. Under deep sodium pentobarbital anesthesia and aseptic conditions, cylinders for head fixation and a stereotaxically positioned, stainless steel chamber were fixed to the skull to permit vertical access with microelectrodes to the left substantia nigra (SN). The dura was left intact. Teflon-coated, multistranded, stainless steel wires were implanted into the extensor digitorum communis and biceps muscles of both arms and led subcutaneously to the head. Ag-AgCl electrodes were implanted into the outer, upper, and lower canthi of the orbits (Bond and Ho 1970). All metal components, including plugs for the muscle and periorbital electrodes, were embedded in several layers of dental cement and fixed to the skull with surgical grade stainless steel screws. The area of SN was localized in the same session by taking lateral and coronal radiographs with a guide cannula installed at a known coordinate in reference to the implanted steel chamber (Schultz et al. 1983). The ventroposteromedial (VPM) thalamus overlying the lateral SN was electrophysiologically explored for trigeminal input 1 wk after implantation under pentobarbital anesthesia and later occasionally in the waking animal.

The activity of single neurons was recorded extracellularly with glass-insulated, platinum-plated tungsten microelectrodes (exposed tips of 5- to 10-μm length and 1.8- to 3.5-μm diam), which were passed each day together with and inside a rigid guide cannula of 0.6 mm OD into the brain. Microelectrodes were moved

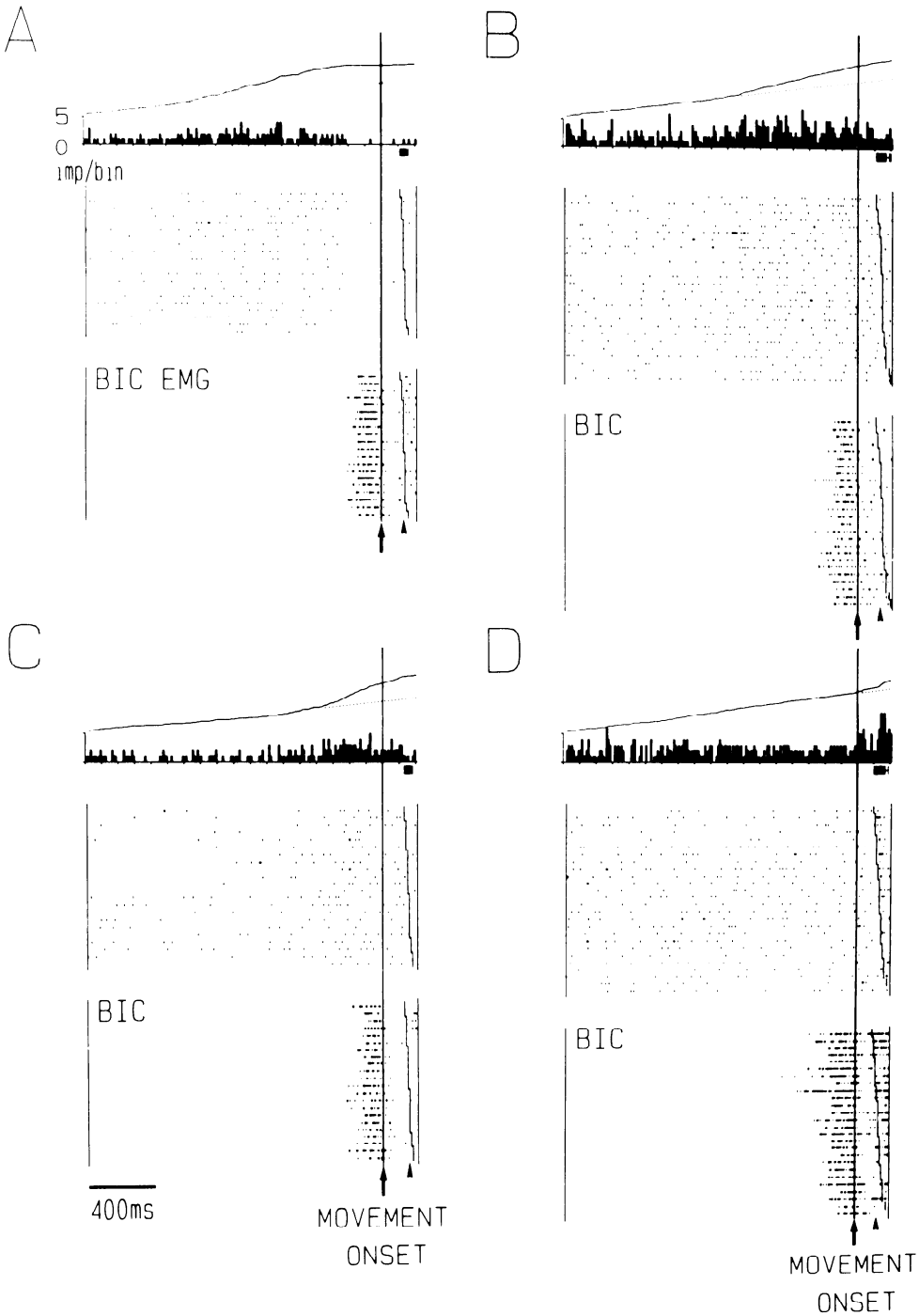

FIG. 4. Activity of 4 DA neurons (*A–D*) preceding self-initiated arm movements. *A*: moderate increase of discharge rate between ~1,200 and 200 ms before key release (Movement onset). *B*: moderate increase beginning ~1,000 ms before movement onset and lasting during the movement. *C*: moderate increase beginning slightly before onset of EMG activity in the biceps (BIC). *D*: unmodulated activity before movement onset. In parts *A–D* are shown, from *top* downward, cumulative frequency distribution of neuronal impulses, perievent time histogram of neuronal impulses, dot display of neuronal impulses, and dot display of EMG activity in the biceps brachii muscle (BIC) 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, key release = movement onset) corresponds to their real time interval. Each line of dots represents activity during performance in 1 trial. Histograms and distributions 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 movement onset and entering the food box. Small bars below right parts of histograms mark the time of entering the food box, as in the dot displays (small arrow). Binwidth is 10 ms; small markers below histograms indicate 10 bins.

in parallel tracks vertically 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 monitored with oscilloscopes and earphones. Full waveforms of impulses from each neuron were displayed on a digital oscilloscope with the use of the pretrigger viewing facility and subsequently stored on computer disks. Somatodendritic discharges were discriminated against those originating from fibers by the use of earlier established criteria, in particular, the very short durations of impulses of fibers (0.1–0.3 ms) (Hellweg et al. 1977; Schultz and Romo 1987). A conventional storage oscilloscope whose beam was triggered by door opening was used to monitor all neuronal responses to this event. Neuronal discharges were also converted into standard digital pulses by means of an adjustable Schmitt-trigger, the output of which was continuously monitored on the digital oscilloscope together with the original waveform.

EMGs were collected during all neuronal recordings through the chronically implanted or other acutely inserted wire electrodes from several flexor and extensor muscles of the arm and

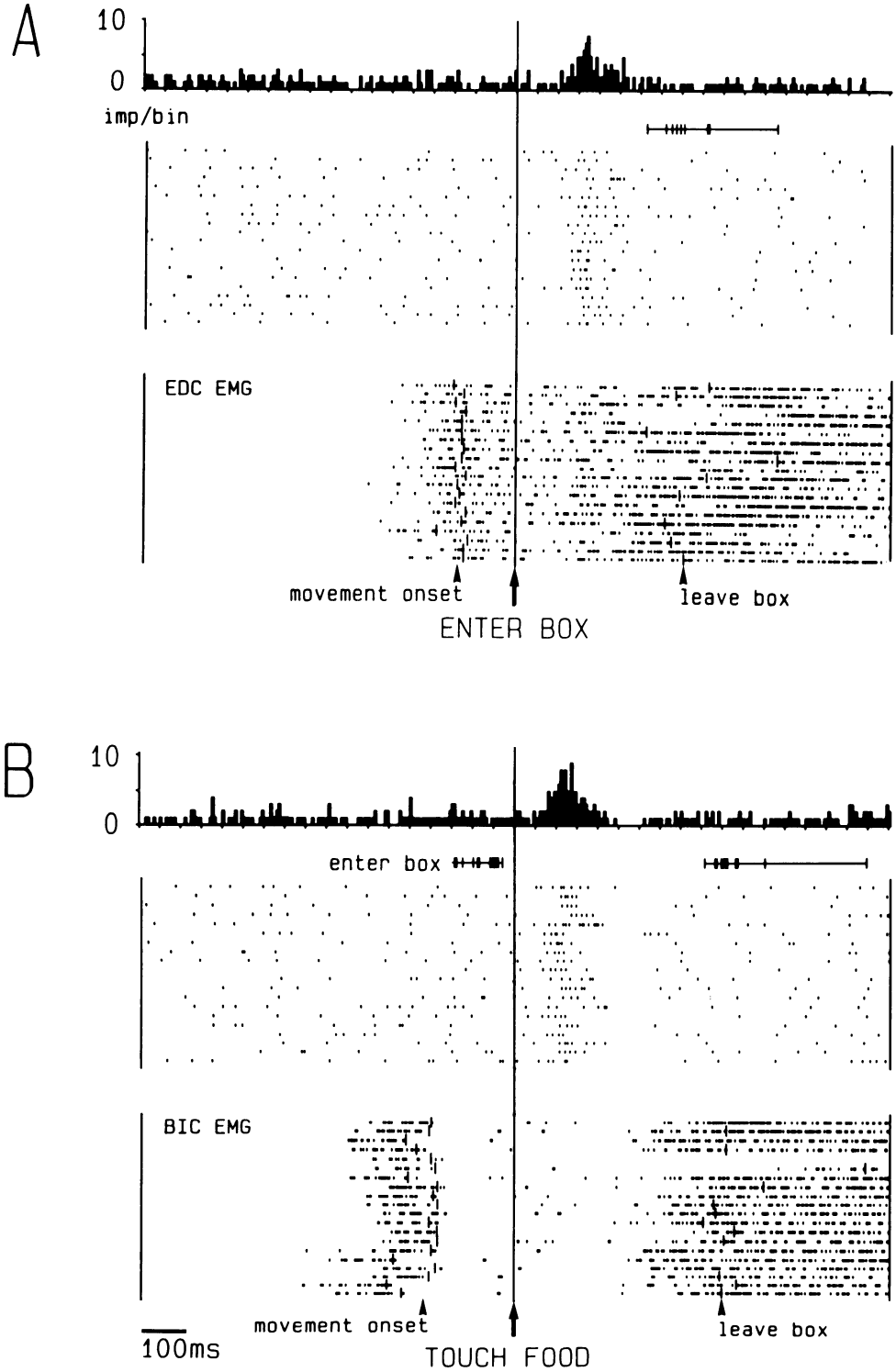

FIG. 5. Activity of 2 DA neurons (*A* and *B*) during self-initiated arm movements. *A*: a burst of impulses occurred immediately after entering the food box. Entering of the food box (vertical reference line) was electronically detected by the interruption of an infrared light beam across its entrance and did not constitute a sensory stimulus. *B*: burst of impulses occurred in direct response to touching the food morsel stuck to the end of a rigid wire inside the food box. Touching the food morsel produced an electric pulse that was used as temporal reference for neuronal impulses. As with all self-initiated movements, vision into the interior of the box was prevented by the cover mounted in front of it. In *A* and *B* are shown, from *top* downward, perievent time histogram of neuronal impulses, dot display of neuronal impulses, dot display of EMG activity in the biceps brachii muscle (BIC) recorded simultaneously with neuronal impulses. The temporal sequence of trials is preserved downward in the dot displays. Small bars below histograms and in the EMG dot displays represent the time of key release ("movement onset") and leaving the food box. Binwidth is 5 ms; small markers below histograms indicate 10 bins.

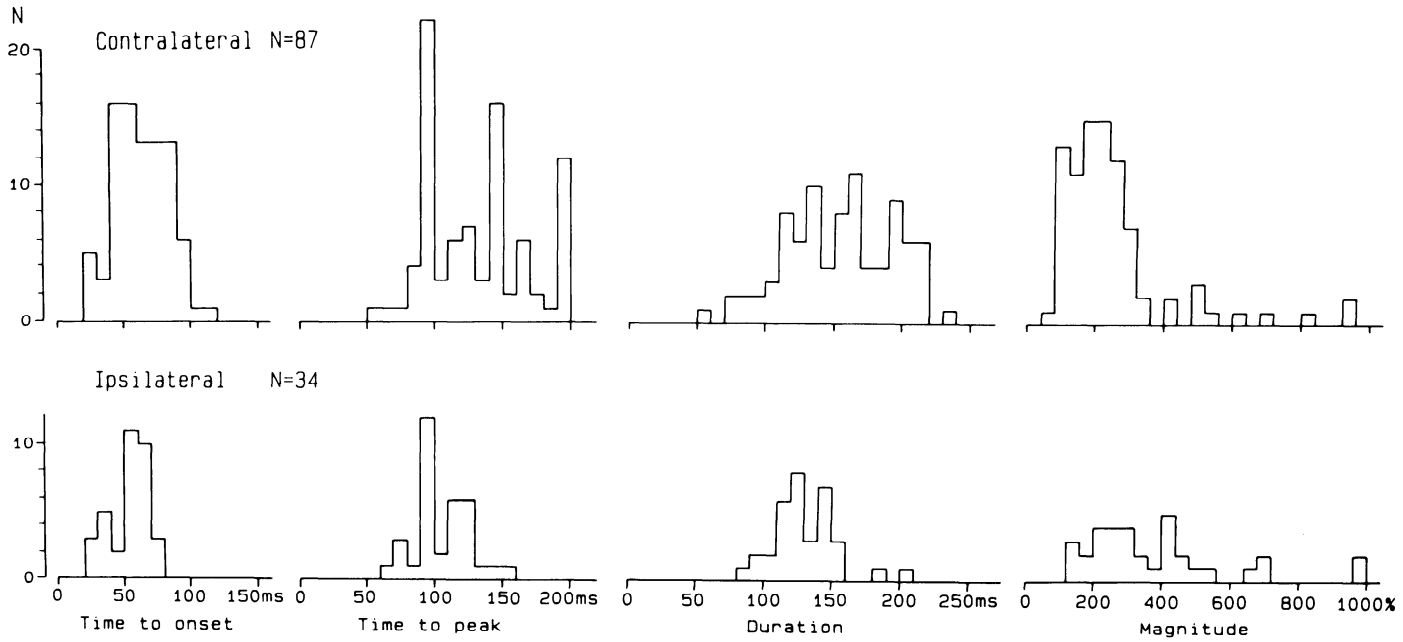

FIG. 6. Histograms of several parameters of touch responses in DA neurons. Only data from responses to the touch of the food morsel at the end of the touch-sensitive wire are shown. Medians of distributions are for contra- and ipsilateral sides, respectively: onset latency, 65 and 60 ms; peak latency, 130 and 100 ms; duration, 160 and 130 ms; magnitude, 210 and 310%. Data are taken from statistically significant responses ($P < 0.01$). N, number of neurons.

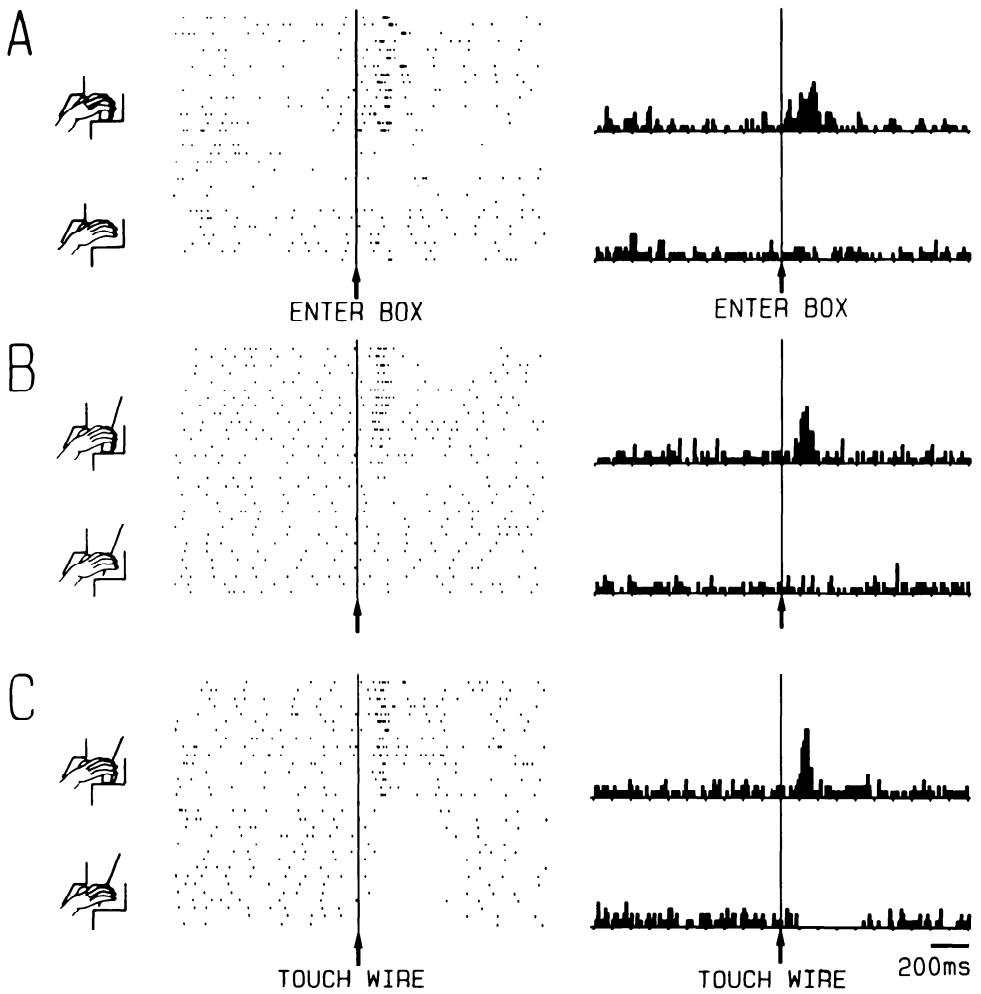

FIG. 7. Object-dependent nature of contralateral touch responses in 3 DA neurons (*A–C*). Activations occurred only when touching a morsel of food, but not when searching the empty box or touching the bare wire. *A*: food positioned at bottom of box vs. empty box. *B*: food stuck to end of wire vs. bare wire. *C*: as *B*, but neuronal activity was depressed after touching the bare wire. In *A–C* are shown, from *left* to *right*, small figures of behavioral situation (presence of food shown above absence of food), dot displays of neuronal activity from 15 trials obtained in behavioral situations shown to the *left*, and perievent time histograms of neuronal activity from the 15 trials shown in dot displays. Base line of each histogram is placed at the lowest line of dots obtained in each behavioral situation. The 2 situations in *A*, *B*, and *C* alternated randomly during experiments and were separated off-line. Apart from this, the temporal sequence of trials is preserved downward in dot displays. Dot displays and histograms are referenced to entering the box in *A* and to touching the food stuck to the wire or the bare wire in *B* and *C*. Binwidth is 10 ms; small markers below histograms indicate 10 bins.

from muscles of the shoulder, neck, trunk, dorsum, and the upper and lower leg, both contra- and ipsilateral to the moving arm. EMG activity was filtered (10- to 250-Hz band-pass; −12 dB at 1 kHz), rectified, and, when used as digital signals, passed through an adjustable Schmitt-trigger. Limb and mouth movements were continuously supervised by two closed-circuit video systems. Horizontal and vertical electrooculograms (EOGs) were collected during all neuronal recordings from the implanted periorbital electrodes. The gain of ocular electrodes and positions of the eyes were calibrated by having the food-deprived animal fixate small morsels of food presented at several known horizontal and vertical eccentricities while the frontal enclosure of the primate chair was kept open.

Data acquisition and analysis

By the use of specifically written Fortran and Assembler routines, all behavior-related digital signals and pulses from neuronal discharges and EMG activity were sampled on-line as bits in parallel at a rate of 2 kHz by a laboratory computer. Analog signals from EOGs and rectified EMGs were sampled after analog-to-digital conversion at a rate of 2 kHz by the computer. Eight consecutive analog values were averaged to obtain a final temporal resolution of 4 ms (0.25 kHz) for data storage. The computer mastered the discrete trial schedule and cancelled trials in the stimulus-triggered task when the key was prematurely released. The behavioral relationships of neuronal discharges, digital and analog EMG activity, and EOGs were displayed in each trial on-line on the computer video screen in the form of dot displays and analog curves. All data were stored uncondensed on computer disks. Only results from neurons sampled by the computer with at least 15 trials of a given test will be considered in this and the accompanying report (Schultz and Romo 1990).

Off-line data analysis was performed on the basis of dot-displays, perievent time histograms, and cumulative frequency distributions of neuronal impulses and with displays of single-trial or averaged analog data, in reference to any of the behavioral events, with the use of both automatized and interactive evaluation programs. Relationships of impulse activity to behavioral events were statistically evaluated in each neuron by the use of a specially programmed implementation of the two-tailed Wilcoxon matched-pairs test. For this test, the dot displays from single trials were visually inspected for possible changes in relation to a behavioral event. The numbers of impulses in two time epochs of equal length, constant in position and length for a given session, were considered as a pair in each trial and submitted to the test. Epochs were before and after stimuli (touch of food or door opening), respectively, and before and during movements or suspected premovement activity. Onset and end of neuronal responses were determined from the times of the first and the last of three consecutive bins, respectively, whose counts were above or below background (binwidth 5 ms). Only changes in activity substantiated by

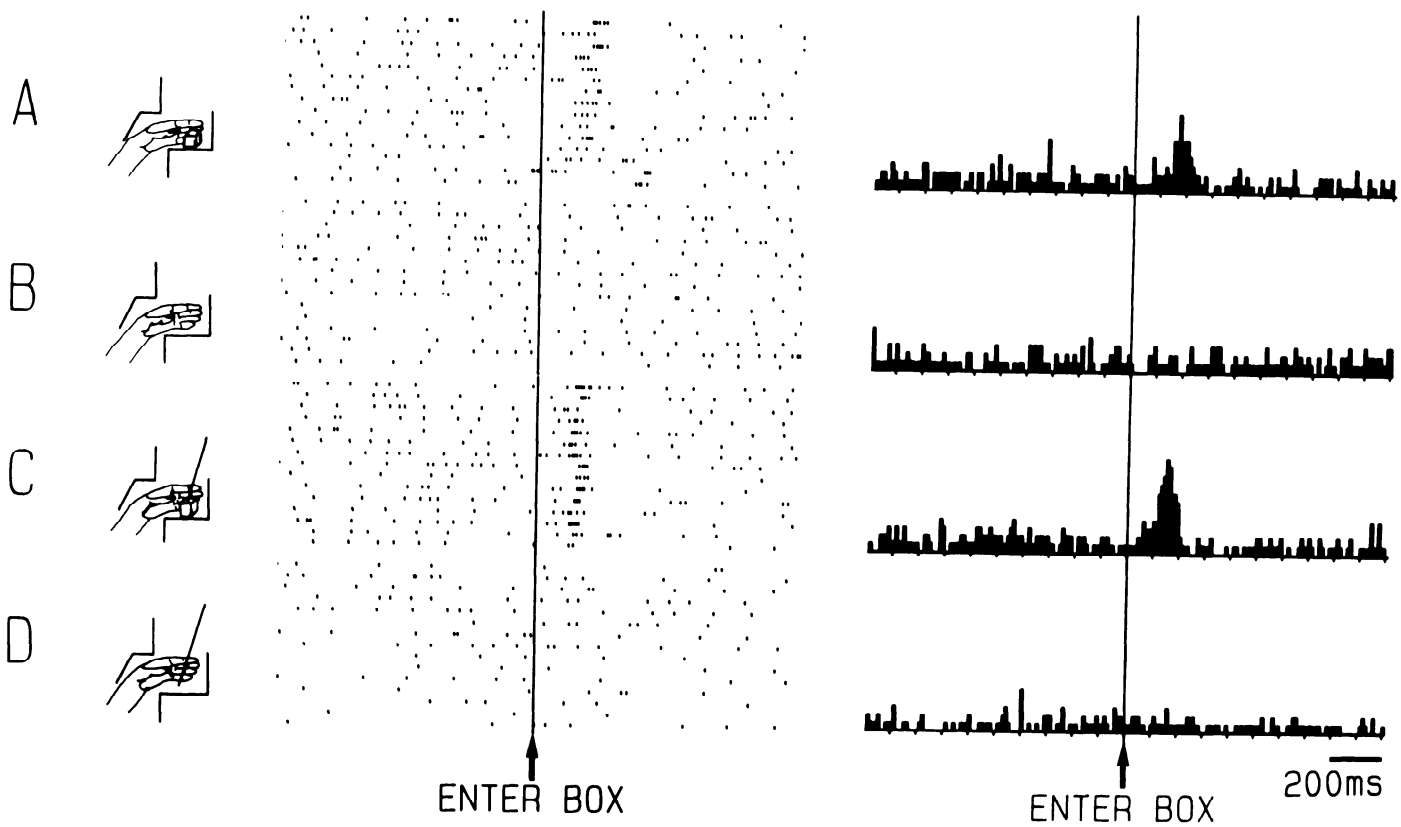

FIG. 8. Object-dependent nature of ipsilateral touch responses in 1 DA neuron. *A*: response to touching the food at the bottom of the box. *B*: no activation when searching the empty box. *C*: touch response to food stuck to the wire. *D*: no activation when touching the bare wire. In *A–D* are shown, from *left* to *right*, small figure of behavioral situation (presence of food morsels in *A* and *C*), dot displays of neuronal activity from 15 trials obtained in behavioral situations shown to the *left*, and perievent time histograms of neuronal activity from the 15 trials shown in dot displays. Base line of each histogram is placed at the lowest line of dots obtained in each behavioral situation. The 2 situations in *A*, *B* and *C*, *D* alternated randomly during experiments and were separated off-line. Apart from this, the temporal sequence of trials is preserved downward in dot displays. All dot displays and histograms are referenced to entering the food box. Binwidth is 10 ms; small markers below histograms indicate 10 bins.

a significant difference at $P < 0.01$ in this test were considered as responses. The magnitude of changes in each session was assessed by counting neuronal impulses between onset and end of responses and expressed as percentage above or below background activity.

Because skewed distributions were observed in several groups of data, the median (50th percentile) was determined as single numerical value for each distribution. Response parameters of neurons tested in two different behavioral situations in separate sessions were considered as pairs and submitted to the conventional two-tailed Wilcoxon test. Because of occasional multiple statistical comparisons between the same parameters, the *P*-value for considering changes to be statistically significant was set to 0.01 in all tests. Results from evaluations were stored and classed with the use of specifically written procedures on a data-base management system.

Histological reconstruction

During the last recording sessions with each animal, small marking lesions were placed by passing negative currents (5–10 μA for 5–20 s) through the microelectrode immediately after recording from a neuron in SN, whereas larger lesions (20 μA for 20 or 60 s) were positioned at a few locations above in the same track. This produced distinct patterns of vertically oriented histological marks. 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 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. All histological sections were projected on paper, and the outlines of brain structures and the marks from lesions and recent electrode tracks were drawn. Recording positions in tracks marked by electrolytic lesions were reconstructed by the use of the distances to the lesions according to protocolled micrometer readings. Positions in parallel neighboring tracks at 1 mm distance were reconstructed at comparable vertical levels (Schultz et al. 1983, 1986, 1987).

RESULTS

General

MUSCLE ACTIVITY. The activity of several muscles during self-initiated movements is shown in Fig. 2. Onset of movement occurred when the hand left the resting key. This consisted of an extension of the fingers and hand, which was driven by the extensor digitorum communis (EDC), and a flexion and partial supination of the forearm, driven by the biceps brachii (BIC). Virtually at the same time, the anterior and lateral deltoid were activated, which moved the arm forward and slightly lateral toward the food box mounted at 27° lateral to the midsagittal plane. The reproducible and strong activation of EDC and BIC made these muscles the prime movers in this movement. Although less consistently activated, muscles of the trunk and dorsum participated in the arm movement, notably the paraspinal group at the thoracic level. Earliest muscle activity occurred in the EDC, BIC, and anterolateral deltoid and preceded key release by 300–400 ms. Task-related activity was absent in lumbar paraspinal muscles and in leg muscles, such as glutaeus maximus, quadriceps femoris, biceps femoris, and lateral gastrocnemius. Contralateral to the moving arm, thoracic and cervical paraspinal muscles showed task-related activity that began later than the earliest muscle activity of the moving arm. A similar sequence of muscle activation was seen with stimulus-triggered arm movements toward the same target. However, premovement muscle activation was shorter, beginning at 100–160 ms before key release in EDC and BIC (Schultz and Romo 1990).

EYE MOVEMENTS. Consistent, task-related saccadic eye movements were predominantly observed in the horizontal plane. Vertical saccades occurred to a minor extent, which was probably due to the position of the food box at eye level. As shown in Fig. 3, horizontal saccades were sporadically seen in the absence of arm movements. A horizontal saccade directed toward the food box regularly preceded release of the resting key by ~300–800 ms, this occurring mostly before earliest activity in skeletal muscles. Subsequently, gaze remained stable on the food box until the hand left the box.

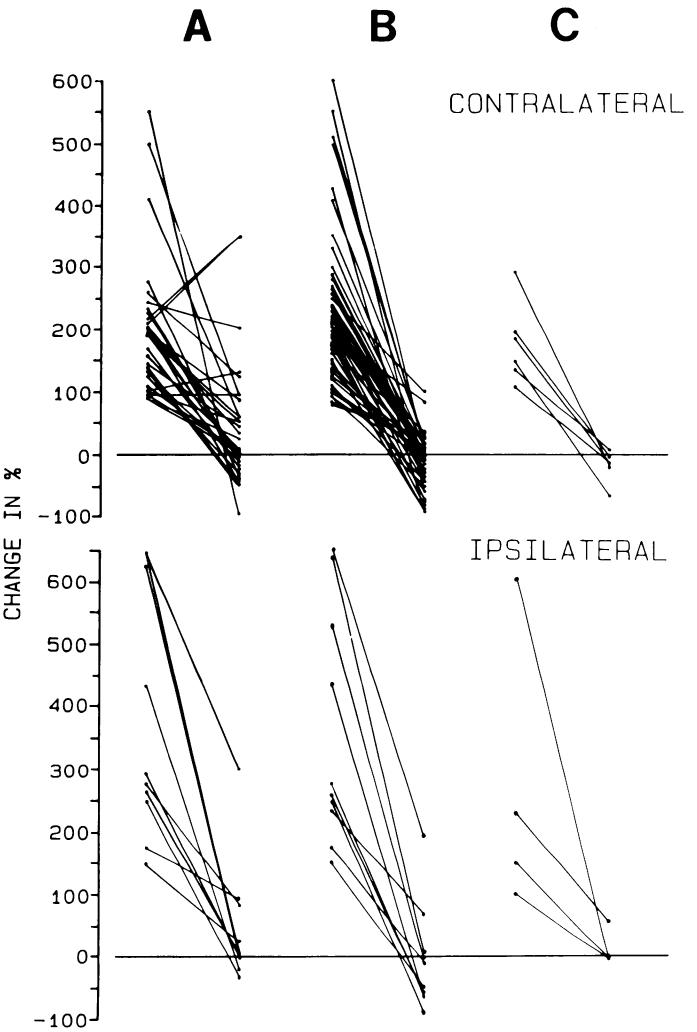

FIG. 9. Comparisons of neuronal responses to touch in all DA neurons tested both with and without food. Oblique lines connect points representing magnitudes of changes in each neuron in the presence and absence of food (*left* and *right*, respectively). The following behavioral situations are compared: *A*: touching the food stuck to the end of the wire vs. touching the bare wire; *B*: touching the food stuck to the wire vs. searching the empty box; and *C*: touching the food at the bottom of the box vs. searching the empty box. Changes are indicated in percent of base-line activity measured over 200 ms immediately preceding movement onset. Numbers of neurons tested: contralateral *A*, 27; *B*, 44; and *C*, 6; ipsilateral *A*, 10; *B*, 10; and *C*, 4.

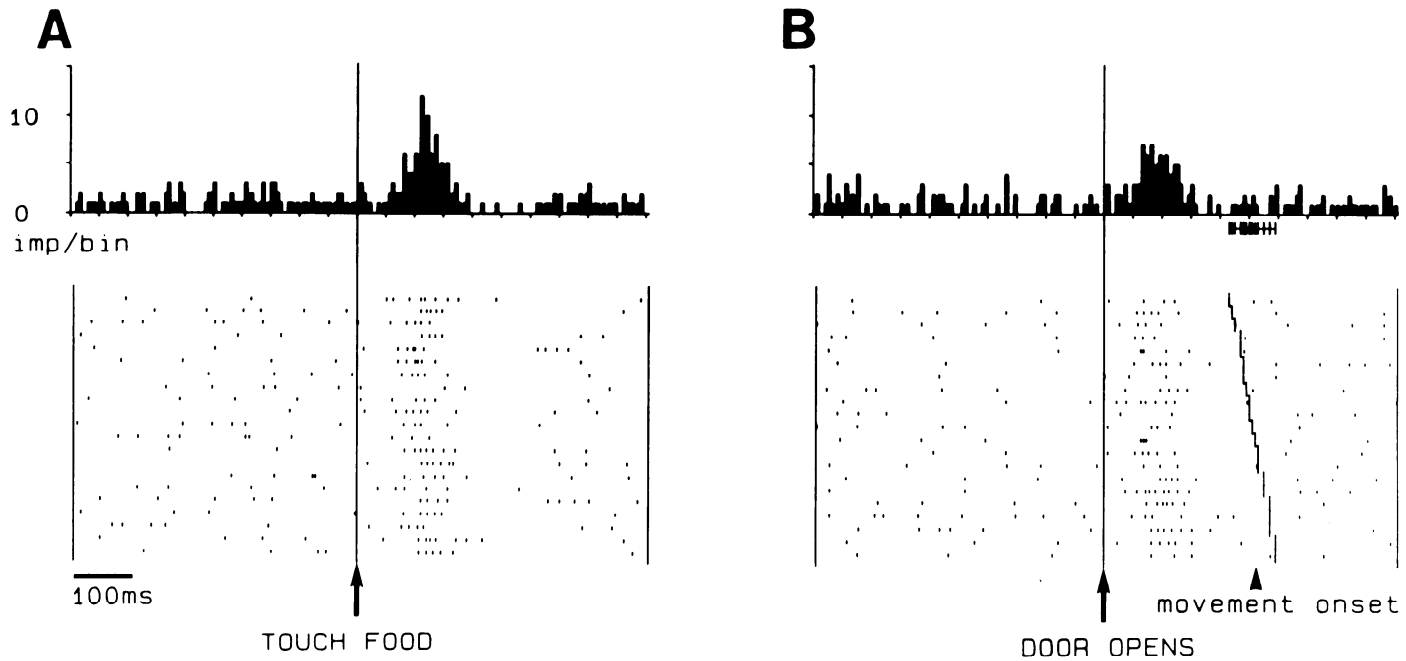

FIG. 10. Comparison of responses to touch during self-initiated movements (*A*) and to door opening in stimulus-triggered movements (*B*) in the same DA neuron. Composite trigger stimulus, consisting of visible and audible door opening, was used in *B*. Perievent time histograms are constructed from those impulses shown in the dot displays below them. Sequence of trials is preserved downward in the dot displays of *A*, whereas in *B* it is rearranged according to the time interval between door opening and key release (reaction time). Time of key release ("movement onset") is marked by small bars below histograms and in dot displays in *B*. Binwidth is 5 ms; small markers below histograms indicate 10 bins.

ELECTROPHYSIOLOGICAL CHARACTERISTICS OF DOPAMINE NEURONS. As described in detail before (Schultz et al. 1986, 1987), DA neurons histologically located in SN (group A9) and adjoining cell groups A8 and A10 in monkeys displayed specific electrophysiological characteristics. At extracellular recording positions, DA neurons discharged initially negative or positive impulses at low frequencies (0.5–8.5 imp/s) and with polyphasic waveforms

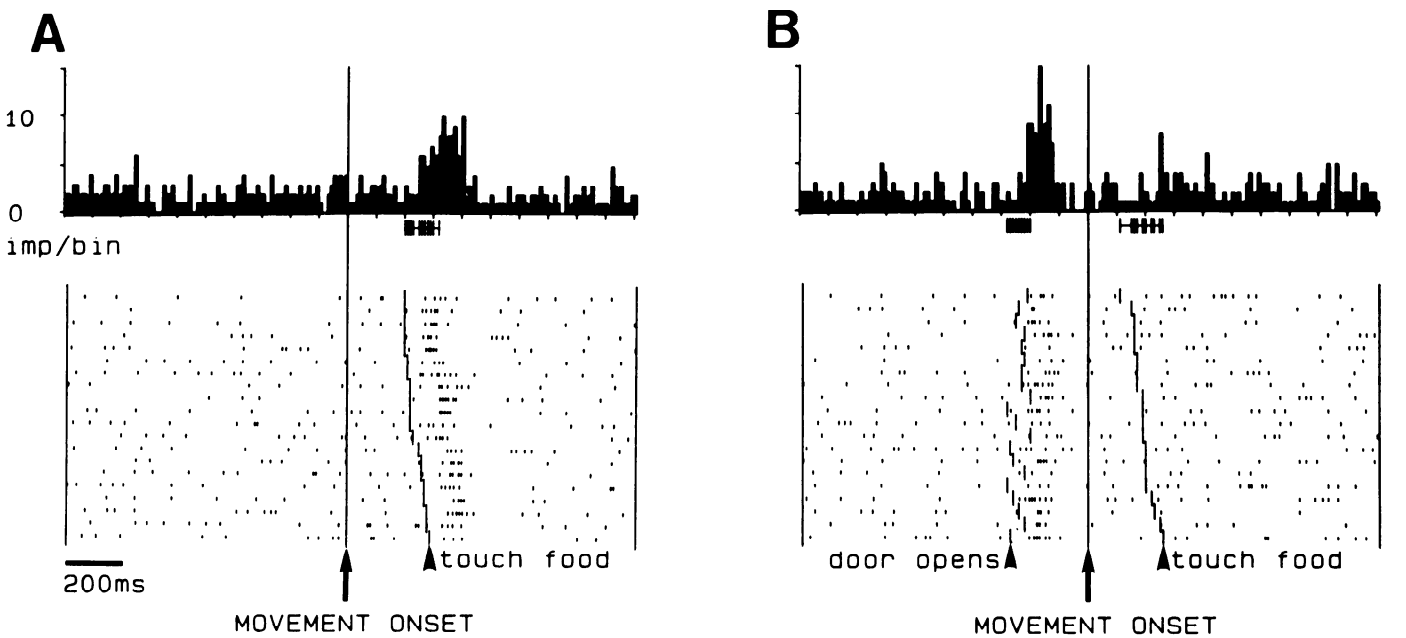

FIG. 11. Transfer of response from food touch to door opening in a DA neuron. *A*: response to touch of food during self-initiated movements. *B*: response to door opening but absence of response to food touch during stimulus-triggered movements. The 2 tasks were performed in separate sessions. In both tasks, food was collected from the end of the wire, with the cover mounted in front of the food box preventing vision but allowing manual access. Perievent time histograms are constructed from those impulses shown in dot displays below. Sequence of trials is rearranged according to the time interval between key release (Movement onset) and the touch of food. Small bars below histograms and in dot displays indicate time of door opening (*B*) and touch of food (*A* and *B*). Binwidth is 10 ms; small markers below histograms indicate 10 bins.

of relatively long durations (1.5–5.0 ms). In these properties, DA neurons in SN contrasted with reticulata neurons discharging impulses of <1.1 ms duration at median rates of 70–90 imp/s, with a few neurons discharging short impulses (<1.0 ms) at low rates and with presumptive fibers discharging very short impulses (0.1–0.3 ms).

Premovement activity

A total of 104 DA neurons were tested during contralateral self-initiated arm movements while their activity was being sampled with up to 60 trials by the computer for >2 s before movement onset. Most of these neurons showed an absence of consistent variations of activity (Fig. 4*D*). Only 12 neurons displayed moderate but statistically significant increases in discharge rate before earliest EMG activity ($P < 0.01$). Increases began 550–1,500 ms before movement onset (median 700 ms) and subsided <600 ms before the movement (Fig. 4*A*), at the time of movement onset, or after the end of reaching (Fig. 4*B*). Quantitative analysis in these neurons revealed increases of activity of 45–128% (median 91%) against background discharge rate preceding onset of activation. Neurons activated before self-initiated movements were distributed over the entire SN, only one of them being located dorsally to SN in DA cell group A8. In 11 other DA neurons, significantly increased activity began together with earliest EMG activity, or slightly before, which usually continued after movement onset (Fig. 4*C*). A total of 16 DA neurons showed significantly increased activity during the reaching movement.

Response to somatosensory touch

A short burst of discharges was seen after the hand entered the food box during self-initiated movements (Fig. 5*A*). The response occurred when the animal's hand touched the food morsel inside the covered box and subsided before leaving it (Fig. 5*B*). Neurons responded equally well to the touch of morsels of apple or cookie or a raisin. Saccadic eye movements were absent at the time of this response (see Fig. 3 for timing of saccades). Statistically significant responses to touching the food morsel with the contralateral hand were seen in 130 of 154 DA neurons (84%). Significant touch responses from the ipsilateral hand were seen during ipsilateral task performance in 38 of 41 neurons (93%). All 38 neurons also responded on the contralateral side. The responses to touching the food were independent of the premovement activity of DA neurons. They were seen in 10 of the 12 neurons showing increases before earliest EMG activity.

Response latencies were measured when the food was stuck to the touch-sensitive wire. On the contralateral side, they showed median values of 65 and 130 ms for onset and peak, respectively (Fig. 6). Responses lasted for median times of 160 ms. Their magnitudes amounted to median increases of activity by 210%. Similar values were seen on the ipsilateral side for all parameters, none of them being significantly different between the two sides ($P > 0.02$).

CONDITIONAL NATURE OF RESPONSE. Because animals were unable to see into the food box, they occasionally entered it without food being present. The hand touched, and occasionally pulled, the bare wire normally holding the food, actively searched the interior of the empty box, or occasionally touched nonfood objects. After having missed the food, animals put the hand directly back on the resting key without moving to the mouth. Accordingly, EMGs of arm muscles terminated earlier after leaving the box, as compared with trials in which food was present. This should not have influenced neuronal responses that terminated before the hand had left the box.

None of the DA neurons showed phasic activations when the animal's hand entered the empty food box (Fig. 7*A*). With the exception of 4 of 27 DA neurons, activations were equally absent when touching the bare wire (Fig. 7*B*), a metal screw, or a small piece of crumbled paper inside the box. In 24 of 77 DA neurons, activity was significantly depressed below base line while the animal's hand searched inside the empty box or touched the bare wire (Fig. 7*C*). Ipsilateral responses equally depended on the presence of food. They were absent when the hand searched inside the empty box (Fig. 8, *A* and *B*) or touched the bare wire (Fig. 8, *C* and *D*).

Quantitative comparisons of touch responses in the presence and absence of food are shown in Fig. 9. Reductions

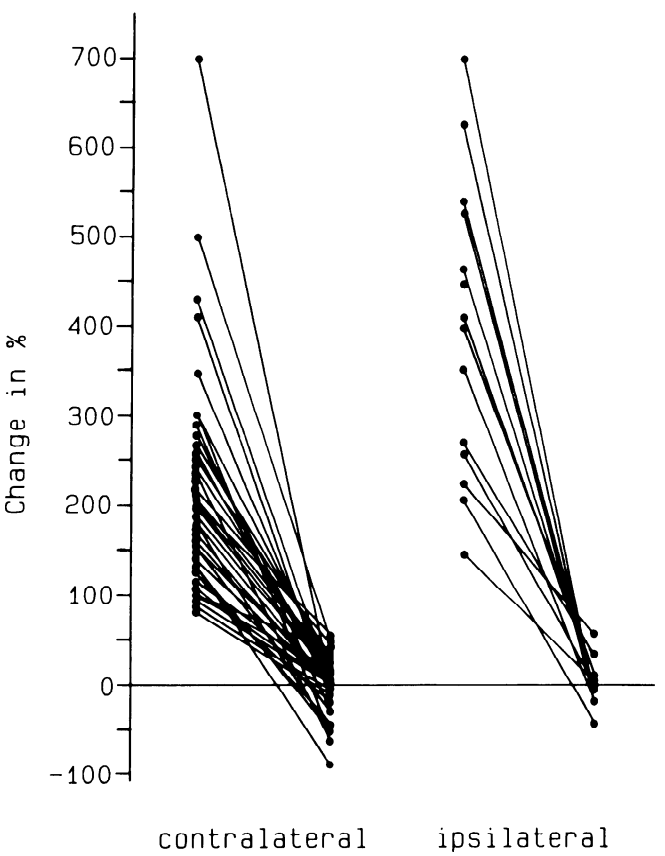

FIG. 12. Quantitative comparisons of neuronal responses to touch in all DA neurons tested both in self-initiated and stimulus-triggered movements. Responses during contra- and ipsilateral performance of both tasks are shown separately. Oblique lines connect points representing magnitudes of touch responses in each neuron during self-initiated movements (*left*) and stimulus-triggered movements (*right*). Changes are indicated in percent of base-line activity, measured over 200 ms immediately preceding movement onset (*left*) or door opening (*right*), respectively. In all tests considered for these graphs, food was collected in both tasks from the end of the wire in the covered box. Numbers of neurons tested: contralateral, 35; ipsilateral, 14.

of activation or even depressions of activity occurred when the bare wire instead of food stuck to the wire was touched (Fig. 9*A*), when the animal's hand searched inside the empty box instead of touching the food stuck to the wire (Fig. 9*B*), and when the hand searched inside the empty box instead of touching the food on the bottom of the box (Fig. 9*C*).

Thus the somatosensory response of DA neurons was conditional on the nature of the object being touched.

Response to door opening with stimulus-triggered movements

A total of 86 DA neurons were tested in both self-initiated and stimulus-triggered movements on the contralateral side. Of these, 60 neurons (70%) responded both to the touch of food in self-initiated movements (Fig. 10*A*) and to the composite or door noise stimulus in stimulus-triggered movements (Fig. 10*B*). A further 12 neurons (14%) responded exclusively to touch, 6 (7%) responded exclusively to the trigger stimulus, and 8 (9%) did not respond to any of these stimuli. During ipsilateral performance, 16 of 17 tested DA neurons responded both to touch in self-initiated movements and to door opening during stimulus-triggered movements.

Contralateral responses to touch and composite door opening showed insignificant differences in onset latencies ($P > 0.02$; Wilcoxon test), whereas median peak latencies and durations of responses to door opening were 26 and 51%, respectively, shorter than touch responses ($P < 0.01$). Median magnitudes of responses to door opening were 186% higher ($P < 0.01$). Ipsilateral responses to door opening showed 17–22% shorter median onset latencies, peak latencies, and durations, and 85% higher magnitudes, than ipsilateral responses to touch ($P < 0.01$). These results demonstrate that responses to door opening during stimulus-triggered movements were slightly more phasic than responses to the touch of food during self-initiated movements, whereas otherwise responses resembled each other.

Absence of touch response during stimulus-triggered movements

None of 72 DA neurons responding to contralateral touch of food during self-initiated movements showed a statistically significant increase of activity after the touch of food during stimulus-triggered movements (Fig. 11). When employing the door noise trigger stimulus, the animal's hand touched different food objects in the covered box in the same manner as during self-initiated movements, this being at the end of the wire (35 neurons tested) or at the bottom of the box (27 neurons). When tested with the composite trigger stimulus, food was touched under visual control at the bottom of the uncovered box (60 neurons). The absence of touch responses was equally seen in the 12 neurons not responding to the trigger stimulus. A quantitative comparison of changes after the touch of food in the two tasks shows that magnitudes were lower on stimulus-triggered trials for every neuron (Fig. 12, *left*).

During ipsilateral performance of both tasks, none of the DA neurons activated by touch in self-initiated movements responded to touch during stimulus-triggered movements (Fig. 12, *right*). This was seen when the food was stuck to the end of the wire in the covered box (14 neurons) or placed at the bottom of the uncovered box (2 neurons).

In a further test, DA neurons failed to respond when the hand touched the food stuck to the wire after being introduced into the open and uncovered box. This measure allowed the animal to see the food entering the box (5 neurons, 3 of which were activated when the food entered the box).

Thus DA neurons responded to the touch of food during self-initiated movements but were activated by the trigger stimulus preceding the touch of food when tested with

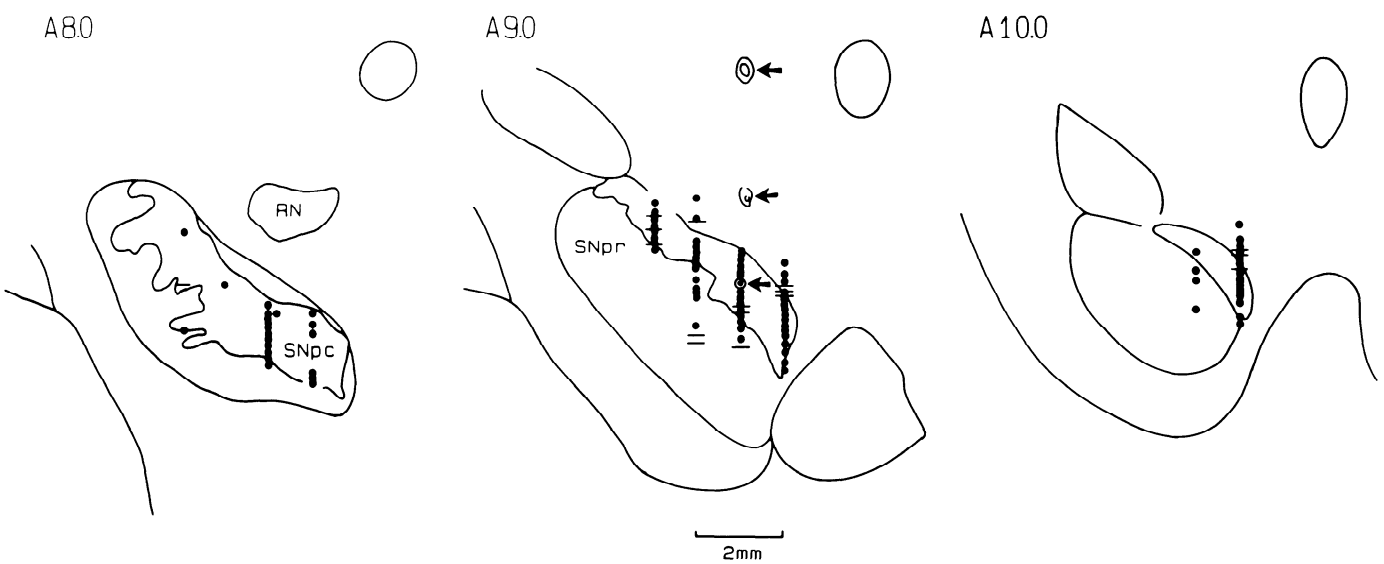

FIG. 13. Histological reconstruction of recording positions of DA neurons on 3 representative coronal sections from 1 brain. Approximate anteroposterior levels are shown in millimeters according to an atlas (Shanta et al. 1968). Filled circles, DA neurons activated by the touch of food; horizontal lines, DA neurons not responding to touch. Arrows point to a lesion 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.

stimulus-triggered movements. Touch responses were absent during stimulus-triggered movements.

Positions of neurons

Histological reconstructions of recording sites in the ventroanterior midbrain revealed that the majority of DA neurons were recorded in catecholamine group A9 (pars compacta of SN; $n = 142$), whereas some neurons were found in groups A8 ($n = 8$) and A10 ($n = 4$) dorsal and medial to SN, respectively. Neurons responding to the touch of food were seen in all 3 DA cell groups (A9, $n = 120$; A8, $n = 6$; A10, $n = 4$). Positions of responsive neurons are shown in Fig. 13 for three representative sections, demonstrating their distribution over the mediolateral extent of groups A8–A10.

DISCUSSION

Most DA neurons of the present study responded phasically in the two tasks to the touch of food and to the trigger stimulus, respectively. In contrast, only a minor percentage of DA neurons showed slow and moderate increases beginning as early as 1,500 ms before onset of self-initiated movements, this being ~1,100 ms before earliest movement-related EMG activity (Fig. 14). A limited number of DA neurons were moderately activated during the movement. This demonstrates that DA neurons are particularly responsive to external stimuli while not showing sufficiently differentiated movement-related activity to be engaged in the details of motor planning and control.

The incomplete anatomic separation of DA cells from other neurons in the midbrain requires additional criteria for ascertaining their dopaminergic nature besides the usual histological reconstruction of recording positions. As in earlier studies (Schultz et al. 1986, 1987), we employed the most pertinent electrophysiological criteria emanating from intracellular recording together with pharmacologic identification in anesthetized animals (Grace and Bunney 1983), methods that are inappropriate for behaving animals. Thus all neurons reported in the present study showed low levels of spontaneous activity together with a particular form and duration of impulses that distinguish DA cells from all other non-DA neurons in the ventroanterior midbrain, notably those of pars reticulata of SN, mesencephalic reticular formation, red nucleus, and pons. In the monkey, DA neurons with these characteristics respond to antidromic stimulation in the striatum and are depressed by low systemic doses of the DA receptor agonist apomorphine (Schultz et al. 1986, 1987), in agreement with results obtained in mice, rats, and cats (Bunney et al. 1973; Guyenet and Aghajanian 1978; Ruffieux and Schultz 1980; Sanghera et al. 1984; Steinfels et al. 1983; Studer and Schultz 1987). We therefore feel confident that the recordings presented in this report were in fact obtained from DA neurons.

Nature of responses to external stimuli

Although responding well to the touch of food presented at various positions in the food box, DA neurons were not activated when the monkey's hand touched the interior walls of the empty food box or encountered nonfood objects in the box, like a bare wire, screws, or paper. This demonstrates that responses depended on the object touched rather than being of purely somatosensory nature.

DA neurons responded to the touch of food only during self-initiated movements. The touch response was absent during stimulus-triggered movements, whereas a similar response in terms of latency, duration, and magnitude occurred to the trigger stimulus, in agreement with data obtained before (Schultz 1986). This argues against a simple relationship of the touch response to the reinforcing properties of food reward. Likewise, the touch response was not

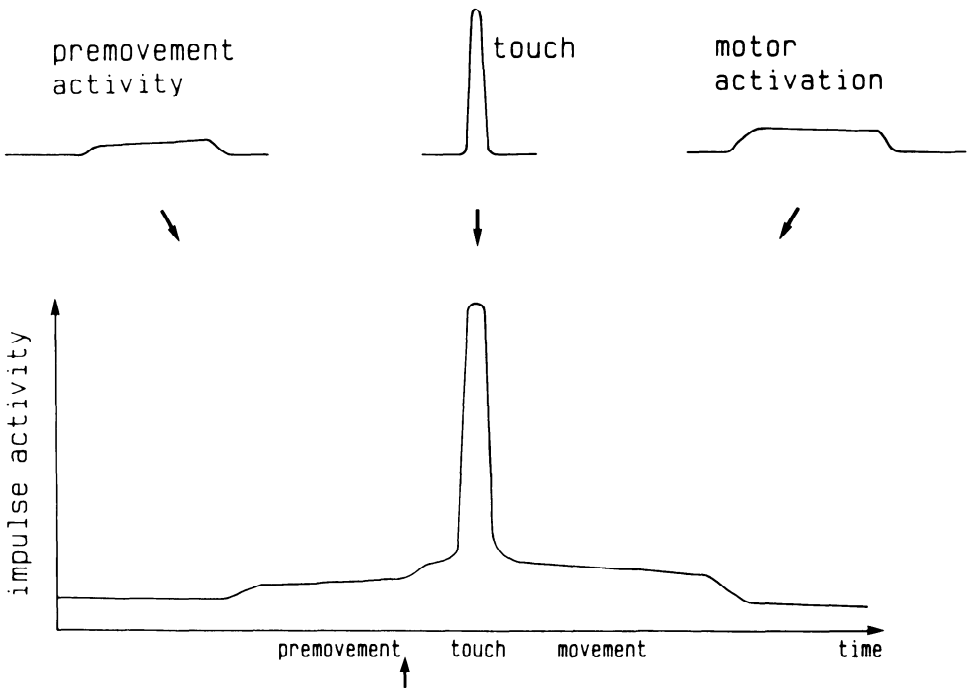

FIG. 14. Schematic diagram of impulse activity of DA neurons during performance of self-initiated arm movements. The 3 types of behavioral relationships shown above schematically represent approximate magnitudes and time courses. These are summed below by taking into account their relative frequencies of occurrence. "Motor activation" denotes changes of activity accompanying arm movements. Bottom arrow indicates time of movement onset.

specifically related to the initiation of arm movement from the food box toward the mouth, because the movement is the same in both tasks. Rather, the responses of DA neurons appear to be associated with the arousal elicited by appetitive stimuli signaling objects of high interest, such as food. Touching the food morsel during self-initiated movements was the first stimulus in each trial that indicated that food was about to be available to the food-deprived animal for ingestion. For stimulus-triggered movements, the appetitive stimulus character was associated through behavioral conditioning with the door opening stimulus that elicited the immediate movement reaction leading to the acquisition of food. Thus the arousal caused by the touch of food and the door opening in the two tasks, respectively, would precede and influence a target-directed behavioral response whose precise form would depend on the environmental situation defined by the behavioral task. Arousal elicited in this behavioral situation has been termed "motivational arousal" (Bindra 1974; Wise 1982).

DA neurons lacked responses to the touch of food during stimulus-triggered movements. Two closely related factors may explain this difference against the touch response observed during self-initiated movements. Opening of the food box triggered the arm movement toward the food box, in which the animal would predictably find a morsel of food. In contrast, obtaining food during self-initiated movements involved a factor of uncertainty, because the food was hidden behind the cover and was not available in all trials, notably when the animal moved too frequently. This uncertainty would have contributed to the arousal elicited when the food was detected and to the touch response. Second, after the trigger stimulus, the animal was in a state of arousal and conceivably was not particularly further aroused by the touch of the expected food morsel. Both of these arguments would be compatible with the arousing properties of stimuli effective for discharging DA neurons.

As outlined before, external stimuli, which, through prior conditioning, are able to predict the availability of goal objects, gain incentive value and elicit behavioral responses well before the animal acquires the object (Bindra 1968, 1974; Bolles 1972). Recent experiments point to an involvement of dopaminergic neurotransmission in behavioral responses to incentive stimuli. Effective loci for sustaining electrical self-stimulation have repeatedly been found in association with the mesolimbic DA system (Fibiger and Phillips 1986). The administration of DA receptor blockers leads to deficits in the performance of operantly conditioned tasks, possibly by interfering with the incentive properties of conditioned stimuli (Beninger 1983). In our experiments, both the touch of food and the trigger stimulus in the two tasks, respectively, represent incentive stimuli for the following behavior of the animal, as they predicted that food would be available after an appropriate behavioral response. It is thus possible that the responses of DA neurons were related to the incentive properties of the stimuli. However, at least two major differences need to be taken into account when comparing the present data with results from self-stimulation behavior and neuroleptic blockade of DA receptors. The present responses were obtained in the majority of midbrain DA neurons of areas A8, A9, and A10, whereas the cited results on self-stimulation and neuroleptics concerned predominantly the mesolimbic projection of the A10 DA system. Although this report concerns the impulse activity of DA neurons, behavioral changes concerning DA-dependent self-stimulation and neuroleptic blockade would conceivably involve the impulse activity of DA neurons, the functional specificity of neurons postsynaptic to mesolimbic DA neurons, and—at least with neuroleptics—presynaptic mechanisms of DA release (Romo et al. 1986). Future experimentation may reveal whether the responses of DA neurons could in fact be related to the incentive properties of environmental stimuli or to the more general motivational arousal provided by a large variety of appetitive stimuli in different behavioral situations.

The relationship of DA neurons to behaviorally significant stimuli may be seen in association with direct reward-seeking behavior, such as touching a morsel of food. However, the behavioral responses elicited by these stimuli would also include other types of appropriate, goal-directed behavior, such as the initiation of movements. The observed responses to trigger stimuli during the reaction time would lend support for this wider role in behavioral responses. It is interesting to note that neurons responding to food touch and trigger stimuli are inconspicuously distributed over areas A8, A9, and A10, which project to target regions with heterogeneous functions, such as striatum, nucleus accumbens, and frontal cortex. This may suggest that DA neurons respond with impulses to a wide spectrum of behaviorally significant stimuli and, through the consecutive release of DA from their terminals, would influence postsynaptic neurons in structures subserving a variety of more specific, goal-directed processes (Schultz 1985).

DA neurons in anesthetized rats and monkeys respond to somatosensory input (Chiodo et al. 1980; Maeda and Mogenson 1982; Schultz and Romo 1987; Tsai et al. 1980). These responses differ in several aspects from those presently observed. Under anesthesia, mechanical stimuli effective for influencing DA neurons are often of noxious character and are likely to cause strong behavioral activation in awake subjects. Less intense, non-noxious somatosensory input is ineffective. The responses to high-intensity stimulation predominantly consist of depressions of impulse activity. Thus DA neurons are activated by behaviorally significant somatosensory stimuli at moderate physical intensities while being influenced independent of the behavioral context by intense mechanical stimuli.

Premovement activity

The impulse activity of DA neurons was studied during self-initiated movements in view of the deficits observed in Parkinsonian patients and animals with experimental lesions of the nigrostriatal DA system. Despite the severe deficits in initiating spontaneous movements after lesions of DA neurons, we presently found only moderate and slow premovement activations in a limited fraction of DA neurons. This form of activation is comparable with the mild increases during the execution of movements observed in the present and earlier studies (Schultz et al. 1983, 1986).

More consistent premovement activity in advance of self-initiated movements is found in other structures of the brain. Neurons of the caudate and putamen, which are the predominant targets of midbrain DA cells, are activated up to 3 s before self-initiated arm movements (Schultz and Romo 1988). Many of these neurons project to the pallidum, which in turn sends axons via the oral ventrolateral thalamus to the supplementary motor area (Schell and Strick 1984). Neurons in the pallidum of cats and the supplementary motor area of monkeys are activated well in advance of self-initiated arm or eye movements (Neafsey et al. 1978; Okano and Tanji 1987; Romo and Schultz 1987; Schlag and Schlag-Rey 1987). In all of these structures, premovement changes occur in a higher percentage of neurons and with higher instantaneous impulse rates than in DA neurons. Thus the obvious implications of DA neurons in self-initiated movements are not reflected in their impulse activity but appear to be expressed in the activation of neurons synaptically linked to them.

The comparison of magnitudes of premovement activity in different structures demands to evaluate the role of impulses of DA neurons during the initiation phase of spontaneous movements. The presence of DA in the striatum apparently is necessary to permit these movements, as judged from their impairment after striatal DA depletions. It is possible that the amount of DA released by unmodulated, spontaneous impulse activity exerts a tonic, permissive influence on neuronal processes more actively engaged in the preparation of self-initiated movements, like those found in the striatum. It is known that impulse rates of DA neurons can rarely be augmented beyond 10–15 imp/s for periods longer than only fractions of seconds without provoking an inactivation of discharges (Lichtensteiger et al. 1976; Scarnati and Pacitti 1982; Skirboll et al. 1981). On the other hand, changes of DA release in the striatum, preceding movements, may be mediated by the presently observed moderate changes of impulse activity or by presynaptic interaction in the striatum with glutamatergic afferents (Romo et al. 1986) from areas of cerebral cortex showing premovement activity. At the present time, it is difficult to estimate whether changes in DA release precede self-initiated movements and whether they might be brought about by the observed moderate changes in impulse rate.

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