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The Primate Subthalamic Nucleus. I. Functional Properties in Intact Animals

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SUMMARY AND CONCLUSIONS

1. The present study tests several key aspects of the current model of the intrinsic circuitry of the basal ganglia, in particular the degree to which basal ganglia–thalamocortical circuits are functionally segregated at the level of the subthalamic nucleus (STN). To this end the responses of STN cells to somatosensory examination (n = 301 cells), the polarity and latencies of neuronal responses to passive and active movements (n = 223 cells), responses to microstimulation (n = 1589 sites), and cross-correlation functions of pairs of neighboring neurons (n = 72 pairs) were studied in STNs of three African green monkeys.

2. The activity of 55% of cells examined in STN was briskly modulated in response to passive movements of individual contralateral body parts. Of these, 86% responded to passive joint rotation of muscle palpation, but in some cases (25% of responding cells) responses were also elicited by light touch. In 91% of the responding cells responses were elicited by manipulations around a single joint only.

3. The caudoventral sector in STN was largely devoid of cells with responses to somatosensory stimulation. Within the rostrodorsal zone a lateral region containing neurons that responded to arm movements and a more medial region with neurons responding to leg movement were found. Cells responding to orofacial movements were located more dorsally and rostrally. Neurons with similar responses to active and passive movements of the limbs tended to be clustered within "arm" and "leg" zones.

4. Of identified arm cells in STN (n = 80), 36% responded to the application of torque pulses to the elbow (43 responses overall). Forty-eight percent of these cells responded to both extension and flexion torques. Ninety-three percent of the responses were initial increases in discharge, which characteristically occurred earlier and were shorter than initial decreases. Fifty-three percent of the responses were biphasic or multiphasic.

5. During active step tracking movements 40% of STN arm cells (n = 53 cells) responded with significant changes in activity. Thirty-six percent of these cells showed responses with both extension and flexion movements. Of the responses, 90% were increases in discharge. Only 14% of all responses were biphasic or multiphasic. Responses tended to occur around the time of movement onset (average latency 2 ms after movement onset).

6. Microstimulation (bipolar pulses, 40 μA, 200–500 ms train duration, 400 Hz) of the core of STN itself did not appear to produce movement. However, stimulation at the lateral borders of STN and of the adjacent white matter often led to limb or eye movement.

7. Cross-correlation analysis of simultaneously recorded pairs of neurons revealed significant synchronized activity in only 11% of pairs.

8. The somatotopic arrangement of neuronal responses and the paucity of neighboring cells discharging in synchrony strongly support the concept of functional segregation in the basal ganglia–thalamocortical pathways. The predominance of brisk increases in discharge in STN in response to movements most likely results from corticosubthalamic activation. The current model of basal ganglia anatomy predicts that this will lead to inhibition of movements. The inhibitory role of STN in motor control is further supported by the failure of electrical stimulation of the nucleus to induce movements. The late onset of responses of STN neurons in the step tracking task suggests that STN and the "indirect" pathway are not involved in the selection or initiation of movements, but may rather have a role in the control of ongoing movements.

INTRODUCTION

The basal ganglia are currently viewed as components of several largely segregated basal ganglia–thalamocortical circuits that subserve motor, oculomotor, limbic, and associative functions (Alexander et al. 1990; Hoover and Strick 1993). The "motor" circuit, which takes origin from precentral motor fields and postcentral somatosensory areas, and involves sensorimotor territories in the basal ganglia and parts of the ventrolateral thalamus, has received the most attention because it is strongly implicated in the pathophysiology of movement disorders (DeLong 1990). Within the basal ganglia this circuit consists of two major connections linking the putamen with the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). These pathways include a "direct" putamen-GPi/SNr connection and an "indirect" pathway from the putamen to the external segment of the globus pallidus (GPe), and connections that link GPe and GPi either directly (Hazrati et al. 1990; Smith et al. 1992) or via the subthalamic nucleus (STN; for instance, Smith et al. 1990). The subthalamopallidal projection is the only excitatory connection in this circuitry (Kitai and Kita 1987; Nakanishi et al. 1991). STN also receives a powerful (primarily motor) cortical projection that is also excitatory (for instance, Hartmann-von Monakow et al. 1978; Kitai and Deniau 1981).

According to this model of the basal ganglia circuitry, basal ganglia output from GPi/SNr may be viewed as being under tight control of inhibitory and excitatory influences arising in the direct and the indirect pathway, respectively. The primary function of the direct pathway would be to facilitate movement by allowing disinhibition of thalamocortical neurons. In contrast, the role of the indirect pathway would mainly be to inhibit movements by increasing the inhibition of thalamocortical neurons. The temporal interplay between the activity of direct and indirect inputs may give the basal ganglia a role in influencing characteristics of movements as they are carried out (the "scaling" hypothesis). Alternatively, basal ganglia output may influ-

ence the overall selection of movements in a center-surround fashion, favoring intended and preventing unwanted movements (the "focusing" hypothesis, see, e.g., Hazrati and Parent 1992a,b; Mink and Thach 1991a–c). If focusing (i.e., the restriction of a movement to a particular pattern of muscular activation) was indeed an important function of the motor circuit of the basal ganglia it would be critical that neuronal responses to active or passive movements were highly segregated and that neurons became active before electromyographic (EMG) activation in these structures, whereas scaling could be accomplished with less segregation and late activation of STN neurons.

In the experiments presented here we approach these issues with a study of the functional properties of neurons in STN portion of the indirect pathway. The hypothesis that the indirect pathway has a primarily inhibitory function in controlling movements was tested by assessing the effects of electrical stimulation of the subthalamic area. Microstimulation of STN was not expected to induce movements, because it would result in excitation of GPi, leading to subsequent inhibition of thalamocortical and cortical cells, in contrast to stimulation of microexcitable zones in the putamen, which induces movements, probably by increasing the inhibition of GPi via the direct projection (Alexander and DeLong 1985a,b). The degree of separation of neurons in STN showing responses to somatosensory input from different body regions was explored with closely spaced microelectrode penetrations during passive movements. At an even finer level the segregation of information passing through the basal ganglia was investigated by assessing the degree of synchronization of activity of neighboring cells in STN with cross-correlation methods. Last, the polarity and timing of neuronal responses were studied in a visuomotor step tracking task.

Some of these topics have been examined in two earlier papers in monkeys (DeLong et al. 1985; Georgopoulos et al. 1983). These earlier papers, however, were based on small numbers of cells sampled with widely spaced microelectrode penetrations in rhesus monkeys. The microelectrode recording results reported here encompass a larger sample of cells obtained during more closely spaced penetrations in STNs of African green monkeys. The number of cells recorded is sufficient to assess for the first time the polarity and latency of neuronal movement-related responses in the monkey STN. The degree of synchronicity between neighboring cells and the effects of microstimulation of STN have not been explored earlier. It was one of the goals of this series of reports to study the effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on the neuronal discharge rate and pattern in African green monkeys, because MPTP treatment in this species results in an animal model for human parkinsonism that is in some respects superior to the previously used models, which mostly used rhesus monkeys (for details see Bergman et al. 1994). Because the electrophysiological characteristics of the basal ganglia have never been determined in African green monkeys, the experiments reported here provide a baseline for the observations detailed in the following reports (Bergman et al. 1994; Wichmann et al. 1994).

Some of the results of this study have been previously reported in abstract form (Wichmann et al. 1989).

METHODS

Animals and behavioral conditioning

Three juvenile African Green monkeys (*monkeys A–C*; *Cercopithecus Aethiops Aethiops*, weight 3–5 kg) were used in these experiments. The studies were performed in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals. All three animals were trained to allow passive manipulation of the extremities, trunk, and orofacial structures. *Monkeys A* and *C* were trained to perform a simple visuomotor step tracking and torque application task that was controlled by a laboratory computer (PDP 11/23). *Monkey B* was trained only in the torque application task.

The monkeys were seated in a primate chair with one arm placed at 75° abduction of the shoulder joint in a low-friction manipulandum. The elbow joint was located over the axis of rotation of the manipulandum, thus allowing flexion and extension movements of the elbow. The other arm was lightly restrained at the side of the animal. The animals faced a display with two horizontal rows of light-emitting diodes (LEDs). Each row of LEDs was 32 cm long and contained 128 LEDs. The target position was indicated by illumination of an LED in the upper row and the position of the manipulandum by illumination of an LED in the lower row.

Behavioral trials were initiated by illumination of a single LED in the center of the upper row of the LED panel. The monkey had to move its arm to align the manipulandum-coupled light in the lower row with the center target LED, which corresponded to a 90° extension of the elbow. After the monkey maintained this position for a randomized interval (1–3 s) a standardized torque pulse (0.1 Nm, 60 ms) pseudorandomly selected in the flexion or extension direction was abruptly applied to the elbow by a brushless DC torque motor that was coupled to the manipulandum. This led to perturbations of the arm, and the monkey had to realign the manipulandum-coupled light with the center light and remain there for a randomized period (1–3 s). Thereafter the upper center light was extinguished and a side light in the upper row simultaneously lit at 12° to the left or right of the center. *Monkeys A* and *C* were required to rapidly flex or extend their arms and realign the manipulandum-coupled light with the target LED and then to maintain this position for a randomized interval (1–3 s) to obtain a liquid reward. *Monkey B* received the reward after a randomized period (1–3 s) after the application of the torque pulse. Entry into the center or the target window was signaled to the animal by brightening of the respective light. If the monkeys failed to stay within the center or target windows (both 3° wide) the trial was aborted. Trials were applied with a randomized intertrial interval of 1.5–3 s.

All three monkeys were later treated with MPTP to allow data collection in the parkinsonian state (Bergman et al. 1994). *Monkeys A* and *B* were also used to test the behavioral and neuronal effects of STN inactivation in parkinsonian monkeys (Bergman et al. 1990; Wichmann et al. 1994).

Surgery

After the animals were fully trained in the task, surgery was performed under aseptic conditions and pentobarbital sodium anesthesia (30 mg/kg). A 20 mm diam hole was made in the skull with a trephine and a cylindrical stainless steel chamber was stereotaxically positioned over the hole. The cylinder was cemented in place with dental acrylic. The cylinder was tilted 36° anteriorly to allow penetrations in parasagittal planes to STN as well as to large parts of GPi (see also Fig. 1; target stereotaxic coordinates A7, H1, L5, (Contreras et al. 1981; Winters et al. 1969). In addition, in *monkey C* a cylinder was positioned so as to permit recording of the activity of pallidal neurons (see Bergman et al. 1994). This cylinder was tilted 50° laterally in the coronal plane, targeting A12, H1, L9. In all three animals screws were also imbedded into

the dental acrylic cap to allow head fixation during recording sessions.

Recording and data collection

During the recording sessions the monkey's head was immobilized. A microdrive (MO-95, Narishige, Tokyo) coupled to a linear potentiometer for depth measurements was used to lower glass-coated platinum-iridium microelectrodes (impedance 0.5–1.5 MΩ at 1 kHz) through the dura and into the brain. The electrode penetrations were carried out in a 0.5 × 0.5 mm grid throughout the subthalamic area. All penetrations were carried out with the same electrode to ensure fine-grain sampling of STN. The signal was amplified and bandpass filtered at 200–6,000 Hz. Extracellular action potentials were discriminated with an amplitude discriminator. Somatic action potentials were recognized by their initial negative biphasic potentials with the initial negativity >0.2 ms in duration. The times of occurrence of neuronal spikes, recorded as interspike intervals (precision 1 ms), as well as the sampled analog data, were stored on-line on the laboratory computer disk, spanning the period from 500 ms before the center light came on to 1,000 ms after the reward was applied. Output from a potentiometer coupled to the axis of the manipulandum provided a record of the position of the handle. Velocity and acceleration information was derived from this signal by differentiation with an analog circuit. Position, velocity, and acceleration data were all sampled at 100 Hz. The data were later transferred for storage and off-line analysis to magnetic tape. The analog neuronal data and position signal were also stored on video recording tape with a digital data recorder (VR-10, Instrutech, Mineola, NY).

Four classes of trials (elbow flexion and extension movements with flexion and extension torque pulses), were presented in a balanced, pseudorandom sequence for each recorded cell. Typically, 8–10 trials of each class were collected. Data from a given behavioral class were subjected to subsequent analysis if at least five successful repetitions of the respective trial class were recorded.

The relation of neuronal discharge to passive manipulation of different body parts was studied by listening to the recorded cellular activity via an audio amplification and speaker system. Movements of the lips, tongue, and jaw were elicited by offering liquid reward. Examination consisted of passive joint rotation, tendon and muscle taps, and light touch to the hairy and glabrous skin.

In *monkeys A* and *B* microstimulation (40 μA, 200- to 500-ms trains, balanced bipolar pulse pairs, 200-μs cathodal pulse/200-μs anodal pulse at 400 Hz) was carried out at regular intervals (200 μm in STN and its immediate vicinity, 500 μm in areas further removed from STN) throughout the subthalamic area as the electrode was withdrawn from each track after completion of neuronal recording for that penetration. The animals were watched by two observers for movements of eyes or limbs or muscle contractions that were directly related to and could be repeatedly elicited by stimulation. Motor responses to microstimulation were considered to be present when either visible movement of a joint or a visible contraction of a muscle occurred in a reproducible manner. To minimize random fluctuations in the animal's level of arousal (which might affect responses to microstimulation; Alexander and DeLong 1985a,b) the limbs and the face of the animals were gently manipulated immediately before delivery of each stimulus train.

Data analysis

The activity of each neuron during the torque application and step tracking task was analyzed off-line using computerized statistical methods (implemented on a VAX station 3200; see also Crutcher and Alexander 1990 for description of statistical methods). Each trial was divided into epochs, centered around the "torque pulse on" and the "target light on" events. Each epoch was further divided into pre- and post-event epochs. The interspike interval data from a neuron were used to calculate average discharge rates across trials for each behavioral class. Mean discharge rates and SDs were calculated for all pre-event epochs (control periods for the respective event) and compared with the discharge in the post-event epoch. A given cell was classified as responding to the behavioral event if its discharge rate deviated at any time during the post-event epoch by >2.5 SD from the mean discharge rate of the pre-event epoch for >20 ms (increases or decreases in discharge). Latencies and durations of responses relative to the behavioral events were calculated using the onset and offset times of the responses relative to the occurrence of the respective event.

The same data analysis program was used to determine reaction and movement times for the step tracking movement from the analog velocity trace, averaged across trials in a given behavioral class for each cell. Movement onset was defined as the time when the velocity deviated by >2.5 SD from baseline; movement offset was defined as the time when the velocity trace reentered the 2.5-SD band around the baseline. From neuronal data and movement onset times latencies of neuronal responses relative to the onset of movement were calculated. The significance of differences between means of firing rates, response latencies and durations, and movement and reaction times between different groups of data was assessed with the two-tailed *t* test.

The raw neuronal data, recorded on video tape before application of the behavioral task and sensorimotor examination, was digitized and subjected to a PC-based spike sorting algorithm (Bergman and DeLong 1992). Interspike intervals were stored on the PC disk and then transferred to a micro-VAX 3900 computer for further analysis. If more than one neuron could be discriminated with the spike sorting algorithm (with <5% double matching between both neurons) the cross-correlation function was calculated, smoothed, and displayed. Confidence limits at the 0.5% and 99.5% level were computed under the (null) assumption that the number of spikes in any bin of the histogram should fit two independent Poisson processes (Abeles 1982a). The cross-correlograms were further analyzed with a feature-extracting program, which graded specific features of the function according to their intensity and significance. If synchronized activity was found it was classified as asymmetric (direct synaptic interaction between the neurons) or double-sided (common input). The strength (area) and duration of these phenomena were calculated.

Histology

At the completion of this experiment and of the studies described in the companion papers the monkeys were killed with an overdose of pentobarbital (100 mg/kg) and perfused transcardially with normal saline followed by 10% neutral Formalin. The brains were then blocked, frozen, and sectioned in the parasagittal plane. Alternate 50-μm sections were stained with cresyl violet and tyrosine hydroxylase immunohistochemistry. Recording sites were reconstructed on the basis of the linear gliosis associated with each microelectrode track and the electrophysiological information concerning the boundaries of STN and surrounding structures. The tyrosine immunohistochemistry data were used to assess the degree of damage inflicted on the midbrain dopaminergic system in subsequent stages of this series of experiments (Bergman et al. 1994).

RESULTS

General aspects

A total of 94 penetrations were carried out in the subthalamic area in three monkeys (*monkey A*: 42 penetrations; *monkey B*: 17 penetrations; *monkey C*: 35 penetrations).

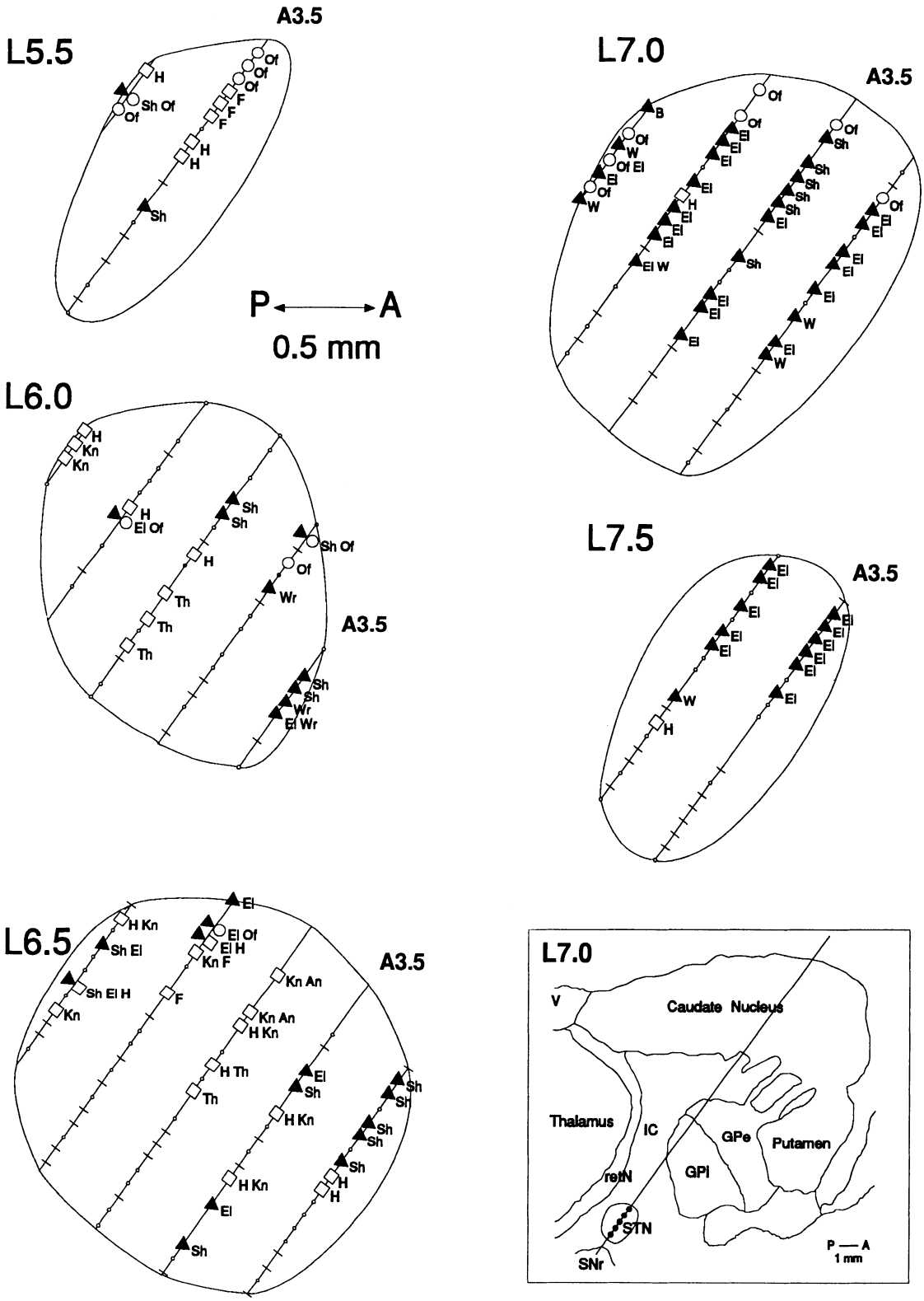


FIG. 1. Distribution of cells responding to somatosensory input in subthalamic nucleus (STN) of *monkey A*. Open squares: leg. Filled triangles: arm. Open circles: orofacial. Dashes: nonresponsive. W, wrist; El, elbow; Sh, shoulder; H, hip; K, knee; Th, thigh; F, foot; Of, orofacial. Each section is labeled by its lateral stereotaxic coordinate. In each section a penetration at A3.5 (chamber coordinate) is labeled as well. *Bottom right*: parasagittal representation of STN and surrounding structures at L7. A penetration at A3.5 is labeled.

STN was easily discernible from surrounding structures by its typical neuronal activity, consisting of densely packed, tonically active cells. The tight clustering of cells, however, often rendered stable recording in this nucleus less than satisfactory, and the isolation of some neurons could not be adequately maintained throughout the entire recording sequence (i.e., recording on video digital data recorder, sensorimotor examination, and step tracking task).

TABLE 1. *Somatosensory response properties of neurons in STN*

Body Region	Responding Cells	
	n	Percent
Arm	99	34.6
Shoulder	29	29.3
Elbow	60	60.6
Wrist	9	9.1
Fingers	1	1.0
Leg	37	12.9
Hip	17	45.9
Knee	16	43.2
Ankle	3	8.1
Toes	1	2.7
Face	14	4.9
Multiple regions	15	5.2
Unresponsive	136	47.6
Total	301	100.0

n = number of cells. The number and proportion of cells being tested for somatosensory responses is broken down according to body region and within a given body region according to body part. Groups of cells designated as "arm," "leg," or "face" contain only neurons that exclusively responded to stimulation of the respective body part. STN, subthalamic nucleus.

The data base therefore contains different sets of neurons for different aspects of the study.

Somatotopic organization

The activity of many cells in STN (165 of 301 cells, 54.8%) was briskly modulated during passive movements of individual body parts on the contralateral half of the body. Table 1 shows a classification of cells in STN based on these responses. In all three monkeys responses were mostly related to passive joint rotation (141 of 165 cells, 85.5%), but a few could also be elicited by light touch (41 of 165, 24.8%). Responses to manipulations of the arm were most frequent, with fewer cells responding to leg manipulations and even fewer responding to orofacial movements or trunk manipulations. The majority of responsive cells (150 of 165, 90.9%) were activated solely by manipulation around a single joint, with the remainder responding to more than one joint. These responses typically involved adjacent joints, with responses from one joint clearly stronger than from the others. Most neurons responded to proximal (shoulder/elbow and hip/knee) manipulation.

Figure 1 shows the distribution of identified arm, leg, and orofacial cells responding to movements in *monkey A*. Similar findings were obtained in *monkeys B* and *C*. Cells responding to movement were found in all parasagittal planes and throughout the entire rostrocaudal extent of the nucleus. It is clear, however, that the caudoventral sector in the nucleus is largely devoid of cells with sensory responses, especially in the more medial planes. Within the rostrodorsal "somatosensory" zone there is a lateral region containing neurons that respond to arm movements and a more medial region with neurons responding to leg movements. Cells responding to orofacial movements were generally located more dorsally and rostrally. A considerable degree of clustering of functionally similar neurons was observed within the arm and leg zones. Thus in a given electrode penetration several cells responding to shoulder movements would be found in a cluster, followed, for instance, by another cluster responding to elbow movements, as shown in Fig. 1, lateral plane 7.0. It is suggested from the data in Fig. 1 that there may exist a central dorsal shoulder representation that is surrounded on four sides (rostral, caudal, lateral, and ventral) by an elbow representation. Finally, it is evident from Fig. 1 that the representation of limb in terms of distal/proximal parts is markedly different. The data suggest that proximal portions of the arm are represented dorsally to distal portions. Clusters of cells representing the same body part were often separated from one another by cells representing a different body part. This suggests either separate representations of the same body areas or a single complex representation whose seemingly separate components were linked in intermediate planes (which were not sampled in our experiment).

Microstimulation

The subthalamic area (STN and surrounding structures) was microstimulated at 1,589 different sites in the three animals (Fig. 2). STN itself did not appear to be microexcitable, because stimulation of its core, including areas that contained cells responding to limb movement, did not elicit movements. However, within the most lateral portion of STN and in the adjacent white matter, microstimulation often evoked movements, typically involving multiple body parts, e.g., arm, leg, and face. Responses within and outside STN did not differ in character. They were brief, jerky movements with the typical appearance of capsular activation. In medial, dorsal, and anterior portions of the area surrounding STN, saccadic eye movements to the contralateral side were often elicited.

Cross-correlation analysis

Seventy-two pairs of neurons simultaneously recorded with a single electrode during periods of quiet wakefulness were used for the cross-correlation analysis. The cross-correlograms for 42 of 72 pairs of neurons (58.3%) were flat (Fig. 3*A*), indicating there was no synchronization between the activity of the two cells. The remaining 30 pairs of cells showed signs of synchronized firing between neurons. However, 22 of them showed very narrow peaks (duration <3 ms) very close to the center, which are probably a sorting artifact, representing the erroneous detection of the final upward deflection of the multiphasic reference action potential as a second action potential. Cross-correlograms of the remaining eight pairs of cells (11.1%) always showed broader symmetric or asymmetric peaks (Fig. 3, *C* and *D*), indicating synchronized firing. Troughs, indicating mutual inhibition between neurons or common input with opposite effect (Abeles 1982b; Eggermont 1990), were not seen. Seven synchronized pairs of cells showed symmetric (double-sided) synchronization, most likely due to a common input mechanism, with an average area of central peak in the cross-correlation of 0.26 ± 0.08 (SD) spikes. Only one pair of cells showed asymmetric (1-sided) synchronization (Fig. 3*B*), which may result from direct synaptic interaction between the two neurons.

Neuronal responses to behavioral events in the task

SPONTANEOUS FIRING RATES. The mean firing rate during the control period of the torque application task of all STN

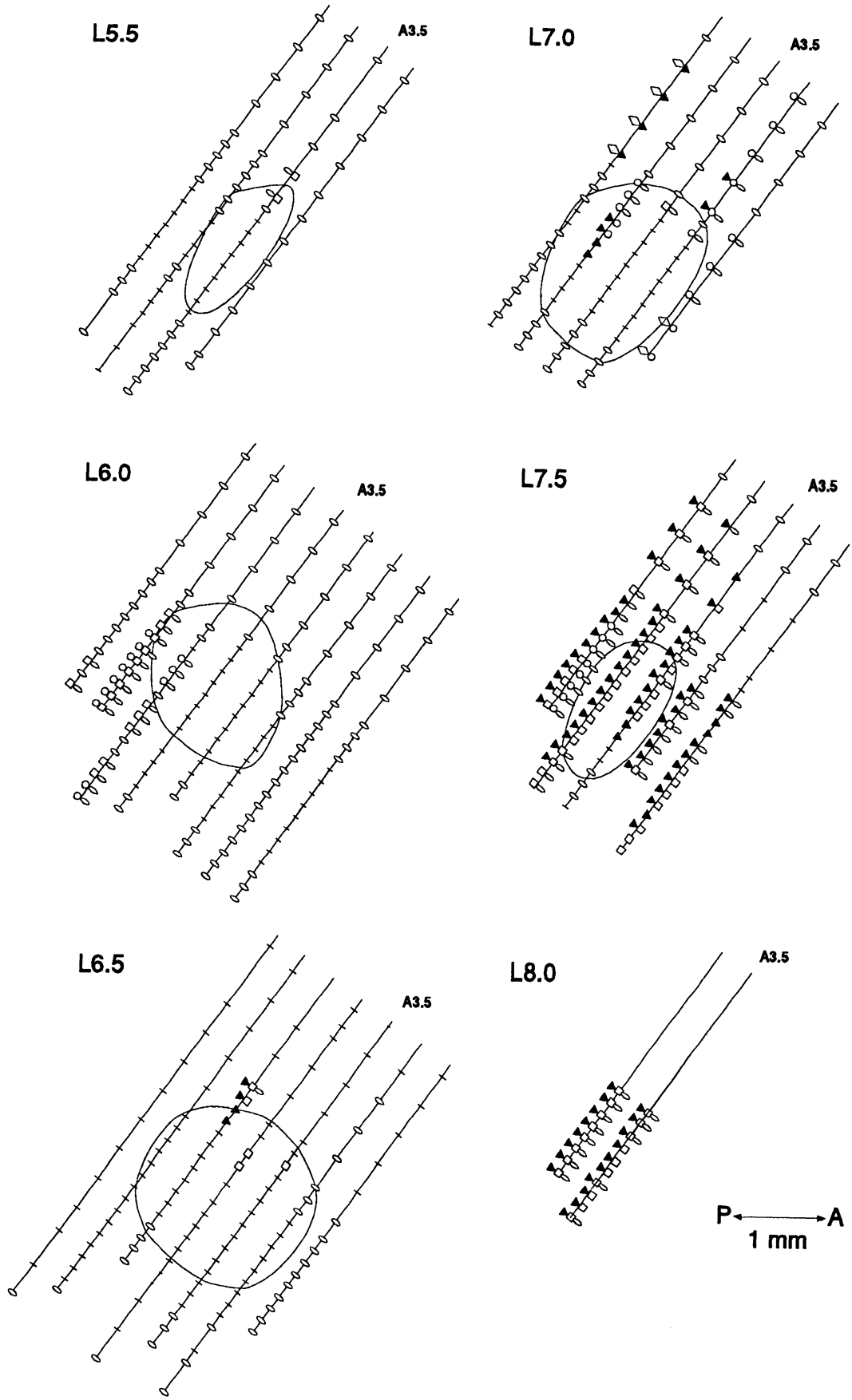


FIG. 2. Microstimulation in STN area in *monkey A*. Open ovals: saccades. Open circles: orofacial movements. Filled triangles: elbow movements. Open squares: hip movements. Open diamonds: trunk movements. Dashes: nonresponsive. Each section is labeled by its lateral stereotaxic coordinate. In each section a penetration at A3.5 is labeled as well.

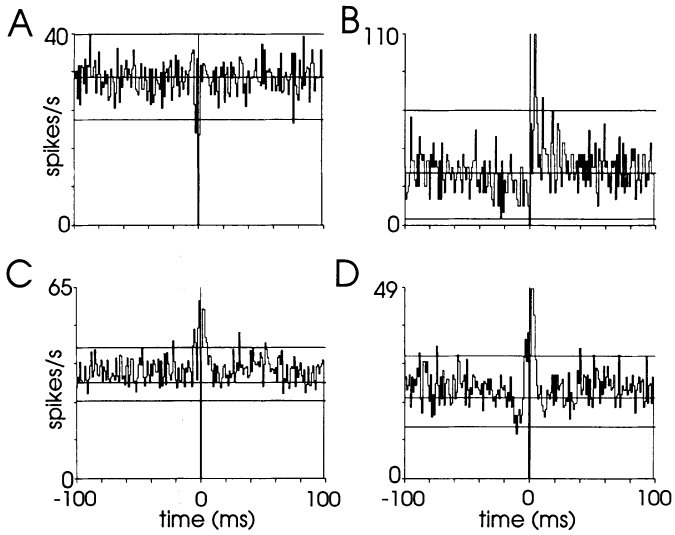


FIG. 3. Cross-correlograms of simultaneously recorded pairs of STN neurons. The correlation functions were calculated with a binwidth of 1 ms. The correlograms are displayed up to a delay of 100 ms with no smoothing. Dashed lines: 99% confidence limits for 2 independent processes. The narrow dip at time 0 is due to the inability of the spike-sorting algorithm to detect simultaneously occurring spikes from 2 different neurons. *A*: example of the most common correlogram in STN, with no significant deviation from the confidence lines. *B*: example of a cross-correlogram indicating increased probability of 1 unit to fire after the firing of the 2nd unit. *C* and *D*: examples of double-sided hills in the cross-correlograms (see text for further explanation).

neurons was 18.8 ± 10.3 spikes/s (individual averages: *monkey A*, 17.22 ± 8.96 spikes/s, $n = 154$; *monkey B*, 21.63 ± 11.82 spikes/s, $n = 12$; *monkey C*, 22.76 ± 12.04 spikes/s, $n = 54$; $P > 0.1$ between monkeys). The distribution of firing rates and the firing characteristics are discussed in more detail in the following paper in conjunction with the results from the post-MPTP treatment period (Bergman et al. 1994).

RESPONSES TO TORQUE APPLICATION. The activity of 80 arm movement-related cells was recorded during application of elbow torque pulses. Twenty-nine (36.3%) of these cells showed a significant response (Fig. 4). Because 14 of these responded to both flexion and extension displacement, a total of 43 responses could be evaluated. Torque responses occurred with similar frequency for flexion and extension: 22 of 29 cells (75.9%) responded to extension torque pulses, 21 of 29 cells (72.4%) to flexion torque pulses. Cells responding to torque in both directions (14 of 29 cells, 48.3%) always responded with the same polarity regardless of direction, although the magnitude of responses in the two directions was often different.

The majority of responses were initial increases in discharge (40 of 43 responses, 93.0%). Increases in discharge occurred significantly earlier (latency 49.3 ± 13.5 ms) than decreases (latency 69.0 ± 24.4 ms; $P < 0.05$, see Fig. 4*C*) and were significantly shorter (duration 72.2 ± 30.4 ms) than initial decreases (duration 127.7 ± 85.5 ms, $P < 0.05$).

Responses were often monophasic (20 of 43 responses, 46.5%). For biphasic or multiphasic responses, the second response was most often a decrease (19 of 23 biphasic or multiphasic responses, 82.6%), and secondary responses occurred with a latency of 149.7 ± 60.5 ms (Fig. 4*D*). The average latency of secondary decreases (142.6 ± 44.4 ms) was not significantly different from those of primary decreases ($P > 0.1$). Responses with three or four phases were seen in 5 of 29 cells (17.2%). In each of these cases an initial increase in discharge was followed by a secondary decrease, a tertiary increase in discharge, and (in the single cell with 4 responses) another decrease.

RESPONSES DURING PERFORMANCE OF THE STEP TRACKING TASK. The monkeys performed the step tracking elbow movement with an average reaction time (time between target light shift and onset of movement) of 242.8 ± 47.2 ms for extension movements ($n = 104$ averaged blocks of 10–15 movements) and 235.9 ± 65.6 ms for flexion movements ($n = 113$, $P > 0.1$). Movements were carried out with an average movement time (time between onset and offset of movement) of 472.8 ± 165.6 ms for extension movements and 486.7 ± 228.7 ms for flexion movements ($P > 0.1$). Reaction and movement times did not differ significantly between monkeys (see Table 2).

The activity of 53 "arm" cells in STN was recorded during the step tracking movement portion of the behavioral task. Twenty-two of these cells responded with significant changes in activity to the step tracking movement (Fig. 5). Of these, eight (36.4%) showed responses in both extension and flexion direction, six (27.2%) showed responses exclusively with extension, and eight (36.4%) showed responses exclusively with flexion.

As for torque-related responses, the initial response in movement-related cells was also often an increase (27 of 30 responses, 90%). Two arm cells, both related to elbow manipulation, showed reciprocal responses, with an increase in discharge for one direction and a decrease in discharge for the other. The remaining five cells with bidirectional responses showed increases in firing for both directions of movement, with different magnitudes of the responses for the two directions.

The movement-related responses were biphasic or multiphasic in only three cells (14.3%). Neuronal responses occurred on average 1.9 ± 114.7 ms after the onset of movement. The mean duration of neuronal responses was 294.6 ± 173.7 ms. There was no difference ($P > 0.1$) between mean latencies and between durations of responses to extension or flexion (extension: latency 26.5 ± 108.1 ms, duration 328.5 ± 207.2 ms; flexion: latency 14.5 ± 119.1, duration 271.9 ± 149.5 ms). If arm cells were further subdivided into "elbow" and "nonelbow" cells, the results were similar.

DISCUSSION

The findings of this study provide further support for functional heterogeneity in STN and for the proposed model of parallel segregated basal ganglia circuits. These studies confirm in the African green monkey earlier findings in the rhesus monkey of a functional segregation of STN into sensorimotor and nonmotor territories, and a clear somatotopic organization of movement-related cells in the sensorimotor territory. In addition, the present study shows little synchronicity between neighboring cells. Further support for the hypothesis that the direct pathway (and thus STN) is not important for initiation but rather for inhibitory modulation of movements is provided by the findings that movement-related responses in STN occur

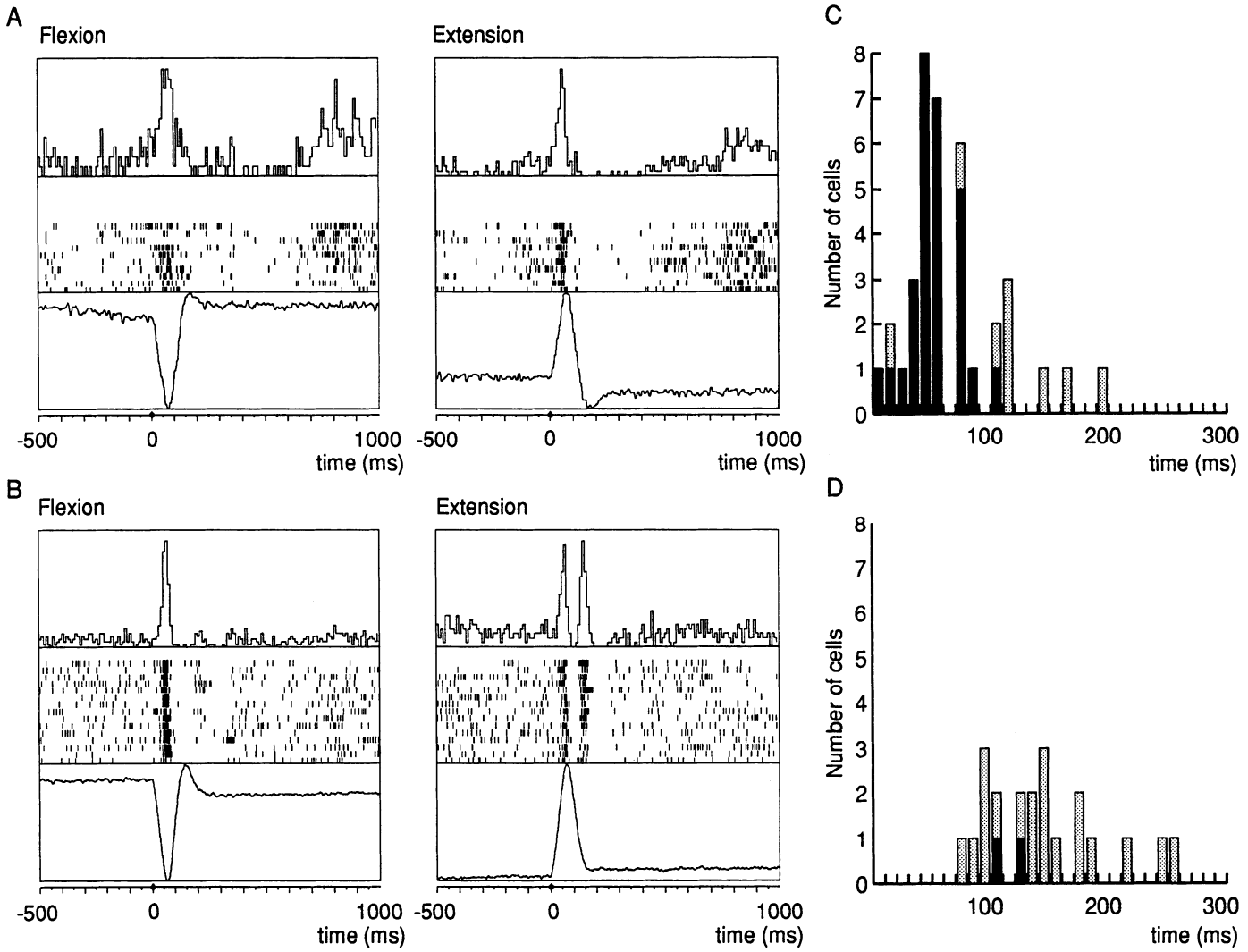


FIG. 4. Neuronal responses to torque. *A* and *B*: raster display (*middle* of each panel) of neuronal activity and peristimulus histogram (*top* of each panel) triggered by elbow torque application. The average elbow perturbation is shown at the *bottom* of each panel. *C*: distribution of latencies of initial responses. *D*: distribution of latencies of secondary responses. In *C* and *D*, filled bars represent increases in discharge rate, striped bars represent decreases.

rather late and that increases in discharge predominate over decreases. Moreover, as predicted by the current working model of basal ganglia circuitry, activation of STN by microstimulation does not evoke movements.

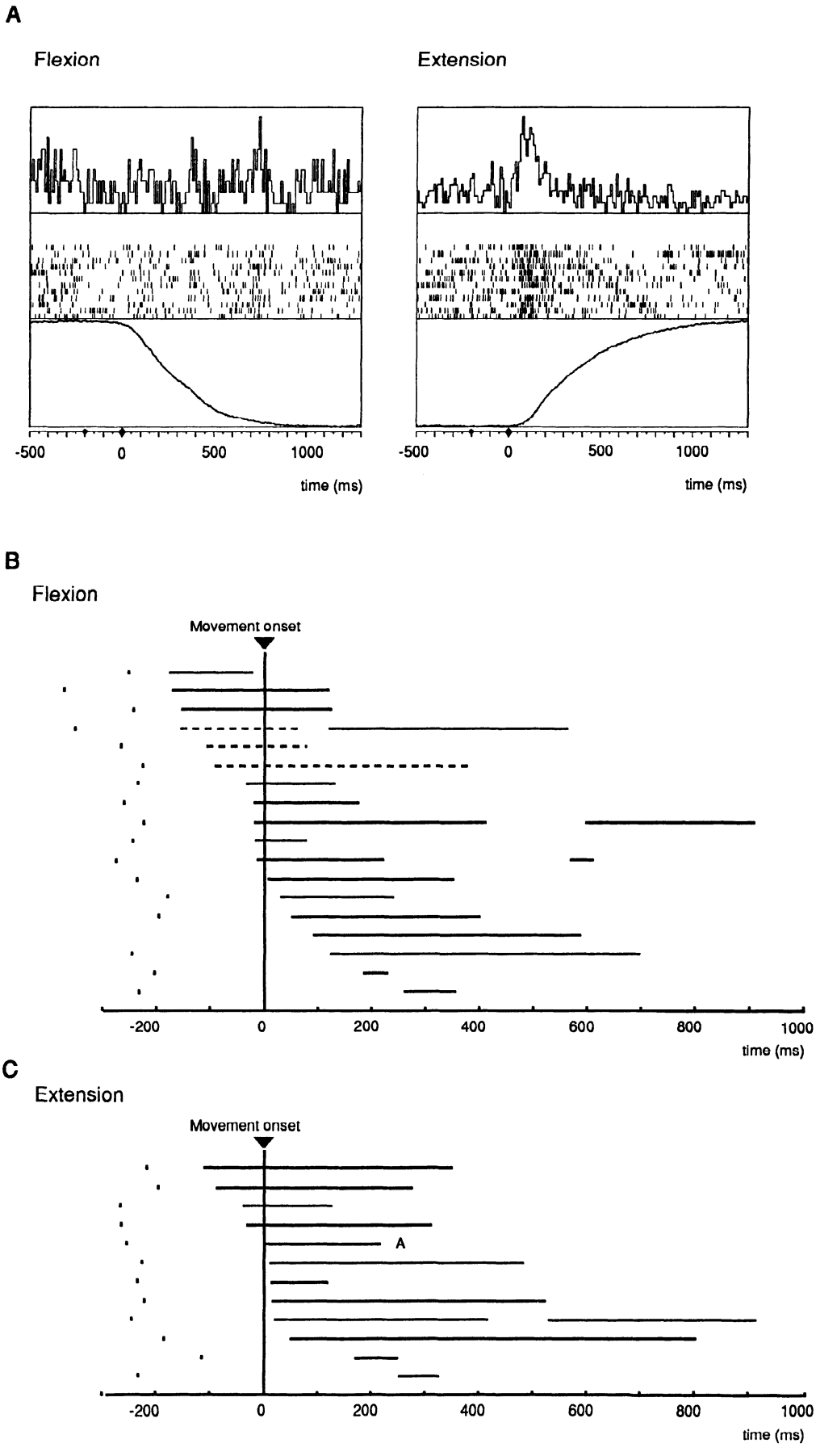
Comparison with earlier studies

Earlier studies on electrophysiologic properties of monkey STN (DeLong et al. 1985; Georgopoulos et al. 1983) differ in several methodological aspects from the present results. Besides the obvious difference in monkey species, in earlier studies STN was explored in penetrations placed 1 mm apart, whereas in this study we examined STN with a greater number of more closely spaced penetrations. The overall sample of cells examined in the earlier studies was relatively small, restricting the analysis of the somatotopic organization to a description of the topography of gross body parts and precluding the evaluation of latencies and polarities of neuronal responses to torque application. Several aspects of the neurophysiology of STN have not been reported before, including the results of microstimulation of STN and surrounding areas and the analysis of the de-

TABLE 2. *Movement and reaction times in the step tracking task*

	Extension			Flexion		
Monkey	Reaction time	Movement time	*n*	Reaction time	Movement time	*n*
A	245.7 ± 28.7	459.8 ± 90.0	33	230.3 ± 31.1	464.4 ± 77.1	43
C	241.4 ± 31.5	478.9 ± 105.3	71	239.3 ± 34.4	500.4 ± 108.8	70

Values, except for *n* values, are means ± SD; *n* = number of sets of individual trials (10–30 trials per set), the mean of which was averaged to yield these results.


A
Flexion
Extension
-500
0
500
1000
time (ms)
B
Flexion
Movement onset
-200
0
200
400
600
800
1000
time (ms)
C
Extension
Movement onset
A
-200
0
200
400
600
800
1000
time (ms)

gree of synchronicity between neighboring STN neurons with cross-correlation methods.

Although mostly in agreement with the earlier reports, the present results differ in some aspects, for instance in the proportion of cells responding to passive manipulation (12% in the earlier studies, 55% in the present report) and in the average discharge rates of STN neurons [23 spikes/s in the earlier study, 19 spikes/s in the present experiments (see also Bergman et al. 1994)]. These differences are most likely due to differences between rhesus monkeys (earlier study) and African green monkeys (present report). The latencies between shift of the target light and onset of neuronal activity changes in the step tracking task were longer in our experiments than in the earlier study (Georgopoulos et al. 1983). This difference is most likely the result of a selection bias, because the neurons in the earlier report were selected on the basis of their response to active arm movements, regardless of their response to passive arm manipulations, whereas we report only on responses of neurons that responded to passive arm manipulation. This conservative approach was taken to exclude all spurious responses to the active movement task that may have arisen from neurons that were related to nonarm movements occurring with regularity during the task, e.g., movement of the trunk for postural adjustment (see also Brotchie et al. 1991; Hamada et al. 1990). This selection may have introduced some bias, because, for instance, neurons solely related to active movement or to movement preparation would have been excluded.

Segregated circuits

The subdivision of the basal ganglia into regions with distinct functional properties is one of the main physiological arguments for the segregated circuit hypothesis (Alexander et al. 1986, 1990; DeLong and Georgopoulos 1981; Hoover and Strick 1993). This organization is most easily demonstrated in the division of STN into an anterodorsal sensorimotor region and a caudoventral area not related to body movement, a finding that was previously suggested by anatomic (Hartmann-von Monakow et al. 1978; Parent and Smith 1987) and earlier physiologic studies (DeLong et al. 1985; Matsumura et al. 1992).

On a second level of organization, the motor portion of STN is subdivided into regions that contain neurons whose activity is related to movements of specific body parts. Our study shows a somatotopic arrangement with cells in lateral planes responding primarily to arm manipulation and cells in more medial planes responding predominantly to leg manipulation. In general the location of cells with somatosensory responses in STN in our study is consistent with results obtained the previous studies. For instance, in the report by Hartmann-von Monakow et al. (1978), anterograde tracers injected into the leg area of motor cortex labeled anteromedial portions of STN, whereas they labeled anterolateral portions of STN when they were injected into the arm area of motor cortex. In contrast to earlier studies, however, we found neurons with responses to orofacial movements in a thin dorsal layer (see also Matsumura et al. 1992). In rhesus monkeys such cells were previously demonstrated mostly in lateral portions of the nucleus (DeLong et al. 1985), consistent with the location of terminals of a projection from the face area of the motor cortex in macaques (Hartmann-von Monakow et al. 1978). The number of cells related to orofacial input, and thus the extent of the orofacial territory, may be underestimated in our sample because the most lateral areas of STN may not have been adequately sampled.

Many of the somatosensory responses of short latency in STN that we demonstrated with passive and active arm movements are probably due to this direct input from motor cortex. The polarity of connections within the intrinsic basal ganglia circuitry, however, suggests that some of the initial increases in discharge of longer latency may also be due to information reaching STN via the polysynaptic indirect pathway (disinhibition from GPe). Although there is relatively little information available about the somatotopic organization of GPe input to STN in monkeys (Carpenter et al. 1968, 1981; Kim et al. 1976; Mitchell et al. 1989), the topographic organization of the termination of these afferents seems to match the topography mentioned above, with the central (arm-related) portion of GPe projecting to more lateral areas of STN than the more dorsal (leg-related) regions of GPe.

A third level of organization is revealed by examining the distribution of responses to manipulation of individual joints. As previously observed (DeLong et al. 1985), cells responding to input from a single joint are often grouped in clusters along individual penetrations, and such clusters can be identified in adjacent tracks, suggesting the possibility of a larger region representing movements around a single joint. Our results indicate that the representation of proximal portions of the limb is far greater than that of distal areas and that representations of the proximal portions (at least in the arm area) are located dorsally to representations of distal portions, in agreement with the previous study (DeLong et al. 1985). The finding of a large representation of the proximal limbs may help to explain the observation that dyskinesias after destruction of STN involve the proximal limbs to a much greater extent than the distal in both humans (Buruma and Lakke 1986; Martin 1927) and monkeys (Carpenter et al. 1950). The rarity of orofacial and trunk dyskinesias after STN lesions may be the result of the relative paucity of cells responding to manipulation of these body regions.

Finally, the cross-correlation analysis of neurons recorded simultaneously sheds light on the degree of functional segregation between neighboring neurons in STN during periods of quiet wakefulness. This analysis assesses whether neighboring cells, typically separated by $\leq$100–200 μm, receive common input or communicate directly with each other. Neighboring cells in STN showed synchronized

FIG. 5. Neuronal responses to step tracking movements. *A*: example of activity of a single unit in STN, shown as raster display and peristimulus histogram, aligned to the onset of elbow movement in flexion and extension direction, which is shown as averaged movement trace. *B* and *C*: latency and duration of neuronal responses to flexion movement. Continuous line: responses with increase in discharge rate. Dashed lines: decreases in discharge rate. Short vertical lines: respective "go" commands. The response depicted in *A* is marked.

firing in <12% of pairs of neurons. The symmetry of peaks in the cross-correlation function of most of these synchronized pairs of cells indicates that both neurons received input from a common source. The proportion of cells in STN receiving common input and the degree of synchronization is much smaller than that found at cortical recording sites (Eggermont 1992; Kruger and Aiple 1988; Vaadia et al. 1991) and more closely resembles the lack of synchronization between pairs of neurons in the pallidal complex (Bergman and DeLong 1989; Bergman et al. 1994). Functional segregation in both pallidal segments and in STN, despite a lower degree of segregation in structures that send prominent projections to them, is indicative of a segregation of basal ganglia–thalamocortical circuits even on a fine-grain level. The modest difference in synchronization between neighboring cells in STN and in the globus pallidus may attest to a slightly higher degree of functional segregation in the pallidum, possibly due to the direct cortical afferents to STN, which may supply more than one STN cell simultaneously.

Organization of basal ganglia circuits

As mentioned earlier, the input and output areas of the neuronal circuits passing through the basal ganglia (striatum and GPi/SNr) are connected via two independent pathways. In the case of the motor circuit the direct pathway is represented by a connection between the putamen and GPi, whereas the indirect pathway involves a putamen-GPe-STN-GPi projection (for instance, see Alexander et al. 1990). The recently described GPe-GPi connection (Hazrati et al. 1990; Smith et al. 1992) adds another avenue for the influence of the indirect pathway on GPi, presumably in the same direction as that of the GPe-STN-GPi circuit.

Because the subthalamopallidal projection appears to be excitatory (Hazrati and Parent 1992b; Kitai and Kita 1987; Nakanishi et al. 1987, 1991; Robledo and Feger 1990; Smith and Parent 1988), activation of the excitatory efferents of STN should lead to increased discharge in GPi neurons, which in turn should result in increased inhibition of thalamocortical circuits, thereby preventing rather than facilitating movements. The negative results of microstimulation in STN on limb movement support this concept. Stimulation-induced limb movements were only observed in areas outside STN or in lateral portions of STN that were very close to neighboring capsular fibers. Stimulation effects were thus most likely due to current spread to neighboring fiber tracts.

Stimulation of the core of STN was also ineffective in evoking eye movements, supporting the hypothesis that the "oculomotor" circuits function in a fashion similar to the motor circuit (Alexander et al. 1986; Hikosaka et al. 1993). Stimulation of the oculomotor territory within STN should lead to increased activation of the SNr by STN efferents along the indirect oculomotor pathway (Matsumura et al. 1992; Nakanishi et al. 1987). This in turn will result in increased inhibition of superior collicular neurons by SNr output, preventing eye movements. The elicitation of eye movements by stimulation of portions of STN close to its borders or by stimulation of surrounding fiber bundles may have resulted from stimulation of inhibitory striatonigral fibers, disinhibiting neurons in the superior colliculus (Hikosaka and Wurtz 1985a,b).

The polarity of STN afferents and efferents is further highlighted by an examination of the responses to active movements and to torque perturbations. For both types of movement the majority of neuronal responses consisted of brisk increases in discharge. As pointed out above, these early increases in discharge are most likely due to activation of the corticosubthalamic pathway, which is the main excitatory and fastest-conducting afferent to STN (Jinnai et al. 1993; Kita 1992; Kitai and Deniau 1981). Secondary responses were generally decreases in discharge occurring at longer latencies. These responses may have resulted from inhibitory input from GPe as part of a negative feedback loop. STN sends a prominent excitatory projection to GPe (Kitai and Kita 1987; Smith and Parent 1988; Smith et al. 1990). Activation of STN by cortical inputs may therefore result in subsequent activation of GPe, which in turn may induce decreases in discharge in STN of longer latency.

Role of STN in voluntary movements

The role of STN and of the basal ganglia in general in voluntary movements remains controversial (for instance, Albin et al. 1989; Alexander et al. 1990; Hikosaka et al. 1993; Marsden 1982; Mink and Thach 1991a–c,; Parent and Hazrati 1993). Most hypotheses concerning the role of the basal ganglia in movement were derived from experience with diseases originating in basal ganglia or from experiments involving activation or inactivation of large parts of basal ganglia nuclei. These results are notoriously difficult to interpret, because gross changes in "motor circuit" activity likely result in rather nonspecific activity changes in multiple parts of the neuraxis, unlike the much more specific effects that the minute alterations in the firing patterns of individual neurons in the basal ganglia may have under physiological conditions.

The most important findings of this study with regard to the motor functions of the basal ganglia are that the majority of the cellular responses to active or passive movements are somatotopically circumscribed increases in discharge occurring in the case of active movements around the time of movement onset, and thus well after the onset of EMG activity. These findings, together with the finding that the majority of responses to movements recorded in GPi (DeLong et al. 1985; Mink and Thach 1991a) are also relatively late increases, suggest that task-related activity in the indirect pathway is neither involved in the initiation nor in the postural preparation for the intended movement. The basal ganglia can at best have a role in later phases of movement, possibly even being involved in their termination.

As pointed out in the INTRODUCTION, the interplay between the direct and the indirect pathway in GPi has been hypothesized to play a focusing role, in some ways analogous to center-surround inhibition in the visual system (Mink and Thach 1991a–c). Cortically initiated activity reaching GPi via the direct pathway would lead to a focus of inhibition in GPi and secondarily to a focus of disinhibition in the motor thalamus, allowing the execution of "intended" movements. At the same time, or even earlier, a halo of "surround" inhibition, opposing the focus, would reach GPi via the excitatory STN-GPi projection, leading

to increased inhibition of those thalamocortical target neurons that are related to the "unintended" movements. It is not clear where this surround would be generated, although a rather literal center-surround mechanism has recently suggested by Parent and Hazrati (1993), with the proposal that STN efferents to GPi may terminate broadly whereas pallidal afferents from the putamen may terminate more specifically on individual pallidal cells. The focusing model is difficult to reconcile with our data. For instance, because a rather large number of arm cells showed increases in discharge in STN during arm movements, indicative of inhibition of components of the ongoing arm movements, the focus would have to be very narrow indeed. As mentioned above, a major problem with the focusing hypothesis is also that the majority of increases in discharge in STN (and in GPi) during active arm movements occur too late to have an impact on the early phases of movement or to provide meaningful stabilization of body posture.

Our data do not directly permit a test of the hypothesis that the temporal interplay and balance between the direct and the indirect pathway may have a role in scaling movements, which represent the second major hypothesis regarding the motor function of the basal ganglia (Berardelli et al. 1986; Draper and Johns 1964; Hallet and Koshbin 1980). The scaling hypothesis, however, is per se not entirely satisfactory, because, for instance, involuntary movements after STN lesions cannot be easily explained by unopposed phasic activity along the direct pathway, because this should lead to hypermetric rather than involuntary movements.

Further evidence against the validity of either hypothesis comes from the fact that lesions in STN or in GPi in monkey (Hamada and DeLong 1992; Kato and Kimura 1992) and in humans (Baron et al. 1993; Laitinen et al. 1992) have little or no effect on voluntary movements in most studies. Thus the contribution of STN and the indirect pathway remains elusive. More is known about the role of the indirect pathway in the pathophysiology of movement disorders such as Parkinson's disease and ballism than in the control of normal movement.

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