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RESEARCH ARTICLES

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Neural responses in multiple basal ganglia regions during spontaneous and treadmill locomotion tasks in rats

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Abstract To investigate the role of basal ganglia in locomotion, a multiple-channel, single-unit recording technique was used to record neural activity simultaneously in the dorsal lateral striatum (STR), globus pallidus (GP), subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr) during spontaneous and treadmill locomotion tasks in freely moving rats. Active and quiescent phases appeared alternately in a spontaneous movement session that lasted 60 min. Principal component analysis of the ensemble neural activity from each region revealed a close correlation with spontaneous motor activity. Most of the neurons in these four basal ganglia areas increased their firing rates during the active phase. In the treadmill locomotion task, the firing rates of neurons in all recording areas, especially in the STN, increased significantly during locomotion. In addition, neural responses related to tone cue, initiation and termination of treadmill were observed in a subset of neurons in each basal ganglia region. Detailed video analysis revealed a limb movement related neural firing, predominantly in the STR and the GP, during treadmill walking. However, the proportion of neurons exhibiting limb movement related firing was significantly greater only in the STR. A few neurons in the STR (4.8%) and the GP (3.4%) discharged in an oscillatory pattern during treadmill walking, and the oscillatory frequency was similar to the frequency of the step cycle. This study demonstrates a variety of neural responses in the major basal ganglia regions during spontaneous and forced locomotion. General activation of all major basal ganglia regions during locomotion is more likely to provide a dynamic background for cortical signal processing rather than to directly control precise movements. Implications of these findings in the model of basal ganglia organization are discussed.

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Introduction

The basal ganglia comprise a group of subcortical nuclei that are in a position to regulate motor functions by processing descending information from cortical regions (Alexander et al. 1990; Berendse et al. 1992a, 1992b). In rodents, these nuclei include the striatum (STR), the globus pallidus (GP), the subthalamic nucleus (STN), and the substantial nigra pars reticulata (SNr)/entopeduncular nucleus (EP). Two basal ganglia-thalamocortical pathways have been proposed to participate in motor information processes regulating motor functions. The direct pathway consists of a GABAergic projection from the STR to the EP/SNr while the indirect pathway reaches EP/SNr via the GP and the STN (Grofova et al. 1982; Wilson et al. 1982; Kita and Kitai 1991; Alexander et al. 1990; Obeso et al. 1997). EP/SNr efferents project back to the cortices via thalamic nuclei, forming a functional loop which regulates the initiation and execution of movement. Dysfunction of basal ganglia neural circuitry has been implicated in many movement disorders including Parkinson's and Huntington's diseases. Identifying the neural responses of the basal ganglia during spontaneous and forced movements is an important step in our efforts to understand the neural mechanisms underlying a variety of movement disorders.

Neural responses in the basal ganglia have been investigated in primates and rodents performing different motor tasks. In the primate, studies have been carried out with the subject sitting in a chair performing instructed arm movements in response to a cue stimulus. In such cases, neural responses in association with cue presentation, initiation and executions of movement have been observed in several basal ganglia regions (Crutcher and DeLong 1984a, 1984b; Georgopoulos et al. 1983; Wichmann et al. 1994a, 1994b; Wannier et al. 2002). Electrophysiological studies of motor action in freely moving rats have focused primarily on the striatum

(Gardiner and Kitai 1992; Haracz et al. 1989; Dolbakyan et al. 1977; West et al. 1997), a basal ganglia input station that receives abundant projections from broad cortical regions and midbrain dopaminergic neurons (Wise and Jones 1977; Donoghue and Herkenham 1986; McGeorge and Faull 1989; Ebrahimi et al. 1992). Striatal neurons revealed phasic responses during a self-initiated navigation task which coded spatial location, head orientation, and the timing of initiation and execution of displacement movement (Wiener 1993; Trytek et al. 1996; Rebec et al. 1997). Gardiner and Kitai (1992) reported that a large number of STR and GP neurons responded during learned head movement in response to an auditory cue. These responses were context (cue responses only associated with task performance) and movement-direction dependent. Detailed studies have been reported by West et al. (1990) describing striatal neural responses during the treadmill locomotion task. Spike activity increased in the dorsal lateral striatum during the treadmill locomotion phase. In addition, many neurons in this area receptive to projections from somatosensory and motor cortices (Wise and Jones 1977; Donoghue and Herkenham 1986; McGeorge and Faull 1989; Ebrahimi et al. 1992) exhibited limb movement related activity during treadmill walking. Taken together, these findings provide strong evidence that the execution of complicated movements involves basal ganglia-mediated sensorimotor processes that integrate cortical information. Questions regarding the ensemble neural responses in the entire basal ganglia complex during locomotion remain unanswered. In the present study, a chronic multiple-channel, single unit recording technique was used to record neural activity simultaneously from 64 electrodes implanted in four different basal ganglia regions (STR, GP, STN and SNr) during spontaneous and treadmill locomotion tasks. The aim of this study is to further examine the role of the basal ganglia in mediating spontaneous and forced locomotion activity.

Materials and methods

Animals

Twelve young adult male Sprague-Dawley rats weighing 350–400 g were used in the experiment. Animals were housed individually under a reversed dark-light cycle (lights off from 7:00 to 19:00) for 7 days before surgery. Animals were treated in accordance with the U.S. Public Health Service *Guide for the Care and Use of Laboratory Animals.* The experiments were approved by the Institute Animal Care and Use Committee of Wake Forest University, Health Sciences.

Surgical procedures

Rats were anesthetized with ketamine (100 mg/kg, i.m.) and xylazine (10 mg/kg, i.m.). An array of eight stainless steel Teflon-insulated microwires (50 μm diameter, NB Labs., Denison, TX, and Biographic Inc. Winston-Salem, NC), soldered to connecting pins on a headstage, were stereotaxically lowered bilaterally into dorsal lateral striatum (STR), globus pallidus (GP), subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr). The stereotaxic coordinates used to target these structures were: 0.5 mm anterior to bregma (A), 3.5 mm lateral (L) to the midline, and 3.7 mm ventral (V) to the surface of cortex for the STR; –1.0 mm A, 3.2 mm L, and 6.0 mm V for the GP; −3.5 mm A, 2.5 mm L, and 7.3 mm V for the STN; and –5.4 mm A, 2.0 mm L, and 7.8 mm V for the SNr, according to the atlas of Paxinos and Watson (1986). In addition, four ground wires were positioned about 2 mm ventral to the cortical surface. The headstage was secured onto the cranium with dental acrylic and with skull screws serving as anchors. Animals received enrofloxacin (2.5 mg/kg i.m.) before surgery to prevent infection. Animals were housed individually and allowed to recover from surgery for at least 10 days before being subjected to the experiment.

Behavioral tests

Spontaneous motor activity

Spontaneous motor activity was measured in a 33×33 cm plastic behavioral chamber over a 60 min experimental session. Six infrared emitters, mounted 10 cm apart and 3.5 cm above the floor, were used to detect the rat's movement (Ericson et al. 1991). Ventilation and computer fans provided background masking noise and experiments were performed in dim light in the morning (2 h into the dark cycle). The rat was placed in the behavioral chamber and a headset for 64 electrodes was gently connected via a lightweight cable to a motor assisted 80 channel commutator to record neural activity in the basal ganglia regions. The neural and motor (number of infrared beam breaks) activities were recorded over a 60 min session. The number of beam breaks detected by the infrared sensors served as the measure of spontaneous movement. The number of beam breaks for each infrared sensor was inspected to detect any large numbers of repetitive beam breaks that can be due to artifacts related to breathing, whisking or grooming. Segments containing repetitive same beam counts were excluded from the appropriate intervals of spontaneous motor activity. Spontaneous motor activity was defined as spontaneous moving from one infrared sensor to another. Video records (33 ms resolution) were used to monitor rat motor activity and to detect the repetitive beam breaks due to breathing and whisking. Rats were placed in the behavior chamber for 1 h each day and data were collected after consistent numbers of beam breaks (less than 15% difference in beam counts) were obtained from three sequential sessions.

Treadmill locomotion task

Treadmill locomotion sessions were carried out in the afternoon following completion of the spontaneous movement task (Chapin et al. 1980) in a transparent acrylic box (length 37 × width 19 × height 39 cm) that was mounted on a conveyer belt driven by a motor with adjustable speed. The belt served as the floor of the chamber. Rats were trained to walk at a moderate pace on the treadmill with a constant speed (12 cm/s). The treadmill cycle consisted of a 20 s walking phase triggered by an auditory cue and a random 10 to 30 s resting period. The cue tone was presented 1.5 s before the onset of treadmill walking. Each session lasted 60 min. Data were collected after 3–4 days of training when rats exhibited smooth locomotion. Video records (33 ms resolution) were used to monitor and record the behavior during the treadmill sessions.

Electrophysiological recording

Extracellular recordings of the four basal ganglia areas were performed at least 10 days after surgery by connecting a FET headstage plug and a lightweight cable between a commutator and the implanted microwire assembly. The commutator was free to turn as necessary, permitting unrestricted movement of the rat in the open

field. Neuroelectric signals were passed from the headset assemblies to programmable amplifiers, filters (0.5 and 5 kHz) and a multi-channel spike-sorting device. As many as 62 neurons from the STR, GP, STN and the SNr were monitored simultaneously from 64 microelectrodes. Spike activity, treadmill operation and infrared beam breaks were recorded (1 ms resolution) and controlled with a data acquisition software Magnet (Biographics Inc. Winston-Salem, NC). Spike train activity was analyzed offline with the PC-based Stranger programs (Biographics Inc., Winston-Salem, NC) and Nex (Plexon Inc., Dallas, TX).

Histology

At the conclusion of the final experimental session, each animal was subjected to the same anesthesia as in surgery. A positive current of 10–20 μA was passed through selected microwires for 10–20 s to deposit iron ions. The animal was then sacrificed and perfused with 4% paraformaldehyde solution. Coronal sections (45 μm thick) were cut through the STR, GP, STN and SNr and mounted on slides. Incubation of the mounted sections in a solution containing 5% potassium ferricyanide/10% HCl revealed iron deposits (recording sites) in the form of blue dots. Boundaries of the four brain areas were assessed with reference to the rat brain atlas of Paxinos and Watson (1986).

Data analysis

Data were processed off-line with Stranger and Nex software for basic analysis and graphics. MatLab and SPSS were used for advanced statistics. Data were analyzed from a single representative session from each rat.

In the spontaneous locomotion task, each session consisted of active and quiescent phases. Motor behavior was quantified by calculating the mean number of beam breaks over a 20 s period. Principal components from each brain area were calculated from the neural firing rates across each experimental session (1 s bin size) to detect major neural activity associated with spontaneous movement. The mean firing rates of each neuron and the average neuronal population firing rates within each region were calculated for the active and quiescent phases. Comparisons of the mean population firing rates between the active and quiescent phases were made for each region (Student's t-test, $P<0.05$).

In the treadmill session, data from a representative 1 h session from each rat were analyzed. The mean firing rates for each neuron during the walking and resting phases and the average neuronal population firing rates within each region were calculated. The walking and resting phase firing rates were compared for each region. A sliding-window method was used to measure and compare neural activity changes. Counts per bin (0.1 s bin size) of single neurons during treadmill locomotion were calculated for each trial. The results were then exported as a matrix to Matlab. Neural activity was then calculated by a time window (typically 1 s, but in some cases 250 ms for extremely narrow peaks) moving at 0.1 s steps across the duration of the treadmill walking phase.

The following two arbitrary criteria were used concurrently to detect significant changes in neural firing rates associated with treadmill walking: (1) firing rate changes (increase or decrease) of greater than 20% during the time periods measured compared with the baseline firing rate measured 10 s before the initiation of treadmill walking; (2) analyses of differences in at least three successive steps of the moving window reached a statistically significant level ($P<0.05$, Student's two-tailed t-test). These measures accounted for slow and fast firing neurons to show both substantial (100%) and significant changes.

A cluster analysis (K-means, SPSS Inc.) was used to sort neuronal firing patterns during treadmill locomotion. A moving window computed values at 0.2 s intervals across the entire record of the treadmill task (including the 10–30 s resting phase and 20 s walking phase) producing running averages smoothed over time. Then the cluster procedure used 200 element vectors to establish six distinct centroids in multidimensional space to group together the neurons with similar patterns of activity.

Normalized firing rate was used to identify activity patterns in populations. For each neuron, 40 s treadmill trials were analyzed using 0.2 s bins; spike/bin was averaged across all the trials in each session to produce mean firing rate and standard deviation. Standardization of neural firing rate was achieved by subtracting the mean firing rate of the corresponding neuron, and dividing the difference by the standard deviation:

$$z = (x - m)/s$$

where x and z are the raw and standardized firing rates (z score) of a neuron at a particular time bin, and m and s are the mean and standard deviation of that neuron's firing rate within the calculated period of the treadmill locomotion task.

Frame by frame video analysis (33 ms resolution) of limb movement during treadmill locomotion was conducted. Two limb movement events were identified by video analysis: footfall, defined as the initial paw contact with the ground (soft contact), and foot off, defined as the onset of the swing phase (when the paw left ground) (Cohen and Gans 1975). To allow a more descriptive analysis, the step cycle was divided into two major phases, stance (paw down) and swing (paw up), defined by the onsets of footfall and foot off, respectively (West et al. 1990). All timestamps for limb movement were compiled and entered into the data file as event nodes. Raster and perievent time histograms (PEH) were constructed around the nodes to reveal the neural activity associated with limb movements.

Principal component analysis (PCA) is a statistical method for reduction and interpretation of multivariate data. PCA is essentially a method for recognizing the information that is distributed across a set of partially correlated variables into an equal number of uncorrelated principal components. Most of the variance related to significant redundant information in the population is consolidated within the first few components. Valid neurons, selected on the base of quality of waveform and noise-free recording, were used in each brain region (with 1 s bin size) to calculate the PCA with software from the Nex program (Plexon Inc., Dallas, TX).

Power spectrum density analysis (Nex) revealed oscillatory neural activity. This analysis was carried out during treadmill walking and resting phases. Power spectrum density during each of these phases was computed with a 20 Hz or 10 Hz band and a 256 or 128 frequency. The formula for power spectrum computation is as follows:

$$\text{Bin size} = 1/(2 \times \text{maximum frequency})$$
$$\text{Number of bin} = \text{number of frequency value}\ .$$

Autocorrelograms were calculated during walking and resting phases to corroborate the results of power spectrum analysis.

Results

Spontaneous motor and neural activities in the basal ganglia regions

A constant number of infrared beam breaks (less than a 15% difference between sequential sessions) could be recorded after three to four sessions as each rat adapted to the experimental environment. The spontaneous motor activity patterns of the 12 rats, as measured by number of beam breaks, are depicted in Fig. 1. Rats typically displayed high levels of exploratory behavior early in the session, as was evident by the high frequencies of beam breaks within the first 10 min, and then became

relatively quiescent. However, some rats resumed a high level of activity later in the session.

Extracellular single neuron activity was recorded in four basal ganglia regions during spontaneous motor activity testing. A total of 129 neurons in the STR, 101 neurons in the GP, 79 neurons in the SNr and 46 neurons in the STN were recorded from the 12 rat subjects. The mean firing rates for the active and quiescent phases in each basal ganglia region are shown in Fig. 2. Firing rates significantly increased in all four recording regions during the active phase.

Principal component analysis was applied to the data from simultaneously recorded neurons within each basal ganglia region throughout the experimental session. Firing rate was also increased in the ensemble neural firing pattern. Figure 3 shows the first principal component (reflecting mainly the ensemble firing rate) of each basal ganglia region during the spontaneous locomotion task for two representative rats. One of these rats displayed a less active behavioral pattern (Fig. 3A) and the other rat a more active pattern with numerous beam breaks during the session (Fig. 3B). In spite of difference in motor activity patterns, the ensemble neural activity (represented by linear weighted population firing rate of each region) was increased during the active phases for both rats.

Single neural activity in the four basal ganglia regions during treadmill locomotion tasks

A regular walking pattern with smooth, active forward steps could be established after three to four training sessions. The rat was usually quiet during the 10–30 s random resting period. Slight movement might occur during the resting period, especially in the first few trials when the rat explored the new environment, but such movement was not comparable with continuous, active

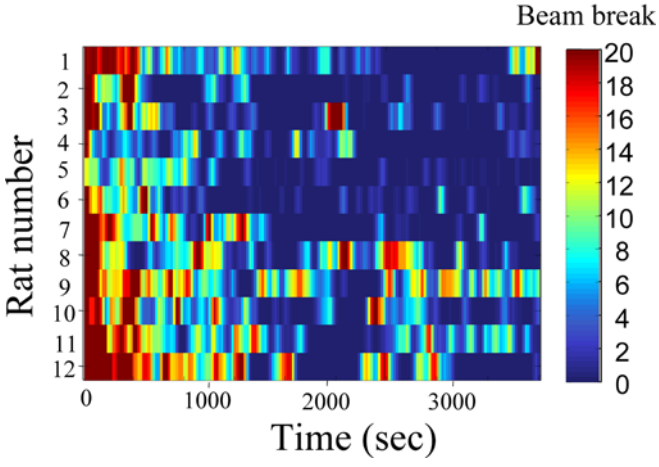

Fig. 1 Spontaneous motor activity of the 12 rats tested over 60 min experimental sessions. Motor activity was detected by infrared beams surrounding the chamber. The number of beam breaks is demonstrated by color scale presentation with 20 s bins. Note the higher motor activity during the first 10 min of the session for all 12 rats

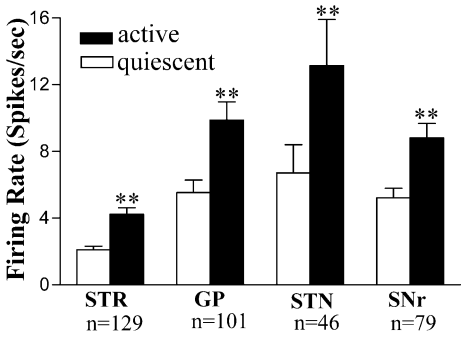

Fig. 2 Neural firing rates during the active and quiescent conditions of the spontaneous motor activity test. Averaged neural activity of neurons from all rats significantly increased during the active phase in all four basal ganglia regions (Student's *t*-test, $P<0.001$)

walking during the treadmill walking phase. A total of 311 neurons from the 12 rats were recorded during the treadmill experiment (105 in STR, 88 in GP, 70 in SNr and 48 in STN). Two major neural responses were found. One was associated with the auditory cue and the other was observed during treadmill locomotion. Peak responses immediately following the onset of tone at the beginning of treadmill locomotion were observed in all four basal ganglia regions. Responses ranged from 14% of the population in the SNr to about 30% of the population in the STR (Table 1).

Neural responses were more prevalent during the treadmill locomotion phase. More than half of neurons in the four basal ganglia regions altered their firing rates during the treadmill walking phase. The greatest portion of responsive neurons was observed in the STN where 85% of recorded neurons altered their firing rates during treadmill walking. Table 1 summarizes the neuronal responses associated with each behavioral event during the treadmill locomotion task for each basal ganglia region. Examples of neural responses are shown in Fig. 4. Similar to what had been found in the spontaneous movement condition, most neural responses during treadmill walking could be classified as excitatory (increased firing rate) and only a few neurons decreased their firing rates during treadmill walking. Figure 5 summarizes the mean firing rates of all neurons in each basal ganglia region during treadmill walking and resting phases. Note the significant increases in firing rate during the treadmill walking phase in all four basal ganglia regions.

Neural response patterns of the four basal ganglia regions were revealed in normalized firing rate plots from all subjects (Fig. 6A). As shown in Fig. 6B, six clusters representing different neuronal firing patterns during the treadmill locomotion were detected by a clustering analysis (K-means, SPSS Inc.). Each cluster includes neurons with similar temporal or scale (excitatory, inhibitory) firing patterns. Neurons in cluster 1 had a transient peak response coincident with the initiation of treadmill walking. Cluster 2 neurons had similar peak responses and their activity was related to the tone cues that preceded the onset of treadmill locomotion. Cluster 3 neurons peaked

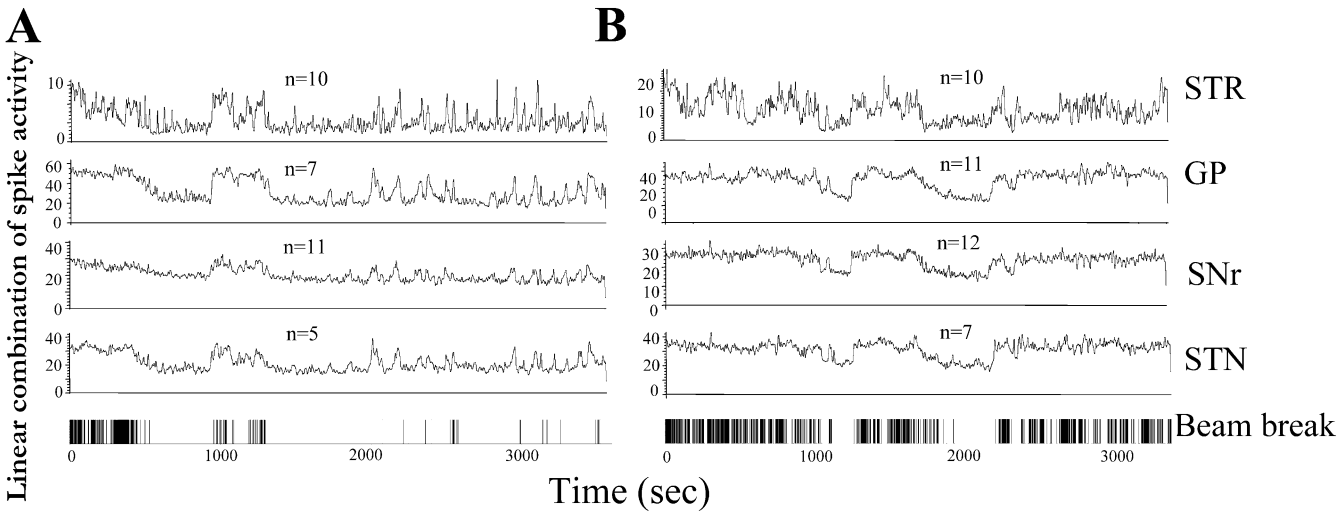

Fig. 3A, B Ensemble neural response as presented by principal component in four basal ganglia regions during spontaneous locomotion task. The first principal component from 5 to 11 neurons in each region is plotted in the *top four rows*. The infrared beam breaks are shown in the *bottom row*. Increases in neural firing rate in all four regions paralleled the increases in motor activity. Clear correlations between neural and motor activities were evident in both lower activity **(A)** and higher activity **(B)** subjects

immediately after treadmill walking initiation and maintained significantly higher discharge rates throughout the entire treadmill walking phase. Cluster 4 neurons were characterized by transient responses both at the start and the termination of treadmill walking and maintained an increased firing rate during treadmill walking. A few neurons with inhibitory responses during treadmill walking were classified into cluster 5. Most of these neurons also exhibited tone related responses. Cluster 6 consists of neurons with inhibitory responses to the tone and transient excitatory responses at the termination of treadmill walking. The distribution of clusters for each basal ganglia region is presented in Fig. 6C. Neural response patterns did not differ among rats. The cluster 3 neurons were most common with up to 78% of STN neurons displaying this kind of response, followed by 55% in the SNr, 41% in the STR and 38% in the GP. Line plots of these six clusters are shown in Fig. 6D to reveal detailed responses.

Basal ganglia neuronal activity related to limb movement

Video analysis of limb movement was performed for nine rats during the treadmill walking phase. Average step cycle, measured as the interval between front paw floor touches, was 0.96±0.33 s at the constant treadmill speed of 12 cm/s. For the forelimbs, the means of stance (when the paw remained on the floor) and swing (when the paw was in the air) phases were 0.72 s and 0.24 s, respectively. For the hind limbs, the means for stance and swing were 0.80 s and 0.16 s respectively. A total of 88 neurons in the STR, 69 neurons in the GP, 58 neurons in the SNr, and 43 neurons in the STN were analyzed to identify limb-related neural responses during treadmill walking.

Examples of neural responses before limb movement are shown in Fig. 7. Neural responses clearly associated with limb movement together with generally increased firing rates during the treadmill walking phase for representative STR and GP neurons are shown in Fig. 7A, B. In contrast, two neurons selected from the SNR and STN did not show limb movement related neural responses yet still fired at a significantly higher rate during the treadmill walking phase (Fig. 7C, D). This clear dissociation between neural responses associated with treadmill locomotion and limb movement was found in many neurons in all four basal ganglia regions. Table 2 summarizes the limb movement related neural responses in each basal ganglia region. Note that there are far fewer neurons with limb related responses than neurons with general motor responses during treadmill walking. Comparing the number of limb movement related neurons among basal ganglia regions revealed that more neurons in the STR and the GP displayed limb movement related activity; however, only the number in the STR differed significantly in comparison with that in the STN and the SNr (25% in the STR vs. 8.6% in the STN and 9.3% in the SNr, chi-square test, $P<0.05$).

Oscillatory neural activity during treadmill locomotion

Oscillatory firing pattern was measured by power spectrum analysis during treadmill walking and resting phases. Only a few neurons located in the STR (5/105 4.8%) and the GP (3/88 3.4%) displayed oscillatory neural firing patterns during the treadmill walking phase. Both the frequencies of oscillatory activity and of the step cycle in the corresponding session were around 1 Hz (Fig. 8). However, many neurons with limb related activity did not show oscillatory firing during treadmill walking. No oscillatory firing pattern was found during the spontaneous locomotion task in any of the basal ganglia regions studied.

Table 1 Neural responses in the four basal ganglia regions during the treadmill task. *Boldface numbers* are from areas with maximal percentage of neurons responded to the respective event. More STR neurons responded after tone delivered (0–1 s after tone), and more STN neurons responded during treadmill walking phase. A response is defined as a significant rate change ($P < 0.05$, Student's *t*-test) compared with background firing (0–10 s before treadmill turned on, and 0–2 s before tone delivered). Total response neurons refer to the number of neurons responded at least once to tone stimuli and different phase of treadmill walking. Initial responses refer to the neural responses occurred at initiation of treadmill walking. Excitatory and inhibitory responses refer to the continuous responses during 20 s treadmill walking phase. Termination responses refer to the responses at the termination of treadmill walking phase

Brain area	Total no. neurons	Tone response neurons		Treadmill walking									
		N	% of total	Total response neurons		Initiation		Excitatory		Inhibitory		Inhib./exc.	Termination
				N	% of total	*N*	% of total	*N*	% of total	*N*	% of total	Ratio	*N*	% of total
STR	105	31	**29.5**	81	77.1	26	24.8	64	61.0	6	5.7	0.09	11	10.5
GP	88	19	21.6	56	63.6	21	23.9	40	45.4	9	10.2	0.22	7	8.0
SNr	70	10	14.3	55	78.6	27	38.6	41	58.6	5	7.1	0.12	3	4.3
STN	48	12	25	41	**85.4**	29	60.4	37	77.1	0	0	0	0	0

Fig. 4A, B Neural responses during tone presentation and treadmill locomotion. **A** Raster and perievent histogram showing the different neural responses to the cue tone (200 ms duration) that was presented 1.5 s before the start of treadmill. A STR neuron (*left panel*) decreased its firing rate and a STN neuron (*right panel*) increased its firing rate immediately after the tone presentation (at 0 s time point). **B** Different neuronal responses in the basal ganglia regions during treadmill locomotion. Transitional responses at the start and termination of treadmill locomotion in a GP neuron. A sizable drop in spike discharge occurred immediately at the start and termination of treadmill walking (indicated by *arrows*). A STR neuron increased its firing rate during treadmill walking. A SNr neuron decreased its firing rate throughout the treadmill walking period. An increase in firing rate was found in a STN neuron during the walking period

Histological localization of recording sites

Potassium ferricyanide staining revealed recording sites as blue dots in the STR, GP, STN and SNr. Figure 9 shows the locations of recording sites included in this report.

Discussion

Despite extensive research in basal ganglia physiology, the question as to how the basal ganglia regulate motor activity is far from clear. The theory of involvement of basal ganglia in movement initiation is based on the close

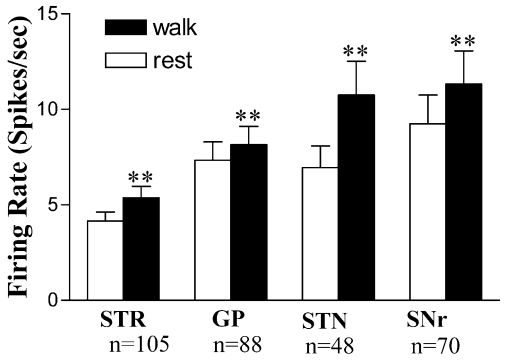

Fig. 5 Mean firing rates of neurons from the 12 rats during treadmill walking and resting phases. *Bars* represent the neural activity in different basal ganglia regions (mean ± SEM). Significant increases in firing rates during treadmill walking phase were found in all four basal ganglia regions recorded (Student's *t*-test, $P<0.001$)

correlation between movement disorders and abnormality of basal ganglia function and is supported by the observation that 'set' signals appear in the basal ganglia before trained movement (Apicella et al. 1992; Romo and Schultz 1992). Another theory emphasizes the regulatory role of basal ganglia in the movement, which is based on findings that more neurons in the cortical regions exhibit anticipatory activity than those in the STR, suggesting that 'set' signals observed in the STR reflect the cortical input (Apicella et al. 1992). Studies also found that basal ganglia neural activity lagged the onset of movement (Alexander and Crutcher 1990; Anderson and Horak 1985, Mink and Thach 1991), further supporting the latter theory that cortical motor signals are processed through direct and indirect basal ganglia pathways to ensure the accurate execution of movement. Two models may account for the regulatory role of the basal ganglia: the scaling model (DeLong 1990; Alexander and Crutcher 1990) and focused selection and inhibition of competing motor program model (Mink 1996). The present study is

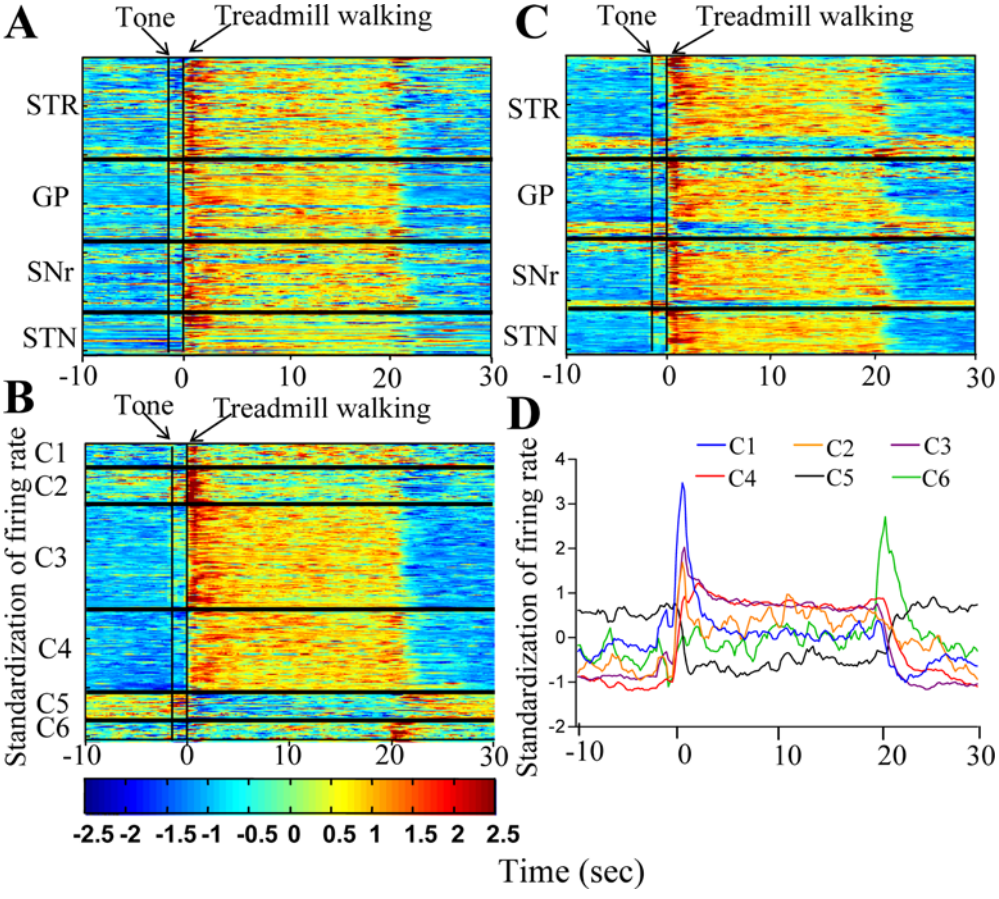

Fig. 6A–D Color-coded neural firing in four basal ganglia regions during the treadmill locomotion test. Each *line* represents normalized firing rate of one neuron averaged from 90 treadmill trials in one experimental session. Normalized firing rate from 10 s before to 10 s after treadmill walking (20 s duration) are shown. Cold color (*blue*) represents lower firing rate and warm color (*red*) represents higher firing rate. **A** Standardized firing rate during a treadmill session sorted according to the recording regions. **B** Six types of firing patterns were revealed by cluster analysis. Most common neural firing patterns were those grouped into clusters 3 and 4, which exhibited significant increases in firing rates during the treadmill walking phase (from 0 to 20 s). Some neurons decreased their firing rates during treadmill walking (*C5*) or had robust peak responses at the start of treadmill walking (*C1, C2*). **C** Clusters arranged according to recording regions. Inhibitory neural responses during treadmill locomotion were found in the STR and GP. **D** Detailed features of six clusters depicted in **B**

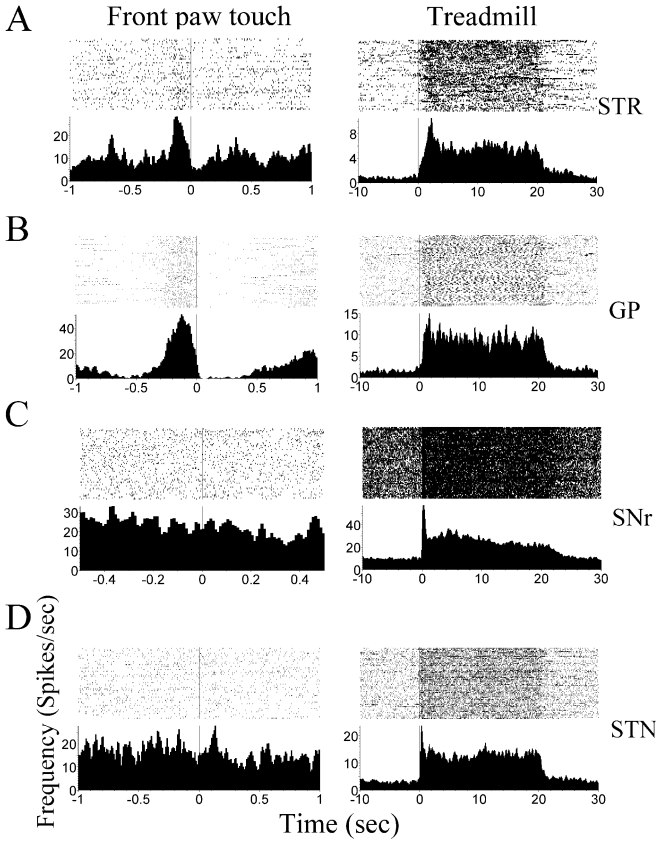

Fig. 7A–D Neuronal responses related to limb movement. **A** A STR neuron responded before the front paw touched the treadmill (*left panel* at 0 s timepoint). A transient increase in spike activity was found 200 ms before touch. The same neurons showed a robust increase in firing rate during treadmill walking (*right panel*). Note that the peak responses before paw touch were much higher (near 30 spikes/s) than the average firing rate during treadmill walking (around 6 spikes/s), which was significantly higher than the firing rate during resting (around 2 spikes/s). **B** An example of a GP neuron that responded before the front paw touched the ground; peak responses took place 200 ms before the touch (*left panel*). An eight- to tenfold increase in firing rate occurred during treadmill locomotion. The peak responses, visualized in the raster plot as dense spots across the 20 s treadmill walking period (*right panel*) before the paw touch (above 40 spikes/s), were much higher than the average firing rate during treadmill locomotion (8–10 spikes/s). **C, D** Examples of excitatory responses during treadmill locomotion unrelated to limb movement in SNr **(C)** and STN **(D)** neurons

designed to seek electrophysiological evidence for the involvement of basal ganglia in the natural movements during modes of locomotion.

Numerous electrophysiological studies have revealed specific relationships between cell discharge and both movement of individual body parts and parameters of movement in the STR (Crutcher and DeLong 1984a, 1984b), the STN (Georgopoulos et al. 1983; Wichmann et al. 1994a, 1994b), and the GP (Georgopoulos et al. 1983; Wannier et al. 2002). Other studies have reported that neurons in the SNr were acutely involved in eye and facial muscle movements (DeLong et al. 1983; Hikosaka and Wurtz 1983; Basso and Wurtz 2002; Sato and Hikosaka 2002). Electrophysiological studies have also been carried out in the basal ganglia in freely moving rats. Both STR and GP neurons responded in similar proportions, to the cue and to head movement (Gardiner and Kitai 1992). Neostriatal neural activity related to general and reaching movements were observed in behaving rats (Haracz et al. 1989; Dolbakyan et al. 1977; Trytek et al. 1996; Rebec et al. 1997; West et al. 1997). These studies demonstrate that the basal ganglia play an important role in motor regulation. However, information obtained from single basal ganglia structures in isolation may not be sufficient to elucidate how the basal ganglia function as an integrated subcortical system to process motor command.

The present study employed a multiple channel, single unit recording technique to investigate basal ganglia neural functioning during general body movement by recording simultaneously from four major basal ganglia regions during spontaneous and treadmill locomotion tasks. Both tasks involved natural movement without complicated behavioral training. In general, all four basal ganglia regions, the STR, the GP, the STN and the SNr, exhibited movement related neural responses and most of these were excitatory. There are differences in resting neural activity between spontaneous and treadmill locomotion tasks, which reach significant levels in the STR and SNr. Different behavioral contexts during these two tasks probably account for the difference in firing rate. During the quiescent phase of spontaneous movement, the rat appeared to rest passively in the freely moving environment, while during the resting phase of treadmill locomotion the rat stopped moving after the termination of treadmill, apparently anticipating the start of next treadmill cycle. The neural activity in these two resting conditions is expected to differ. The firing rate of SNr neurons is

Table 2 Neural responses before limb movement in each basal ganglia region during treadmill walking. Neurons in different regions showed different response percentages to limb movement during treadmill walking. The STR and GP had a higher percentage of neurons that responded to limb movement during treadmill walking, but there was only a significantly greater percentage of responsive neurons in the STR (chi-square test, $P<0.05$)

Brain area	STR	GP	SNr	STN
Rate of response	25.0% (22/88)	18.8% (13/69)	8.6% (5/58)	9.3% (4/43)
GP	$P=0.3574$			
SNr	$P=0.0126$	$P=0.1000$		
STN	$P=0.0344$	$P=0.1712$	$P=0.9054$	

$\chi^2=8.826$, $P=0.0317$

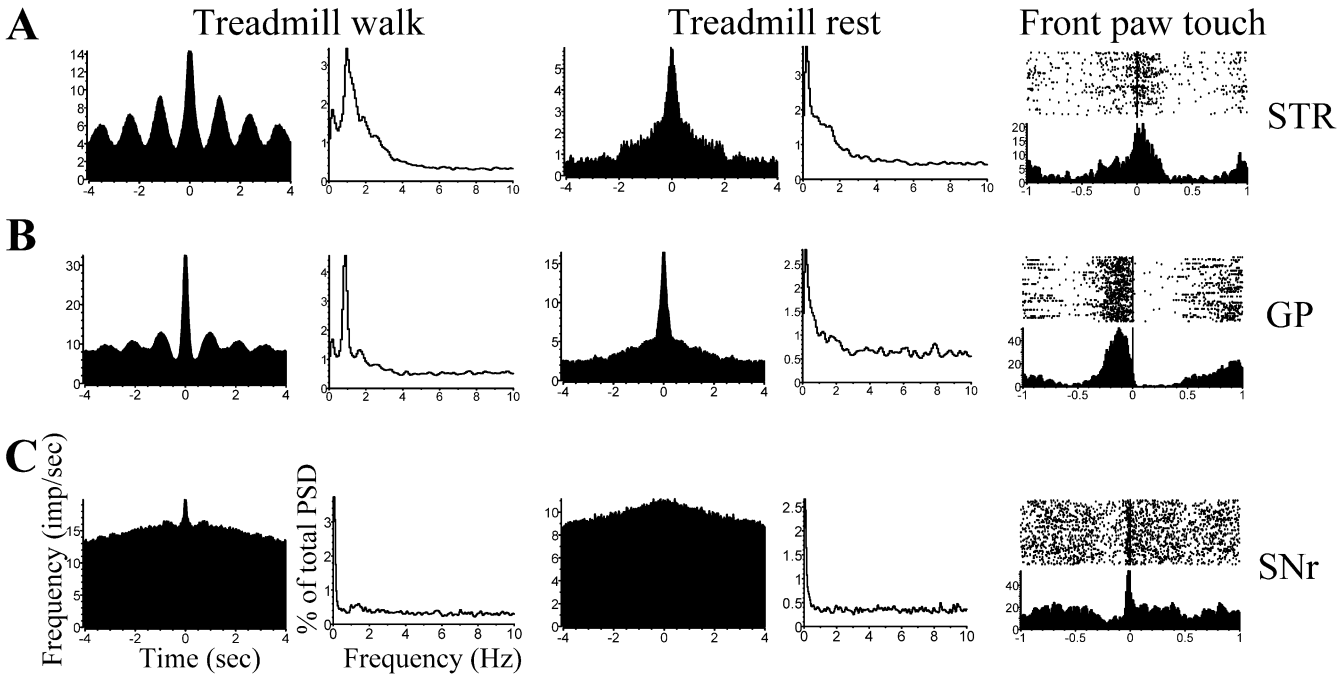

Fig. 8A–C Oscillatory neural activity during treadmill locomotion. **A** A STR neuron oscillated during treadmill walking but not resting. An autocorrelogram showed an oscillatory firing pattern during treadmill walking (*top left panel*) but not in the resting (*top middle panel*) phase. Power spectrum density analysis (displayed besides the autocorrelogram plot) revealed a peak at 0.9 Hz during treadmill walking phase. Raster and perievent histogram (*right panel*) revealed increased spike activity around the time the front paw touched the ground. **B** A similar phenomenon appeared in this GP neuron. **C** A SNr neuron with limb related neural responses did not oscillate during treadmill walking

relatively lower in this study in comparison with other reports (Burbaud et al. 1995; Gulley et al. 1999; Benazzouz et al. 2000). The lower firing rate could be due to a feature of the neuron sorting method used in this study. In addition to amplitude, the computerized spike sorting system employed in our experiment also used spike duration and ascending/descending trajectory of waveforms to sort neurons. This method may have imposed more strict criteria for neuron selection and give rise to a lower firing rate in comparison with other recording methods.

Such overall excitatory neural responses among all four basal ganglia regions during locomotion seem to be inconsistent with the current simplified model of the basal ganglia thalamocortical pathways. According to the model, motor signals initiated from cortical regions activate medium spiny GABAergic neurons of the dorsal striatum. The excitatory responses in the dorsal lateral striatum observed in the present study are in accordance with this model, and are consistent with numerous results obtained from studies in both primate and rat (Crutcher and DeLong 1984a, 1984b; Gardiner and Kitai 1992;

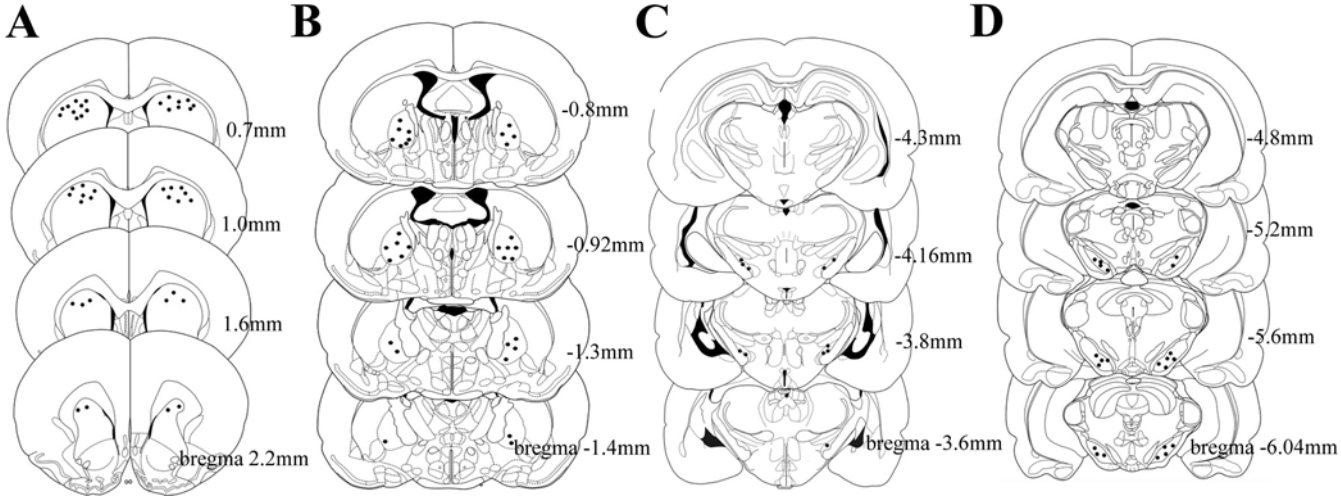

Fig. 9 Histological localization of tips of recording electrodes in the four basal ganglia regions: **A** STR; **B** GP; **C** STN; **D** SNr

Rebec et al. 1997; West et al. 1997). Striatal outputs are divided into direct and indirect pathways. In the direct pathway, an enhanced inhibitory striatal output should suppress the neural activity in the SNr, one of the final output stations of the basal ganglia system. However, activation of SNr neurons during movement was observed in the present study, a result potentially in conflict with the direct pathway model. A previous study also revealed a similar increase in SNr activity during spontaneous movement in an open field arena (Gulley et al. 1999). An explanation for this paradoxical outcome may be that the indirect pathway, via inhibitory (striatum)-inhibitory (globus pallidus)-excitatory (subthalamic nucleus) connections, exerts its final excitatory effects on SNr neurons. In addition, motor signals from the cortex have been found to drive the STN via direct glutamatergic projections (Kitai and Denian 1981; Ryan and Clark 1991; Fujimoto and Kita 1992; Maurice et al. 1999; Nambu et al. 2000). Activation of this proposed "hyperdirect" pathway would increase the neural activity in the SNr (Nambu et al. 2002). The predominantly excitatory responses found in the SNr suggest indirect and hyperdirect pathways may both play a significant role in regulating movement.

According to a model postulated by Mink (1996), the basal ganglia may regulate voluntary movement by simultaneously inhibiting competing movement and facilitating desired movement. This could be achieved by broad elevation of basal ganglia inhibitory output from the GPi/SNr (via an excitation of the STN), thus inhibiting competing movement, and by a selective decrease in basal ganglia inhibitory output triggered by direct inhibitory input from the STR, thus releasing the desired voluntary movement. Overwhelming excitatory responses found in the STN seem to be in line with the scenario of a broad elevation of basal ganglia output which inhibits competing movement. The few neurons in the SNr exhibiting inhibitory responses during locomotion may represent the neural circuits responsible for desired movement, which occurs when the motor signals are released from the tonic basal ganglia inhibition.

In primate studies, one paradoxical phenomenon was that both the GPi and the GPe neurons were found excited during the movement (Anderson and Horak 1985; Mitchell et al. 1987; Mink and Thach 1991). Similar excitatory GPe responses were found in the present study. In spite of a majority of neurons exhibiting excitatory responses (4:1 ratio for excitatory/inhibitory neurons), more inhibitory neurons were found in the GP than in any other basal ganglia regions. Since the GP receives enhanced striatal inhibitory (indirect pathway) input during locomotion, a relatively larger number of inhibitory neurons found in the GP may reflect the activation of the indirect pathway during movement. A predominance of excitatory neuronal responses exhibited in the GP during locomotion suggests that sources other than striatal input may play additional roles in the motor processing. A candidate for such sources is the excitatory input from the STN (Nambu et al. 2000). Overall the present study did not provide evidence for the postulated indirect pathway linkage between inhibitory (GP) and excitatory (STN) sites. The results imply that complex basal ganglia thalamocortical neural processes may be involved in motor control, which requires precisely coordinated information flow within the basal ganglia thalamocortical pathway to regulate voluntary movements. This information can be transmitted not only in the form of firing rate, but can also be coded in the form of temporal and spatial firing patterns of ensemble neural activities within the basal ganglia neural circuit.

More neurons in the STR and STN displayed auditory responses to the cue tone immediately before the onset of treadmill locomotion. Similar sensory responses have been reported in the STR of rat (Gardiner and Kitai 1992; White and Rebec 1993) and primate (Crutcher and DeLong 1984a, 1984b; Schulz and Romo 1988, 1992). Plentiful neural responses in the STR and STN to poly-sensory stimuli were not unexpected since these regions receive abundant distributed cortical afferents (Wise and Jones 1977; Donoghue and Herkenham 1986; McGeorge and Faull 1989; Ebrahimi et al. 1992; Kitai and Denian 1981; Canteras et al. 1988; Kolomiets et al. 2001). The finding that some of the neurons responded to both tone cue and locomotion indicates that sensory and motor signals can converge in the same basal ganglia neurons. One striking feature of sensory response neurons is that many of them decreased their firing rates during treadmill locomotion, while most motor related neurons increased in their firing rate. This result suggests that sensory processing is partially separated from the major motor circuit in the basal ganglia and may be engaged in preparation, but not execution, of motor action during the cued treadmill locomotion task.

Detailed studies carried out in rats provide clear evidence for functional representations of individual limbs in the dorsal lateral striatum of the rat, within a subregion containing projection terminals from the sensorimotor cortex (West et al. 1990). A similar percentage of limb movement related neurons was found in the dorsal lateral striatum in the present study (25% in our study versus 18% in West's study). The dorsal lateral striatum receives abundant input from the sensorimotor cortex and is likely to differ functionally from the medial striatum region where few limb movements related neural responses were found (West et al. 1997; Haracz et al. 1989). To a lesser extent, other basal ganglia regions also exhibited neural responses related to limb movement. Overall, the neurons in the STR and the GP, the upstream part of the basal ganglia, revealed more limb movement related neural responses than the STN and SNr. Fewer limb related neural responses in the STN and SNr could be attributed to the diminished dorsal lateral striatal inputs owing to the convergence of the inputs from other parts of the striatum onto the same STN or SNr neurons. Furthermore, the convergence of direct/indirect pathway inputs into the SNr and of cortical/indirect pathway inputs into the STN may further compound the specific motor signals related to limb movement. Few studies have described in detail the topographic distribution of motor inputs to the STN and SNr in the rodent (Deniau and

Thierry 1997). In addition, specific targeting of the subregions of these structures is very difficult due to the small size of the STN and SNr. For example, in the present study the successful targeting rate for the STN was only around 30% of rats implanted. This indiscriminant targeting may also account for low percentages of limb related neurons in the STN and the SNr being detected. In light of the high rate of general motor responses and the low rate of limb related responses in all basal ganglia areas, we postulate that rather than directly conveying motor command signals from the cortex, the basal ganglia may provide an active background within which the cortical motor signals can be processed properly to control body movement.

Oscillatory firing in the basal ganglia was rarely found in this study and only occurred during the treadmill walking phase. Since the oscillatory neurons also exhibited limb movement related neural responses and the oscillatory frequency was similar to that of the step cycle, it is most likely that the oscillatory firing patterns reflected the step cycle during treadmill walking. Although few oscillatory firing patterns were detected in the basal ganglia of intact animals, increased oscillatory firing patterns have been detected frequently in the animal model of Parkinson's disease in which the nigrostriatal dopamine system has been destroyed (Bergman et al. 1994; Hutchison et al. 1997; Wichmann et al. 1999), and clinical reports have revealed tremor related oscillatory firing in the GP and STN in PD patients. Such results support the idea that dopamine normally plays an important role in maintaining separate, parallel basal ganglia neural processing. Oscillations with multisecond range periods have been found in the basal ganglia of different species and this low frequency oscillation was unaffected by dopaminergic lesions (Allers et al. 2000; Wichmann et al. 2002). The functional implication of this slow oscillation is unclear, but appears to be related to the state of arousal and task performance (Steriade 1999; Trimmel et al. 1990). Our analytic methods (power spectrum analysis in Nex program) are unable to explore the oscillatory frequency at very low ranges and whether such low frequency oscillation is involved in motor activity remains to be analyzed.

In summary, the present study demonstrates an extensive activation of major basal ganglia regions during the spontaneous and treadmill locomotion tasks. Neural responses associated with sensory cue, and the initiation and termination of treadmill locomotion, were also detected in multiple basal ganglia regions in different proportions. Limb movement related neural activity was found primarily in the striatum and to a much less extent in the STN and SNr downstream. The results suggest that activation of the entire basal ganglia is associated with executing normal motor function. This overall activation of the basal ganglia is more likely to provide active background for processing of cortical command signals, possibly by tonic inhibition of competitive movement, rather than to be directly involved in the programming of precise movements.

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