Exp Brain Res (2005) 162: 407–416
DOI 10.1007/s00221-004-2035-6

RESEARCH ARTICLE

Ziv M. Williams · Joseph S. Neimat
G. Rees Cosgrove · Emad N. Eskandar

Timing and direction selectivity of subthalamic and pallidal neurons in patients with Parkinson disease

Received: 11 February 2004 / Accepted: 15 May 2004 / Published online: 6 January 2005

Abstract Current models of basal ganglia function suggest that some manifestations of Parkinson disease (PD) arise from abnormal activity and decreased selectivity of neurons in the subthalamic nucleus (STN) and globus pallidus internus (Gpi). Our goal was to examine the timing and direction selectivity of neuronal activity relative to visually guided movements in the STN and Gpi of patients with PD. Recordings were made from 152 neurons in the STN and 33 neurons in the Gpi of awake subjects undergoing surgery for PD. Corresponding EMG data were obtained for half the cells. We employed a structured behavioral task in which the subjects used a joystick to guide a cursor to one of four targets displayed on a monitor. Each direction was tested over multiple trials. Movement-related modulation of STN activity began on average 264 ± 10 ms before movement initiation and 92 ± 13 ms before initial EMG activity, while modulation of Gpi activity began 204 ± 21 ms before overt movement initiation. In the STN, 40% of cells demonstrated perimovement activity, and of these 64% were directionally selective. In Gpi, 45% of cells showed perimovement activity of which 80% were selective. In both nuclei, directionally selective cells had significantly lower baseline firing rates than non-selective cells (41 ± 5 vs 59 ± 4 spikes/s in STN, and 50 ± 9 vs 74 ± 15 spikes/s in Gpi). These results suggest that STN activity occurs earlier than previously reported, and that higher neuronal firing rates maybe associated with decreased direction selectivity in PD patients.

Z. M. Williams · J. S. Neimat · G. R. Cosgrove
E. N. Eskandar (✉)
Department of Neurosurgery, Massachusetts General Hospital,
Harvard Medical School, 15 Parkman Street,
ACC-021, Boston, MA 02114, USA
E-mail: eeskandar@partners.org
Tel.: +1-617-7246590
Fax: +1-617-7240339

Keywords Subthalamic nucleus · Globus pallidus internus · Direction selectivity · Neurons

Introduction

The current understanding of basal ganglia circuitry suggests that loss of dopaminergic neurons in Parkinson disease (PD) results in abnormal neuronal activity in the subthalamic nucleus (STN) and globus pallidus internus (Gpi) (Albin et al. 1989; Alexander and Crutcher 1990a; Bergman et al. 1990; Delong 1990; Wichman et al. 1994b). Based on these findings, and a growing body of clinical data, the Gpi and STN are now the preferred targets for the treatment of PD (DBS Study Group 2001). Options for treatment include the placement of deep-brain stimulating electrodes (DBS) in either nucleus or ablating a portion of the Gpi (pallidotomy), with the goal of reducing or modifying abnormal neuronal activity (Alkhani and Lozano 2001; DBS Study Group 2001). During surgery, microelectrode recordings are commonly used to localize the target nuclei (Hutchison et al. 1998; Lozano et al. 1996). Neuronal activity related to movement is usually assessed intraoperatively by using passive limb movements or relatively unconstrained voluntary movements (Abosch et al. 2002; Magarinos-Ascone et al. 2000; Magnin et al. 2000; Rodriguez-Oroz et al. 2001). While these techniques are useful for identifying motor territories, they are not reproducible and do not allow for precise determination of the timing of behavioral events relative to neuronal activity.

The timing of basal ganglia activity relative to movement has been the subject of some controversy. Many manifestations of PD encompass difficulties in movement initiation. However, primate studies have suggested that modulation of activity in the STN and Gpi occurs at about the same time as EMG activity,

and is thus too late to be involved in movement selection or initiation (Anderson and Horak 1985; Georgopoulos et al. 1983; Mink and Thach 1991b; Wichmann et al. 1994a). To investigate this issue, we employed a structured behavioral paradigm in the operating room, similar to tasks previously used in awake behaving primates, to determine the timing of movement-related activity in the STN and Gpi (Eskandar and Assad 1999).

Another important property of basal ganglia neurons is direction selectivity, which has been demonstrated in the primate putamen, Gpi, and STN (Crutcher and Alexander 1990; Crutcher and Delong 1984a; Delong et al. 1985; Georgopoulos et al. 1983; Jaeger et al. 1995; Mitchell et al. 1987; Wichman et al. 1994a). Direction selectivity refers to the propensity of neurons to exhibit increased firing rates in relation to a particular direction of movement and to a lesser extent for other directions of movement. It has been suggested that increased firing rates in the STN and Gpi are associated with decreased selectivity and may thus contribute to the pathology of PD (Bergman et al. 1998; Boraud et al. 2000; Levy et al. 2001).

In the present study, we find that changes in the activity of STN and Gpi neurons of PD patients can occur relatively early in relation to movement initiation. Furthermore, we find that direction selectivity exists in a significant fraction of neurons, and that there may be a relationship between higher firing rates and diminished direction selectivity in PD patients.

Materials and methods

Patient selection

We recorded the activity of single neurons in the STN or Gpi of patients undergoing surgery for the treatment of PD. Informed consent was obtained in accordance with a protocol approved by the Massachusetts General Hospital Institutional Review Board. Patients included in the study had idiopathic PD with a duration of greater than 4 years and a Hoehn-Yahr score of 3 or higher. Candidates were excluded from surgery if they had a Parkinson ''plus'' syndrome, cognitive impairment, active psychiatric disorders, or anatomic abnormalities on magnetic resonance imaging (MRI). None of the patients had prior surgery for treatment of PD. Data were obtained from the STN of eight subjects and the Gpi of two subjects. This included five males and five

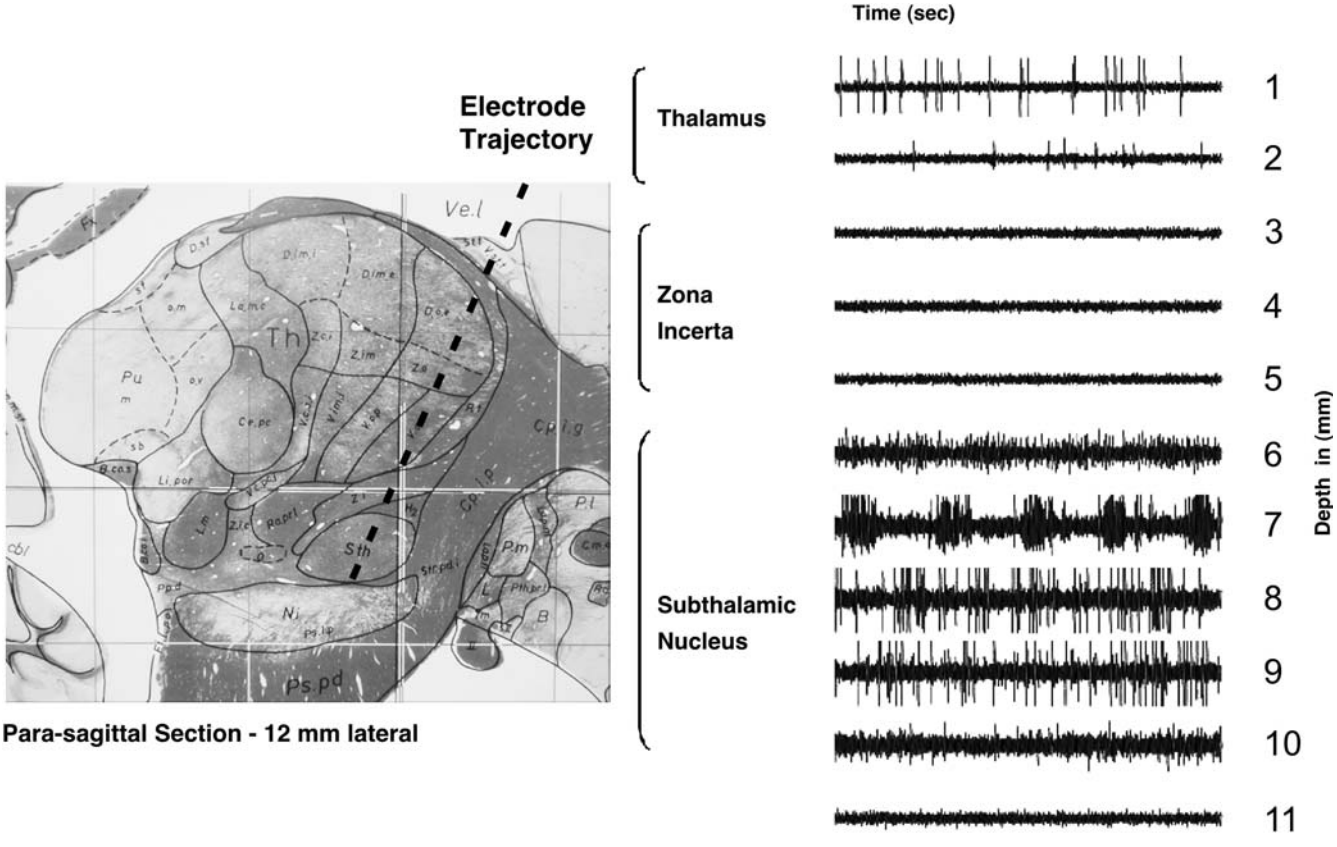


Fig. 1 Subthalamic nucleus (STN) localization. Reconstruction of single electrode trajectory superimposed on a sagittal atlas section 12 mm from midline is shown on the *left* (Schaltenbrand and Wahren 1977). Corresponding neuronal activity tracings recorded over 1-s intervals are shown on the *right*

females. The average age was 62 years (range 45–75 years).

Electrophysiology

In all patients, anti-parkinsonian medications were withheld starting the night before surgery. Patients were given a short-acting benzodiazpene (midazolam) while the stereotactic frame was being placed, but no other sedatives were given during the surgery. The stereotactic localization and general techniques of intraoperative microelectrode recordings are described elsewhere (Eskandar et al. 2000; Hutchison et al. 1998; Lozano et al. 1996). We used an array of three tungsten microelectrodes, separated by 2 mm and placed in a parasagittal orientation. The electrodes were advanced simultaneously using a motorized microdrive. Amplification of the neuronal signal and control of the microdrive were handled by a dedicated intraoperative system (Alpha Omega, Nazareth, Israel). The behavioral paradigm was controlled by a Macintosh G4 computer. Neuronal activity was band-pass filtered (300 Hz to 6 kHz) and sampled at 20 kHz. The neuronal, behavioral, and EMG data were stored on a third computer equipped with a Cambridge Electronics Design (CED) system (Cambridge, England). Spikes were sorted off-line using a standardized template-matching algorithm (Lewickiy 1998).

EMG activity was recorded at 1,000 Hz using tin-disk surface electrodes to ensure broad and early detection of activity (Lee and Assad 2003). We recorded EMG activity primarily from the biceps and triceps. Early on, we made recordings from the forearms, biceps, triceps, and deltoid. We found that the biceps and triceps had the earliest, largest, and most reliable activation. These results are similar to those obtained in primates performing a nearly identical task (Lee and Assad 2003).

Anatomic localization

During surgery, microelectrode recordings were used to localize the STN or Gpi. Both nuclei have characteristic high firing rates in comparison to the surrounding structures and have clear dorsal and ventral borders that are evident when reconstructing neuronal activity along the electrode trajectories (Fig. 1). Cells used for analysis were recorded from the motor subterritories of each nucleus based on stereotactic localization, reconstructions of the electrode trajectories, and the presence of audible responses to passive or spontaneous limb movements. Once we were in the motor subterritory of either nucleus, as identified by activation on passive movement, we began recording at relatively regular 0.5-mm intervals. Subthalamic neurons were recorded primarily from the dorsal-lateral portion of the nucleus whereas pallidal neurons were recorded from the posterior-ventral Gpi.

Behavioral paradigm

Once the microelectrodes were in the target nucleus, we asked the patients to view a computer monitor and perform the behavioral task while using a joystick with the contralateral hand. The joystick was mounted such that movements were in a horizontal orientation with the elbow flexed at about 45°. Each trial began with the presentation of a small central fixation point (Fig. 2). After a brief delay, four small gray targets appeared arrayed in a circular fashion around the fixation point. After another delay period, a randomly selected target turned green. At this point the subject used a contralaterally mounted joystick to guide a small cursor arising from the center of the monitor toward the green target. Once the target was reached, a tone sounded indicating the patient had successfully completed the task, and the stimuli were erased. Patients were required to reach the target within 5 s of the green cue presentation, although in practice, they typically reached the target within 1 s of

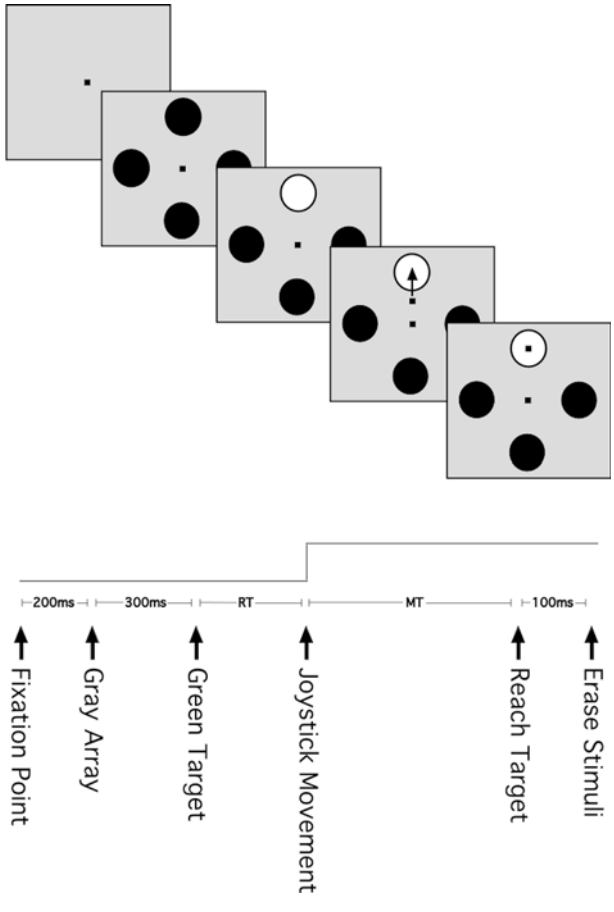


Fig. 2 Behavioral task. *Top* Schematic representation of what the patient sees on the monitor while performing the task. *Bottom* Sequence of events for a single trial

the onset of the stimulus. There was an intertrial interval of 1,000 ms. The patients were required to return the joystick to the center position before a new trial started. If the patient prematurely moved the joystick, strayed beyond the confines of an invisible corridor, failed to reach the target, or failed to return the joystick to its central position, the trial was aborted and excluded from analysis. All trials were pseudorandomized to ensure an equal number of trials in each direction. Patients typically performed 12–24 correct trials in each direction. Each recording run lasted about 3–5 min

Analysis

Auto-correlograms were computed for all spike trains and only those with a clear refractory period of at least 3–5 ms were included in the analysis. Rasters and peristimulus histograms were constructed for all recorded neurons, and were aligned on the start of hand movement as determined by an initial 1° deflection of the joystick (from a possible range of 18°). The onset of neuronal activity was determined using an algorithm wherein two adjacent sliding windows 100 ms in length were advanced by 10-ms increments along the histogram. At each position, a Mann-Whitney *U*-test was used to determine whether the firing rates within the two windows were significantly different ($P < 0.05$). The onset of activity was defined as the midpoint of the pair of windows having the greatest difference in firing rates (Jaeger et al. 1995; Fig. 3A). We elected to use the greatest rate of change instead of the first significant change as it exhibited less variability and was less sensitive to sporadic changes in activity (Fig. 3C). We calculated the onset times using alternative methods and the results were quite similar (Anderson and Horak 1985; Bergman et al. 1994; Georgopolous et al. 1983; Mink and Thach 1991a; Mitchell et al. 1987). The onset time of EMG activity was assessed in a similar fashion. The EMG tracings were aligned to the start of joystick movement and the onset of activity was again defined as the midpoint of the two windows with the greatest difference in amplitude (Fig. 3B).

In order to assess perimovement modulation, a paired *t*-test ($P < 0.05$) was used to compare a 500-ms epoch of baseline activity, beginning 1,500 ms prior to movement, to a 500-ms epoch centered at the time of hand movement (Anderson and Horak 1985; Anderson and Turner 1991; Mitchell et al. 1987). If there was a significant change for any of the four directions then the cell was defined as having movement modulation. To assess direction selectivity, a one-way ANOVA ($P < 0.05$) was performed on the responses for the four different directions in each of two epochs, a 500-ms epoch prior to the initiation of hand movement and a 500-ms epoch following the initiation of movement (Crutcher and Delong 1984b; Mitchell et al. 1987).

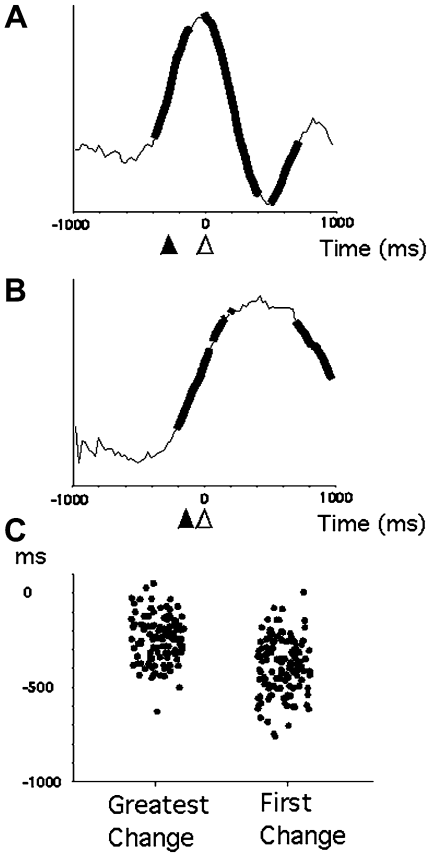


Fig. 3A–C Method for calculating neuronal and EMG activity onset times. Peristimulus histogram of neuronal activity for one direction of movement in a single cell (**A**), and average EMG activity for the same cell and same movement direction (**B**). *Thick lines* indicated areas along the curve with a significant change in activity between the two adjacent sliding windows (Mann-Whitney *U*-test, $P < 0.05$). *Solid arrowheads* indicate the time of greatest change in activity and *open arrowheads* indicate onset of joystick movement. **C** Distribution of neuronal activity onset times calculated according the largest change versus first significant change using the above method. Only cells with significant perimovement modulation are displayed

Results

Movement modulation and activity onset

A total of 185 cells were recorded from ten patients undergoing surgery for the treatment of PD. Of these, 152 cells were recorded from the STN and 33 cells from the Gpi. In the STN, 61 cells (40%) demonstrated significant perimovement modulation compared to baseline (two-tailed *t*-test, $P < 0.05$). In the Gpi, 15 cells (45%) were significantly modulated by hand movement (two-tailed *t*-test, $P < 0.05$). In STN cells with significant perimovement modulation, the change from baseline activity began on average 264 ± 10 ms prior to movement (see Materials and methods; Fig. 4A). The timing of activity onsets occurred over a wide range with some cells exhibiting a change in firing rate preceding the actual movement by up to 400 ms. Movement-related

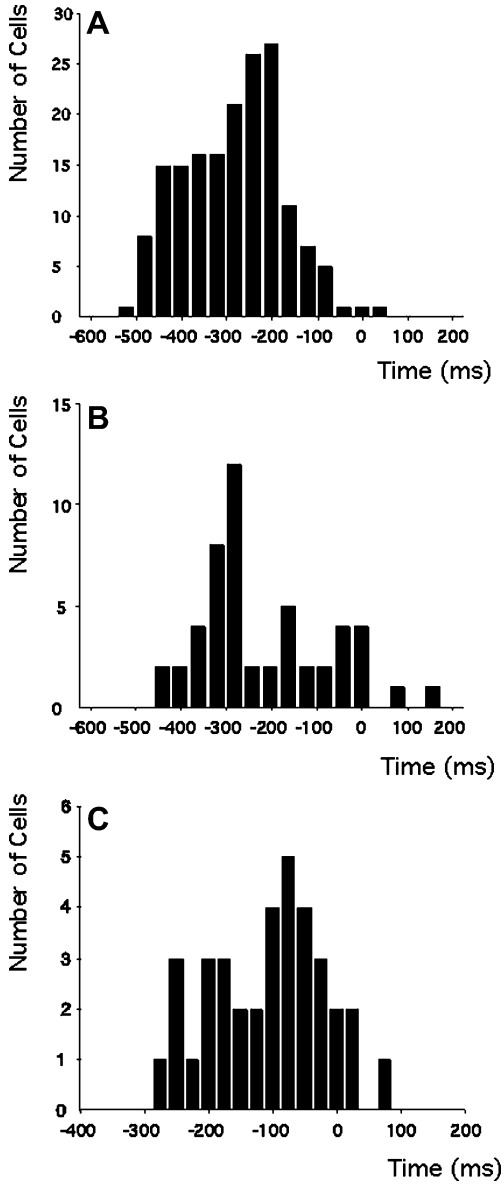


Fig. 4A–C Onset time of neuronal activity. **A**, **B** Distribution of neuronal activity onset times relative to the start of joystick movement (time 0) for the STN and globus pallidus internus (Gpi), respectively. **C** Distribution of neuronal activity onset times relative to the start of EMG activity (time 0) for STN neurons

changes in Gpi cells with significant modulation began somewhat later than the STN with an average onset beginning 204 ± 21 ms prior to movement (Fig. 4B). Once again the initial change from baseline activity occurred over a broad range of times.

In total, 89 STN cells were recorded in conjunction with simultaneous EMG recordings from the biceps and triceps. Among the STN cells tested in conjunction with EMG recordings, the average onset of neuronal activity occurred 266 ± 14 ms prior to the hand movement, and 92 ± 13 ms prior to the first EMG activity (Fig. 4C). The mean reaction time (RT) between the onset of the cue stimulus and the beginning of joystick movement was 497 ± 29 ms. The mean time from beginning of joystick movement and maximum joystick deflection (MT) was 608 ± 105 ms. There was no significant difference in mean RT or MT between the STN and Gpi patients (*t*-test, $P > 0.05$).

Direction selectivity of subthalamic and pallidal neurons

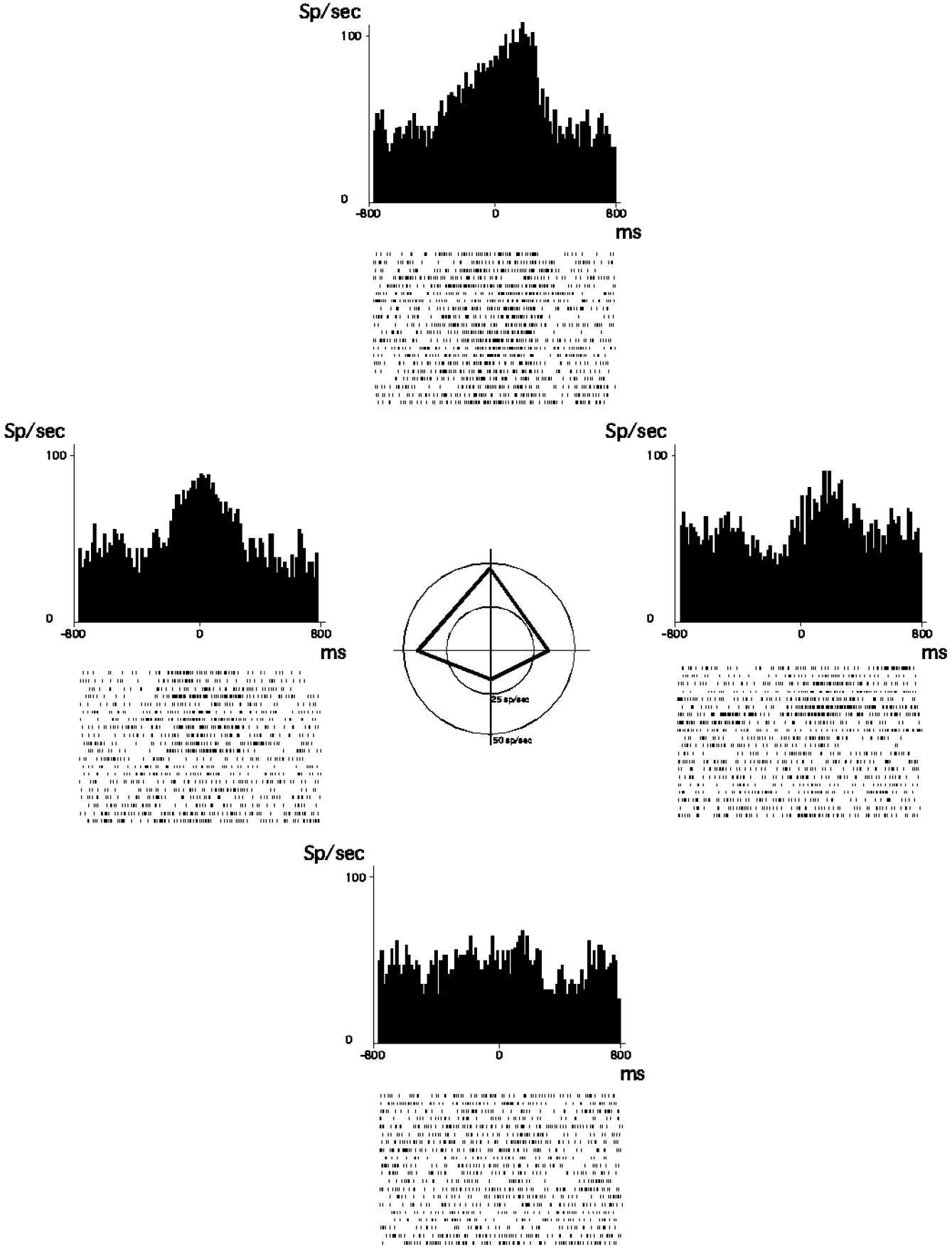
Of the 61 STN cells that demonstrated movement-related modulation, 39 (64%) were modulated in a selective manner (Fig. 5). These cells were twice as likely to be directionally selective in the 500-ms epoch immediately preceding movement onset compared to the 500-ms following movement onset. In Gpi, 12 of 15 movement-modulated cells (80%) were directionally selective. In contrast to STN, Gpi cells were twice as likely to show directional selectivity after initiation of the hand movement. There was a small trend toward selectivity for movements in the forward direction in both the STN and Gpi (Fig. 6).

Some of the cells demonstrated an increase in peri-movement activity relative to baseline and while others exhibited a decrease in activity. The ratio of cells exhibiting primarily increased activity compared to decreased activity was 3:1 in the STN and 1.5:1 in the Gpi. However, the pattern of activity in relation to hand movement was not always monophasic. Biphasic responses were noted in 28% and 40% of movement-modulated cells in the STN and Gpi, respectively.

Firing rates and direction selectivity

The average baseline firing rates were 56 ± 4 spikes/s in the STN and 67 ± 10 spikes/s in Gpi. In both nuclei, cells displaying direction selectivity had a significantly lower baseline firing than nondirectional cells (Wilcoxon rank-sum test, $P < 0.05$; Fig. 7A, B). In the STN, directionally selective cells had a mean baseline firing rate of 41 ± 5 spikes/s, whereas nondirectional cells had rate of 59 ± 4 spikes/s. In Gpi, directional cells had a mean baseline firing rate of 50 ± 9 spikes/s whereas nondirectional cells had a rate of 74 ± 15 spikes/s. Among 16 STN cells with significant oscillatory activity (power spectrum analysis, SD > 2.5, following method of Raz et al. 2001), 5 (31%) exhibited movement modulation and 2 (13%) were directional.

There did not appear to be a direct relationship between direction selectivity and depth of penetration (Fig. 8). Rather, within the dorsal-lateral STN, there was a considerable overlap in location between the two cell populations ($P = 0.2$, two-sample Kolmogorov-Smirnov test). In addition, there were no significant differences in RT, MT, or in the kinematics of the four directions for any of the patients (one-way ANOVA, $P > 0.05$; Fig. 9) that could otherwise account for the presence of directional selectivity or change in firing


Sp/sec
100
0
-800
0
800
ms
Sp/sec
100
0
-800
0
800
ms
25 sp/sec
50 sp/sec
Sp/sec
100
0
-800
0
800
ms
Sp/sec
100
0
-800
0
800
ms

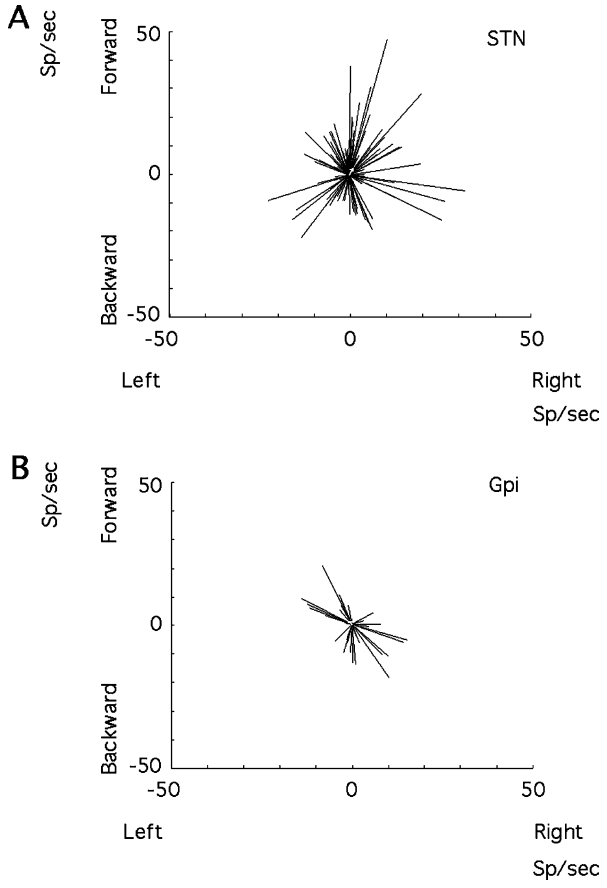


Fig. 6A, B Vector diagrams representing the net activity of individual neurons in the STN and Gpi, respectively, along the four directions of motion. The population vectors are illustrated by the *central white arrows*

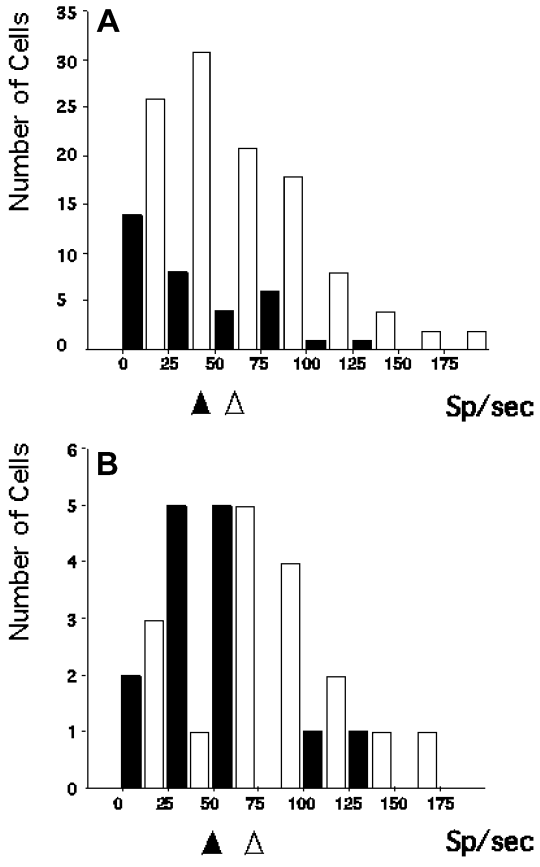


Fig. 7A, B Distribution of baseline firing rates for directional and nondirectional cells in the STN. **A** Firing rates are represented on the *horizontal axis* while number of cells is represented on the *vertical axis*. *Filled bars* indicate directional cells while *open bars* indicate nondirectional cells. *Closed arrowhead* indicates the mean firing rate for directional cells and *open arrowhead* the mean firing rate for nondirectional cells. **B** Distribution of directional and nondirectional cells in Gpi, same conventions as above

rates. Finally, no correlation was found between patient RT and baseline firing rates (linear regression, $P = 0.4$).

Discussion

Timing of neuronal activity, and the role of STN and Gpi in movement control

The timing of STN activity relative to movement is not well established. One primate study found that STN cells were modulated on average 50 ms before movement (Georgopoulos et al. 1983) while another found that modulation occurred about 2 ms after movement initiation (Wichmann et al. 1994a). One explanation for this discrepancy is that in the latter study neurons were selected based on their response to passive movements, which might have selected for somatosensory versus motor-related neurons. In comparison, studies in which

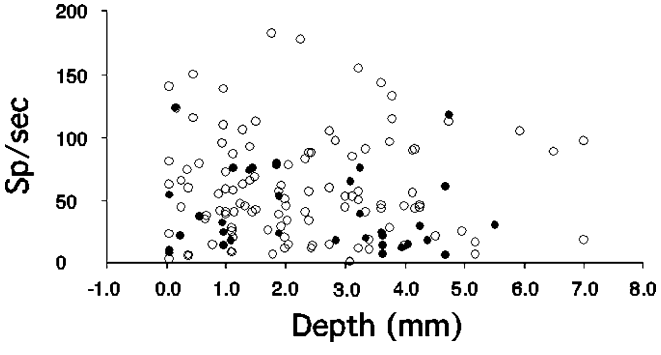


Fig. 8 Relationship of firing rates and location in the STN. Scatter plot of all cells as a function of depth in mm (*horizontal axis*) and firing rate (*vertical axis*). Depth zero indicates the superior border of the STN. *Filled dots* indicate directional cells while *open dots* indicate nondirectional cells

◀

Fig. 5 Direction selectivity. Peristimulus histograms for one STN cell during movement in each of the four directions. The responses are aligned on the start of joystick movement (time 0). *Central polar plot* shows the change in neuronal activity above baseline for the four directions tested

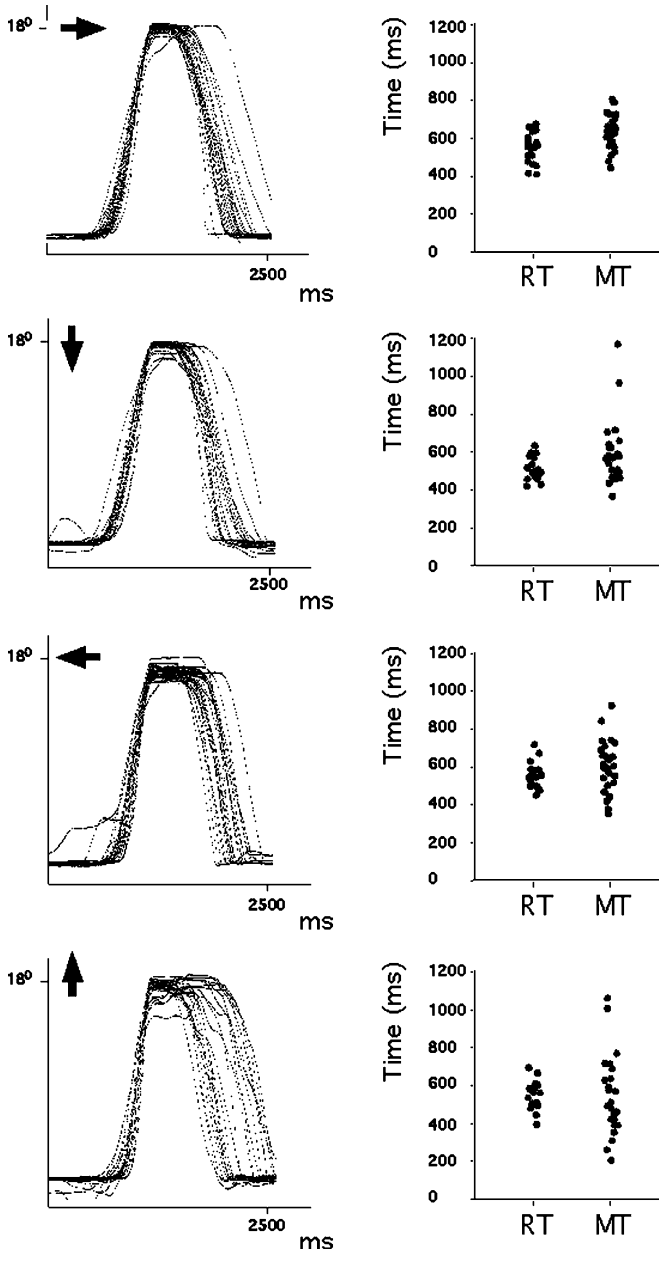


Fig. 9 Movement kinematics. Joystick movement tracings from a single session are shown for each direction in the *left column*. Reaction times (*RT*) and movement times (*MT*) are also displayed for the corresponding direction of movement in the *right column*. Data points are randomly scattered in the horizontal axis for clarity

recordings were made from the striatum of primates performing self-generated movement have shown that some neurons exhibit change in activity hundreds of milliseconds prior to movement (Alexander and Crutcher 1990b; Lee and Assad 2003). A recent study examining self-paced movements in humans also found that movement-related field potentials in the STN precede movement onset by up to several hundred milliseconds (Paradiso et al. 2003). In the current study, STN cells demonstrated a significant change in activity about 290 ms before movement initiation and 90 ms before the first EMG activity. This early activity may reflect the known direct inputs from motor and premotor areas to the STN, which bypass the indirect cortical-striatal-subthalamic pathway (Canteras et al. 1990; Carpenter et al. 1981; Nambu et al. 1996). Alternatively, early activity in the STN could reflect manifestation of the disordered circuitry of PD. Primate studies have shown that movement-related modulation of precentral neurons began somewhat earlier in MPTP-treated monkeys compared to that of normal animals (Doudet et al. 1990). In agreement with prior studies, we find that average initial changes in pallidal activity occur at about the same time as the first EMG activity (Anderson and Horak 1985; Mink and Thach 1991b).

Movement modulation

Direction selectivity has only been demonstrated in a limited fashion in humans. In most studies, direction selectivity was determined by passive movements of the limbs and by audible changes in the firing rates (Abosch et al. 2002; Levy et al. 2001; Magarinos-Ascone et al. 2000; Magnin et al. 2000; Rodriguez-Oroz et al. 2001). Using this approach, it is difficult to objectively assess the degree of direction selectivity. Furthermore, passive movements likely reflect sensory input to the STN as opposed to motor-related information. Nevertheless, previous results are qualitatively similar to ours in regard to firing rates and the percentage of neurons related to arm movements. Prior studies have shown that 30–50% of STN neurons respond differentially to passive movements of the upper extremities, whereas 40% of cells were observed to have direction selectivity in the present study (Abosch et al. 2002; Levy et al. 2001; Rodriguez-Oros et al. 2001).

Neuronal firing rates and directional selectivity

It has been suggested in primate models of PD that loss of dopaminergic neurons results in increased activity of the STN and Gpi (Bergman et al. 1994). However, it is less clear in what manner this change leads to the symptomatic derangements observed in PD. One theory suggests that dopamine serves to facilitate independent action of basal ganglia circuits and that loss of dopamine results in increased synchronization and loss of specificity of individual neurons (Bergman et al. 1998). Studies in primates have shown an increased likelihood of pallidal neurons responding to movements around multiple joints in MPTP-treated animals compared to healthy animals (Boraud et al. 2000). Similarly, a recent study in parkinsonian subjects revealed that administration of apomorphine, a dopaminergic agent, resulted in a decrease in the percentage of STN and Gpi neurons responding to movements around multiple joints (Levy et al. 2001).

The data presented in the current study suggest that higher firing rates are associated with decreased selectivity within STN and Gpi. In both nuclei, nondirectional cells had significantly higher firing rates than directional cells. In comparison, we did not find this trend to be true of pallidal cells in healthy nonhuman primates. In an analysis of 81 Gpi cells recorded from healthy monkeys (*Macaca mulatta*) performing an identical task, we found that directional and nondirectional cells had baseline firing rates that were not significantly different (Eskandar and Assad 2003).

There are a number of possible alternatives that may explain the inverse correlation found in this study between firing rates and directional selectivity. One possibility is that the relationship between firing rate and directionality reflected recordings from different parts of the STN. However, most of our recordings were obtained in the dorsal-lateral STN and only a few recordings were obtained from the ventral nonmotor portion of the STN (Wichman et al. 1994b). It is also unlikely that the observed directionality was due to eye movements since many directional cells also responded to limb movements outside the task. Moreover, the recordings were made from the dorsal-lateral STN whereas oculomotor cells are typically found more ventrally in the primate STN (Matsumura et al. 1992). The responses aligned well to onset of hand movement, which would not have been the case if they were due to eye movements. Another possibility is that the observed modulation was, in part, a visual response to the target stimulus. However, in this population, only three cells showed a significant time-locked response to the onset of the visual cues and these responses were short lived with a peak activity occurring at around 100 ms after stimulus onset, well before the movement-related activity.

One other explanation for the apparent difference in firing rates is that directional cells were better isolated whereas apparently nondirectional cells were actually recordings from multiple units. However, the spikes were sorted using a standardized template-matching algorithm that allows for relatively accurate spike isolation (Lewickiy 1998). In addition, units without a clear 3- to 5-ms refractory period in the auto-correlograms were excluded from analysis. Finally, there was a significant degree of overlap in the firing rates as well as locations between the two cell types (Figs. 7, 8) arguing against a systematic problem with neuronal isolation or spike sorting.

Predominance of excitatory cells in the STN and Gpi

The basal ganglia play an important but as yet undefined role in movement inhibition (Delong 1990; Mink 1996). It has been suggested that for a particular movement a relatively small number of neurons in Gpi decrease their activity and thus facilitate the appropriate movement while the remaining neurons increase their activity, presumably inhibiting other possible movements. In normal primates the percentage of pallidal cells exhibiting a decrease in activity lies between 20% and 50% (Boraud et al. 2000; Georgopolous et al. 1983). In MPTP-treated monkeys, on the other hand, only about 3% of pallidal neurons exhibit a movement-related decrease in activity (Boraud et al. 2000). Here, we found that the majority of cells in both the STN and Gpi exhibited increased movement-related activity. However, the percentage of cells exhibiting a decrease in activity was considerably higher than what might have been expected based on primate studies. This may reflect differences between humans and primates, differences in severity of disease between idiopathic PD and MPTP-induced parkinsonism in primates, or differences in the behavioral tasks.

Conclusions

This report represents one of a few studies in which a structured behavioral task was used to assess the properties of pallidal and subthalamic neurons in human subjects. Modulation of the STN appears to occur earlier than previously reported. In addition, higher firing rates appear to be associated with decreased direction selectivity in PD patients.

References

Abosch A, Hutchison WD, Saint-Cyr JA, Dostrovsky JO, Lozano AM (2002) Movement-related neurons of the subthalamic nucleus in patients with Parkinson disease. J Neurosurg 97:1167–1172

Albin RL, Young AB, Penney JB (1989) The functional anatomy of basal ganglia disorders. Trends Neurosci 12:366–375

Alexander GE, Crutcher MD (1990a) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 13:266–271

Alexander GE, Crutcher MD (1990b) Preparation for movement: neural representations of intended direction in three motor areas of the monkey. J Neurophysiol 64:133–150

Alkhani A, Lozano AM (2001) Pallidotomy for Parkinson's disease: a review of contemporary literature. J Neurosurg 94:43–49

Anderson ME, Horak FB (1985) Influence of globus pallidus on arm movements in monkeys. III. Timing of movement-related information. J Neurophysiol 54:433–448

Anderson ME, Turner RS (1991) A quantitative analysis of pallidal discharge during targeted reaching movement in the monkey. Exp Brain Res 86:623–632

Bergman H, Wichmann T, DeLong MR (1990) Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 249:1436–1438

Bergman H, Wichman T, Karmon B, DeLong MR (1994) The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. J Neurophysiol 72:507–520

Bergman H, Feingold A, Nini A, Raz A, Slovin H, Abeles M, Vaadia E (1998) Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. Trends Neurosci 21:32–38

Boraud T, Bezard E, Bioulac B, Gross CE (2000) Ratio of inhibited-to-activated pallidal neurons decreases dramatically during passive limb movement in the MPTP-treated monkey. J Neurophysiol 83:1760–1763

Canteras NS, Shammah-Lagnado SJ, Silva BA, Ricardo JA (1990) Afferent connections of the subthalamic nucleus: a combined retrograde and anterograde horseradish peroxidase study in the rat. Brain Res 513:43–59

Carpenter MB, Carleton SC, Keller JT, Conte P (1981) Connections of the subthalamic nucleus in the monkey. Brain Res 224:1–29

Crutcher MD, Alexander GE (1990) Movement-related neuronal activity selectively coding either direction or muscle pattern in three motor areas of the monkey. J Neurophysiol 64:151–163

Crutcher MD, Delong MR (1984a) Single cell studies of the primate putamen. I. Relations to direction of movement and pattern of muscular activity. Exp Brain Res 53:244–258

Crutcher MD, Delong MR (1984b) Single cell studies of the primate putamen. II. Relations to direction of movement and pattern of muscular activity. Exp Brain Res 53:244–258

Deep-brain stimulation for Parkinson's disease study group (2001) Deep-brain stimulation of the subthalamic nucleus of the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 345:956–963

Delong MR (1990) Primate models of movement disorders of basal ganglia origin. Trends Neurosci 13:281–285

DeLong MR, Crutcher MD, Georgopoulos AP (1985) Primate globus pallidus and subthalamic nucleus: functional organization. J Neurophysiol 53:530–543

Doudet DJ, Gross C, Arluison M, Bioulac B (1990) Modifications of precentral cortex discharge and EMG activity in monkeys with MPTP-induced lesions of DA nigral neurons. Exp Brain Res 80:177–188

Eskandar EN, Assad JA (1999) Dissociation of visual, motor and predictive signals in parietal cortex during visual guidance. Nat Neurosci 2:88–93

Eskandar EN, Assad JA (2003) The role of putamen and pallidum in movement suppression. Soc Neurosci Abstr http://sfn.scholarone.com/itin2003/index.html

Eskandar EN, Shinobu, LA, Penney JB, Cosgrove GR (2000) Nonmicroelectrode-guided pallidotomy: Surgical technique and 2 year results. J Neurosurg 92:375–383

Georgopoulos AP, DeLong MR, Crutcher MD (1983) Relations between parameters of step-tracking movements and single cell discharge in the globus pallidus and subthalamic nucleus of the behaving monkey. J Neurosci 3:1586–1598

Hutchison WD, Allan RJ, Opitz H, Levy R, Dostrovsky JO, Lang AE, Lozano AM (1998) Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Ann Neurol 44:622–628

Jaeger D, Gilman S, Aldridge JW (1995) Neuronal activity in the striatum and pallidum of primates related to the execution of externally cued reaching movements. Brain Res 694:111–127

Lee IH, Assad JA (2003) Putaminal activity for simple reactions or self-timed movements. J Neurophysiol 89:2528–2537

Levy R, Dostrovsky JO, Lang AE, Sime E, Hutchison WD, Lozano AM (2001) Effects of apomorphine on subthalamic nucleus and globus pallidus internus neurons in patients with Parkinson's disease. J Neurophysiol 86:249–260

Lewickiy MS (1998) A review of methods for spike sorting: the detection and classification of neural action potentials. IOP Publishing, London

Lozano A, Hutchison W, Kiss Z, Tasker R, Davis K, Dostrovsky J (1996) Methods for microelectrode guided posteroventral pallidotomy. J Neurosurg 84:194–202

Magarinos-Ascone CM, Figueiras-Mendez R, Riva-Meana C, Cordoba-Fernandez A (2000) Subthalamic neuron activity related to tremor and movement in Parkinson's disease. Eur J Neurosci 12:2597–2607

Magnin M, Morel A, Jeanmonod D (2000) Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. Neuroscience 96:549–564

Matsumura M, Kojima J, Gardiner TW, Hikosaka O (1992) Visual and oculomotor functions of monkey subthalamic nucleus. J Neurophysiol 67:1615–1632

Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 50:381–425

Mink JW, Thach WT (1991a) Basal ganglia motor control. I. Nonexclusive relation of pallidal discharge to five movement modes. J Neurophysiol 65:273–300

Mink JW, Thach WT (1991b) Basal ganglia motor control. II. Late pallidal timing relative to movement onset and inconsistent pallidal coding of movement parameters. J Neurophysiol 65:301–329

Mitchell SJ, Richardson RT, Baker FH, DeLong MR (1987) The primate globus pallidus: neuronal activity related to direction of movement. Exp Brain Res 68:491–505

Nambu A, Takada M, Inase M, Tokuno H (1996) Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. J Neurosci 16:2671–2683

Paradiso G, Saint-Cyr JA, Lozano AM, Lang AE, Chen R (2003) Involvement of the human subthalamic nucleus in movement preparation. Neurology 61:1538–1545

Raz A, Frechter-Mazar V, Feingold A, Abeles M, Vaadia E, Bergman H (2001) Activity of pallidal and striatal tonically active neurons is correlated in MPTP-treated monkeys but not in normal monkeys. J Neurosci 21:RC128,1–6

Rodriguez-Oroz MC, Rodriguez M, Guridi J, Mewes K, Chockkman V, Vitek J, DeLong MR, Obeso JA (2001) The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics. Brain 124:1777–1790

Schaltenbrand G, Wahren W (1977) Atlas for stereotaxy of the human brain. Thieme, New York

Wichman T, Bergman H, DeLong MR (1994a) The primate subthalamic nucleus. I. Functional properties in intact animals. J Neurophysiol 72:494–506

Wichman T, Bergman H, DeLong MR (1994b) The primate subthalamic nucleus. III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. J Neurophysiol 72:521–530