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A neural model of basal ganglia–thalamocortical relations in normal and parkinsonian movement

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Abstract. Anatomical, neurophysiological, and neurochemical evidence supports the notion of parallel basal ganglia–thalamocortical motor systems. We developed a neural network model for the functioning of these systems during normal and parkinsonian movement. Parkinson's disease (PD), which results predominantly from nigrostriatal pathway damage, is used as a window to examine basal ganglia function. Simulations of dopamine depletion produce motor impairments consistent with motor deficits observed in PD that suggest the basal ganglia play a role in motor initiation and execution, and sequencing of motor programs. Stereotaxic lesions in the model's globus pallidus and subthalamic nucleus suggest that these lesions, although reducing some PD symptoms, may constrain the repertoire of available movements. It is proposed that paradoxical observations of basal ganglia responses reported in the literature may result from regional functional neuronal specialization, and the non-uniform distributions of neurochemicals in the basal ganglia. It is hypothesized that dopamine depletion produces smaller-than-normal pallidothalamic gating signals that prevent rescalability of these signals to control variable movement speed, and that in PD can produce smaller-than-normal movement amplitudes.

1 Introduction

The understanding of the organization of the basal ganglia–thalamocortical motor channels, the development of primate models of parkinsonism, and the study of motor impairments associated with basal ganglia dysfunction have advanced considerably over the past two decades (Alexander et al. 1986; Stelmach et al. 1989; Bergman et al. 1990; Graybiel 1990; Flaherty and Graybiel 1993).

Behavioral, neurophysiological, and anatomical studies have implicated the basal ganglia in selecting, maintaining, and suppressing postural and/or movement-related subsystems (Penney and Young 1983; Schneider 1987; Albin et al. 1989; Chevalier and Deniau 1990; Mink and Thach 1991b; Golani 1992). Furthermore, the activity of basal ganglia neurons appears to be closely dependent on the behavioral context of the task (Mink and Thach 1991a; Gerfen 1992).

A related approach to the study of movement control involves the study of motor impairments, as they are manifested in neurological disorders. For example, Parkinson's disease (PD) is used as a window to examine the role of the basal ganglia in movement control (Stelmach and Phillips 1991). In this regard, current views of hypokinetic disorders point to a loss of striatal dopamine (DA) that leads to overactivation of pallidal neurons that inhibit thalamocortical neurons influencing the frontal lobe (DeLong and Wichmann 1993). However, some experimental observations of motor activity related to basal ganglia function have produced divergent results: (1) behavioral and neurophysiological data investigating the involvement of the basal ganglia do not always show an effect on motor initiation (Montgomery et al. 1991; Montgomery and Buchholz 1991); (2) focal basal ganglia lesions or inactivations do not consistently impair reaction time, only movement time and amplitude (Mink and Thach 1991b); and (3) stereotaxic lesions directed at the thalamus or globus pallidus, which improve rigidity and tremor, do not always influence hypokinesia, bradykinesia, or dyskinesias (Marsden and Obeso 1994).

In this paper we integrate experimental data on the anatomy, neurophysiology, and neurochemistry of the basal ganglia and related structures, as well as data on motor impairments in PD, to develop a neural model of basal ganglia interactions during movement production. Computer simulations of normal and parkinsonian movement are used to help understand the many divergent views of basal ganglia function.

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2 Neural network model of basal ganglia functioning

Our approach is to model the brain in an incremental manner, by simulating the operation of increasingly sophisticated neural circuits and networks in increasingly complex behavioral scenarios. In Contreras-Vidal et al. (1994) we showed how smaller-than-normal movement-gating signals can affect movement amplitude and duration in a way similar to that observed in parkinsonian movement. In this paper it is postulated that abnormal opponent processing in the basal ganglia alters outputs that create some parkinsonian motor symptoms. We are interested in understanding how alterations in the neurochemistry may alter the function of neural populations that produce abnormal motor behavior. Diagrams of the major basal ganglia circuits and their activity under normal (Fig. 1A) and PD (Fig. 1B) conditions show that damage to the nigrostriatal projection system causes differential expression of D1 and D2 DA receptor mRNA and neuropeptides [e.g. substance P (SP), dynorphin (DYN), and enkephalin (ENK)] in separate populations of striatal neurons (Gerfen 1993; Fink 1993). This produces an enhancement (depression) in the response of pallidal neurons in the indirect (direct) pathway (Gerfen 1992) which leads to a loss of dynamic range in the activity of the internal segments of the globus pallidus (GPi) due to smaller-than-normal striatopallidal activity (Georgopoulos et al. 1983; Anderson and Horak 1985). The net outcome is the overinhibition of thalamic target neurons by overexcited GPi cells (Montgomery et al. 1991).

The circuits depicted in Fig. 1 form dynamic systems that evolve on several time scales (e.g. short-, medium-, and long-term interactions due to neural activations, neurotransmitter interactions, and receptor dynamics respectively). In this (Fig. 1) and the following simulations, non-linear, ordinary differential equations are employed to represent neuronal and/or neurotransmitter dynamics.

The activity of a striatal output projection neuron S_k is modeled as

$$\frac{d}{dt}S_k = -A_s S_k + (B_s - S_k)\left(\sum_n I_n + I_{ACh} + f(S_k)\right) - (D_s + S_k)\sum_{n \neq k} S_n \quad (1)$$

where S_k represents the activity over time of a medium spiny neuron in the striatum; A_s is the passive decay rate of neural activity; B_s and D_s are the upper and lower bounds in the activity of neuron S_k respectively; $\sum_n I_n$ represents the net corticostriatal input from cortex; $f(x) = x^3/(0.25 + x^3)$ is a sigmoid function; and I_{ACh}

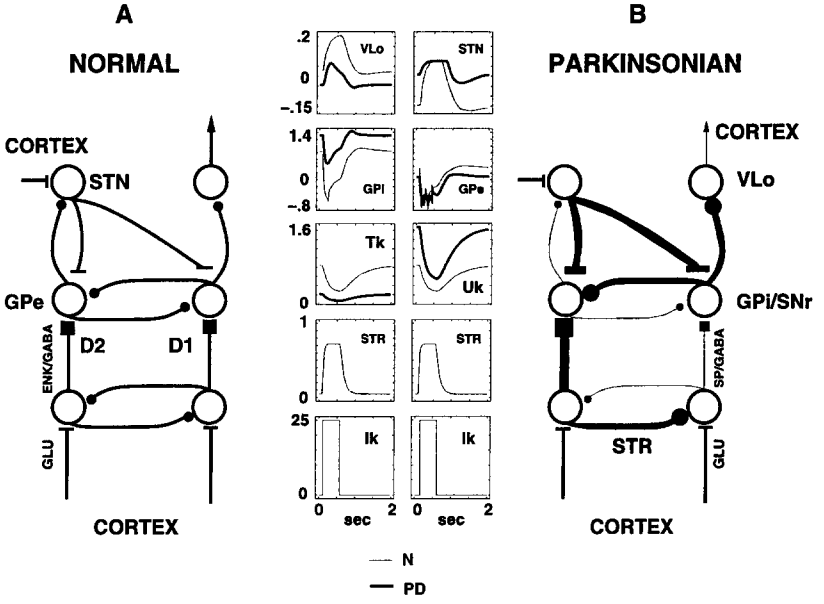

Fig. 1A, B. Neural network depicting the anatomical, neurophysiological, and neurochemical relations (diagrams) of the basal ganglia, and their activity (plots) under normal conditions (**A**) and following damage of the substantia nigra pars compacta (**B**). Each plot represents the neural activity of an intact (*thin line*) or parkinsonian (*bold line*) model cell type shown in the diagrams, except for U_k and T_k which represent the neurotransmitter/receptor dynamics in the indirect and direct pathways respectively. Parkinson's disease(PD) was simulated by 50% dopamine (DA) depletion. The basal ganglia input (I_k) was shared by a pair of neighboring striatal output neurons (STR) within a matrisome. U_k and T_k represents the neurotransmitter dynamics for the GABA/ENK and GABA/SP pathways respectively, which depend on DA dynamics. The product STR × U_k or STR × T_k represents the net postsynaptic potential in the indirect and direct striatopallidal pathways respectively. Note the smaller modulatory range of neurotransmitter dynamics, pallidum and thalamic activities, as well as the smaller-than-normal (in amplitude and duration) VLo activity in the PD network. *VLo*, ventrolateral thalamus; *GPi*, *GPe*, internal and external segments of the globus pallidus respectively; *STN*, subthalamic nucleus; *SNr*, substantia nigra pars reticulata; *GABA*, gamma-aminobutyric acid; *GLU*, glutamate; *ENK*, enkephalin; *SP*, substance P. *Black circles* and *black squares*, inhibitory neurotransmitter/neuropeptides; *bars*, excitation. Parameters for this and the next simulations are in the Appendix

represents a baseline input (e.g. from cholinergic interneurons). If the net excitatory input is small compared with the decay rate and inhibitory inputs, the striatal neuron S_k will usually be hyperpolarized (e.g. silent). Equation (1) states that neuron S_k integrates excitatory corticostriatal inputs at a rate $(B_s - S_k)$, and it is inhibited by axon collaterals from neighboring neurons (or through inhibitory interneurons) at rate $(D_s + S_k)$.

Pallidal neurons in the internal and external segments of the globus pallidus (GPi and GPe) are modeled separately to reflect the differential anatomical and neurochemical interactions involved in the direct and indirect pathways, as follows:

$$\frac{d}{dt}G_k = 2[- A_g G_k + (B_g - G_k)(10J_k + f(G_k)) - (D_g + G_k)(50S_k T_k + 0.2H_k)] \quad (2)$$

where G_k is the activity of GPi neurons; J_k is an excitatory bias from subthalamic nucleus; $f(G_k)$ represents positive feedback from neuron G_k to itself; S_k denotes the inhibitory striatal input; T_k represents the amount of neurotransmitter available for transmission (or neurotransmitter expression) in the direct pathway; and H_k is an inhibitory input from GPe neurons, as follows:

$$\frac{d}{dt}H_k = - A_h H_k + (B_h - H_k)(10J_k + f(H_k)) - (D_h + H_k)(50S_k U_k + 0.2G_k) \quad (3)$$

where H_k is the activity of GPe neurons; U_k represents the amount of neurotransmitter available for transmission in the indirect pathway; and G_k is an inhibitory input from GPi neurons. The pair of GPi and GPe neurons form an opponent system through mutual inhibition (Grossberg 1984).

The neurochemical specialization of the direct and indirect pathways is taken into consideration to reflect the differential neurochemical and neurophysiological disturbances due to DA depletion. These modifications include increases (decreases) in D2 (D1) receptors in the indirect (direct) pathways (Neve et al. 1991), and increases (decreases) in expression of ENK (SP/DYN) in the indirect (direct) pathways (Graybiel 1990; Fink 1993). Such changes are consistent with increases and decreases in activity of the indirect and direct pathways respectively (Gerfen 1992).

Striatal neuropeptides may produce physiological effects by facilitating or inhibiting the activity or output in the major classical neurotransmitter pathways by enhancing or suppressing motor activity. In the direct pathway gamma-aminobutyric acid (GABA), SP, and DYN coexist. The main neurotransmitters GABA and DA interact with SP/DYN to increase/decrease the level of neural activity. This modulation is modeled as a medium-term effect dependent on the amount of neurotransmitter available at the striatopallidal pathways which in turn depend on the DA resources in the system:

$$\frac{d}{dt}T_k = b(B_{SP/DYN}(DA) - T_k) - cS_k T_k \quad (4)$$

Equation (4) states that the amount of neurotransmitter available (T_k) for signaling in the direct pathway is depleted at rate cS_k provided that striatopallidal activity is non-zero, namely $S_k > 0$; otherwise the neurotransmitter is reaccumulated at rate $b(B_{SP/DYN}(DA) - T_k)$. The upper and lower limits of neurotransmitter production and depletion are given by $B_{SP/DYN}(DA)$ and zero respectively. The maximum amount of neurotransmitter available is a function of the amount of DA (which regulates the expression of DA receptors and neuropeptides). This relationship is direct: decreases in DA reduce the expression of D1 receptors as well as SP/DYN. Conversely, the relationship in the indirect pathway is inverse, and the amount of neurotransmitter resources ($B_{ENK}(DA)$) increases with decreasing DA level:

$$\frac{d}{dt}U_k = b(B_{ENK}(DA) - U_k) - cS_k U_k \quad (5)$$

In this formulation, if DA is depleted (DA < 100%), then the activity of striatal neurons projecting to GPi/SNr (substantia nigra pars reticulata) is reduced by the decreased expression of SP/DYN and D1 receptors in the direct pathway. The smaller-than-normal striatal activity will disinhibit the GPi and SNr neurons. Furthermore, the pathway striatum → GPe → subthalamic nucleus (STN) circuit will increase further the activity of GPi and SNr through disinhibition of STN neurons projecting to GPi/SNr due to increased expression of ENK and D2 receptors (Albin et al. 1989).

STN neurons, denoted by J_k, are modeled as follows:

$$\frac{d}{dt}J_k = - A_j J_k + (B_j - J_k)(I_k + I_s + f(J_k)) - 10(D_j + J_k)H_k \quad (6)$$

where I_k denotes direct excitatory input from cerebral cortex; and I_s provides a level of tonic activity which is modulated by the inhibitory input from GPe (Georgopoulos et al. 1983). The basal ganglia outputs target the thalamic neurons (P_k):

$$\frac{d}{dt}P_k = 5[- A_p P_k + (B_p - P_k)I_{tonic} - 0.5(D_p + P_k)G_k] \quad (7)$$

where I_{tonic} is a baseline tonic input; and G_k is the inhibitory input from GPi neurons.

Several levels of opponent processing can be found at the anatomical, neurophysiological, and neurochemical levels. It is shown next that an imbalance in these opponent interactions, e.g. by neurotransmitter depletion, may cause movement impairments such as parkinsonian movement.

2.1 Gating of thalamic activity by pallidal neurons

Figure 1 depicts a simulation of the generation of a gating signal at the thalamus by the basal ganglia for a normal and a PD network. The bottom panels (I_k) show the basal ganglia inputs, presumably generated by premotor or motor cortical areas. In this network, the pair of

neighboring striatal neurons (STR, represented by S_k) form part of a matrisome whose neurons project differentially to GPe and GPi. These projections are weighted by the amount of neuromodulators (SP/ENK) available in the system. Therefore, the activity of GPi and GPe neurons (defined above as G_k and H_k respectively) depends on the product $S_k \times T_k$ and $S_k \times U_k$ respectively. Note that in the normal case (thin traces), the system's neurotransmitter curves are balanced; however, in the PD case (bold traces) the expression of neurotransmitter is altered: there is a higher level of ENK (labeled U_k) expression than SP (labeled T_k). This imbalance produces a higher-than-normal activity in GPi neurons, and a smaller-than-normal activity of GPe neurons with respect to the normal simulation. The latter effect produces a larger activity of STN neurons which contributes to the overexcitation of GPi cells. The net effect is a smaller-than-normal (in amplitude and duration) gating signal at the ventrolateral thalamus (VL_o). The simulations suggest changes not only in pallidal firing rates in PD, but also in the patterns of these discharges.

3 Basal ganglia–thalamocortical relations and movement control

Bullock and Grossberg (1988) have postulated a neural network model for the kinematics of point-to-point arm movements called the Vector-Integration-To-Endpoint or VITE model. This network, depicted in Fig. 2, models motor cortical operations performed during pointing movements. The model computes a difference vector (DV) by substracting an arm target position vector (TPV) from its present position vector (PPV). The DV codes information about the direction and magnitude of the desired movement. Neuronal populations broadly tuned around a particular direction of movement have been found in motor cortical areas (e.g. Georgopoulos et al. 1986). The information computed by the vector cells at the DV is used to update the PPV in the direction of the vector difference. In particular, the PPV integrates the DV gradually until the TPV is equal to the PPV, in which case the DV will be zero. Bullock and Grossberg proposed that a GO signal could gate execution of a primed movement vector and at the same time regulate the rate at which the DV updates the present position vector. Thus, this GO signal would have the dual role of: (a) being a neural correlate of a volitional command to start movement, and (b) setting the global speed of the movement. Typically, this signal grows slowly at the beginning of the movement reaching peak values late into the movement to allow for smooth bell-shaped movements. However, the dynamics of the GO signal (e.g. shape and duration) are underspecified by assuming varying time dependencies (e.g. a sigmoidal function), presumably selected according to the movement requirements.

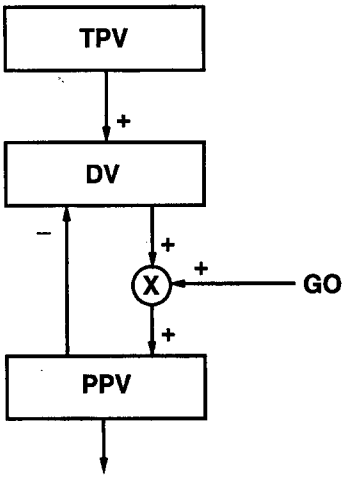

Fig. 2. VITE model of trajectory formation from Bullock and Grossberg (1988). *TPV*, target position vector; *DV*, difference vector; *PPV*, present position vector; *GO*, 'go' signal. The model computes the difference between the TPV and the PPV at the DV stage. The DV × GO outflow command is integrated at the PPV stage. As the PPV approaches the TPV, the DV tends to zero. The GO signal has the dual purpose of gating movement initiation and modulating movement speed

3.1 Cortical–subcortical interactions during movement

Section 2.1 showed how normal and abnormal gating GO signals can be generated by intact and parkinsonian basal ganglia networks. Now, it is suggested how the basal ganglia cooperate with other structures to specify the movement components required to generate arm movements.

Figure 3 depicts a single basal ganglia–thalamocortical motor loop in terms of cortical and subcortical networks for trajectory formation and movement gating. Corticocortical projections are present within the VITE model (Fig. 2). Corticostriatopallidal and pallidothalamic projections are present in the basal ganglia network depicted in Figs. 1 and 2. Thalamocortical projections are depicted within VITE and from VITE to other cortical areas such as supplementary motor (SMA), premotor (PMA) and motor (MA) areas.

In terms of input signals SMA projects to both the basal ganglia model and VITE, and may be involved in movement sequencing (Kunzle 1975). Motor and premotor projections to basal ganglia may modulate movement dynamics in simple and multiple-component movements (Kunzle 1975; Jinnai et al. 1989). The patchiness of these cortical projections to the striatum may allow for a redistribution of inputs so that different cortical areas can be combined and processed according to different movement-related programs (Flaherty and Graybiel 1993, 1994). Such coupling may be critical in linking different motor subprograms that may be started simultaneously and in parallel. However, the postulated existence of parallel channels in the basal ganglia is not compromised by the convergence of inputs from different cortical areas in the striatum, because the segregation may be purely functional. Predominance of some inputs over others will tend to provide some degree of segregation; and striatal interneurons may serve to gate 'on and off' glutamatergic inputs to striatal output projection neurons adaptively, depending on the task.

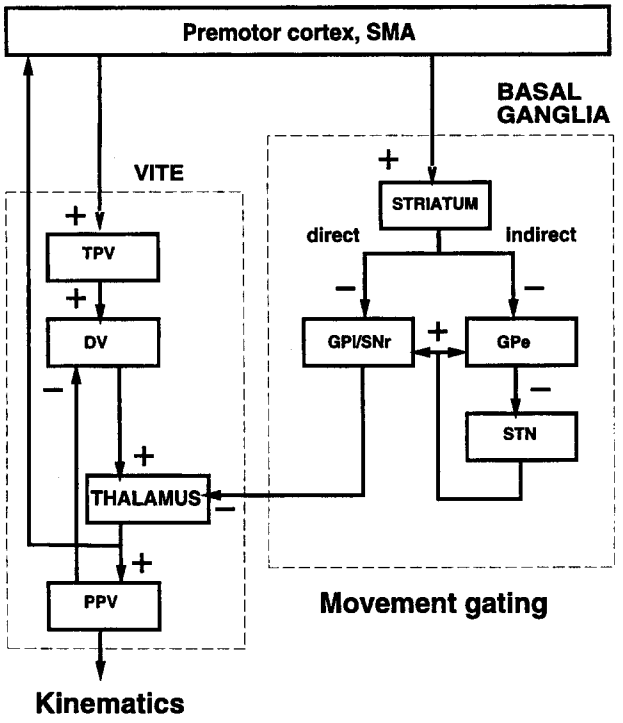

Fig. 3. A model basal ganglia–thalamocortical circuit. The basal ganglia gate or modulate the dynamics of the trajectory generated by a trajectory formation network (VITE), and are involved in higher-order motor control (e.g. sequencing of motor programs and selection of motor components). Abbreviations as in Figs. 1 and 2

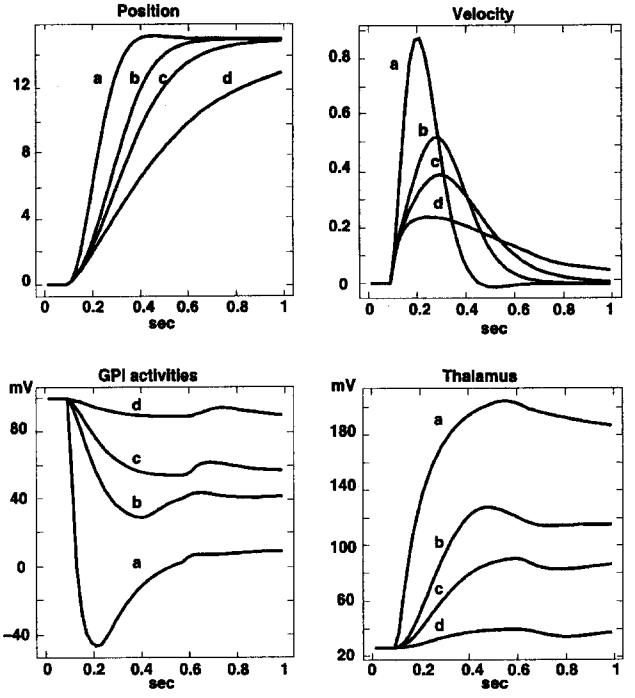

Fig. 4. Simulations of joint movements performed at different speeds. The arm started at the middle position of the flexion–extension range (0°). The target position vector (TPV) was 15° flexed. The size of the input to the basal ganglia was varied according to: *a*, $I = 15$; *b*, $I = 1$, *c*, $I = 0.5$; and *d*, $I = 0.1$. Joint position (degrees), joint velocity (deg/s), GPi and thalamic activities are shown. For the fastest movement (*a*), the GPi (thalamus) activity is suppressed (disinhibited) the most. The simulations show that input size controls movement speed (and duration)

In terms of output signals (see Fig. 3), pallidothalamic projections to motor cortex perform movement gating operations that modulate the dynamics of trajectory formation (VITE). In this regard, Hoover and Strick (1993) have found a discrete pallidal output region that projects primarily to motor cortex. For sequential movements, the movement plan consists of a sequence of normalized, directional motor subprograms, specified in terms of TPVs, with specific temporal relationships (Bullock et al. 1993). During sequential movements (as in handwriting), the DV × GO outflow command from VITE is sent to SMA to trigger successively each component of the movement, concurrently with pallidothalamic afferents that modulate the kinematics of each movement segment. Alternatively, other discrete pallidal output regions would project to premotor areas that may be involved in temporal coordination of multiple parallel movements (Hoover and Strick 1993). It is hypothesized that the modulation of the difference vector output and the sequencing of motor commands could be performed concurrently at the functionally segregated pallidal-receiving areas of the thalamus that project to motor cortex and premotor (including SMA) cortex, respectively, forming multiple basal ganglia–thalamocortical motor loops (Hoover and Strick 1993).

Simulations of the proposed network are presented next. Figure 4 depicts a parametric plot for a single-joint arm movement performed at several speeds. In this simulation, the size of the input to the basal ganglia network was varied to account for fast (a), intermediate (b, c), and slow (d) movements (see Appendix). These corticostriatal inputs may originate in motor or premotor areas. The plots show that peak velocity increases with input size in a monotonic fashion. Accordingly, movement time decreases with increasing input size as has been demonstrated in putamen-based microstimulation experiments (Alexander and DeLong 1985). GPi and thalamic activity follow inverse relationships: faster joint velocities are characterized by higher inhibitory GPi modulation by striatal output neurons, resulting in larger thalamic activities.

4 Basal ganglia and Parkinson's disease

Stimulated by the discovery of the importance of DA, the last two decades have witnessed an explosion of research into many aspects of the basal ganglia including anatomical, neurophysiological, and behavioral relations during normal and abnormal behavior (Alexander and Crutcher 1990; DeLong and Wichmann 1993; Jaeger et al. 1993; Flaherty and Graybiel 1994), MPTP primate models of basal ganglia motor dysfunction (Bergman et al. 1990), lesion studies (Kato and Kimura 1992; Guridi et al. 1993), and motor impairments associated with PD (Stelmach et al. 1989; Stelmach and Phillips 1991; Marsden and Obeso 1994).

Movement can be analyzed in terms of deficits in reaction time (RT), movement time (MT), and movement amplitude caused by basal ganglia impairment in PD. Figure 5 depicts a simulation of a simple elbow movement (15° rotation) in which the percentage of DA in the basal ganglia is varied. The simulation parametrically explores the output of the system from a normal state (curve 'a') to a DA-depleted state (curve 'g') in terms of joint velocity and RT (shown in the inset). Several features of simulated PD behavior are in agreement with experimental data. First, RT increases with increasingly larger amounts of DA depletion. In fact, for DA levels of less than 40%, the system shows akinesia. Second, motor impairment is more apparent at high levels of DA depletion (>50%). Third, MT increases with decreasing levels of DA as seen from smaller peak velocities and longer velocity profiles (bradykinesia); however, this relationship is not monotonic and at higher levels of DA depletion the system becomes hypometric.

The model predicts that akinesia and bradykinesia do not result from malfunction of independent basal ganglia processes, but rather that these features of PD form a continuum that goes from normal RT and MT to delayed RT and prolonged MT, and finally akinesia. Thus, the model makes the additional observation that, within patients, the degree of motor impairment is correlated with the amount of DA depletion. These simulations correspond to a PD network with DA depleted uniformly across the striatum. A non-uniform distribution of neurotransmitters in the basal ganglia may result in differential deficits that may account for the motor variability seen in parkinsonian movement and the apparent lack of correlation between MT and RT.

Behavioral and neurophysiological data regarding the role of the basal ganglia in motor initiation, as evidenced by changes in RT, have not been as consistent as changes in MT (Montgomery et al. 1991; Montgomery and Buchholz 1991; Mink and Thach 1991b). Montgomery and Buchholz (1991) have suggested that the inconsistencies in RT data between studies may be related to anatomical and neurochemical differentiation within the striatum. In particular, they point to evidence indicating separate pathways from association cortex to caudate nucleus, and from sensorimotor cortex to putamen (Kunzle 1975; Goldman and Nauta 1977) that may suggest separate mechanisms for motor initiation and execution respectively at the level of the striatum.

Furthermore, an uneven pattern of DA loss in the striatum may also be responsible for inconsistencies in RT data between studies. In particular, patients with PD show more consistent patterns of DA depletion in the putamen, but incomplete and variable patterns of DA depletion in the caudate (Kish et al. 1988). At the level of the globus pallidus, Baron et al. (1993) have found that lesions confined within the caudal and lateral portion of GPi improve RT and MT in PD patients. Thus regional functional differentiation within the globus pallidus may explain apparently contradictory data on RT. This functional differentiation is consistent with the anatomical differentiation (in terms of the discrete pallidal output projections to distinct cortical areas) found by Hoover

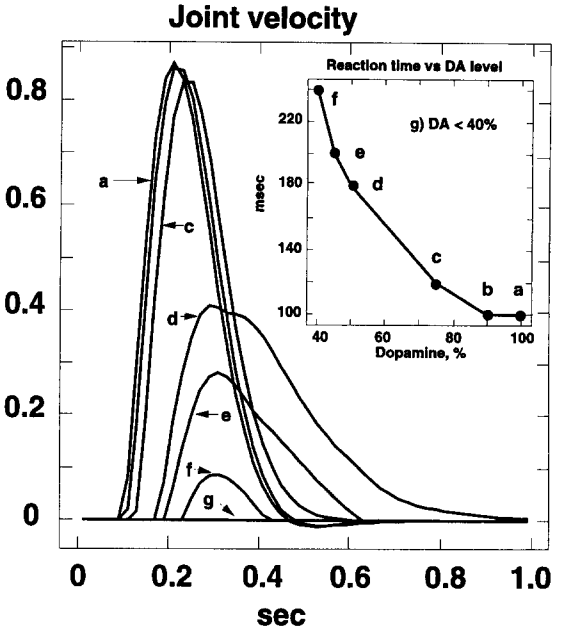

Fig. 5. Parametric simulation of a simple movement when DA level is varied from: *a*, 100% (intact); *b*, 90%, *c*, 75%; *d*, 50%; *e*, 45%; *f*, 40%; to *g* less than 40%. As the amount of DA decreases, the output of the network shows increased reaction time, slowness in movement (bradykinesia), and finally akinesia. The effects of small percentages of DA depletion are subtle, suggesting that in order to detect early PD, fine complex motor tasks requiring precise coordination of movement components, such as handwriting, should be analyzed. Parameters: *a*, $B_{SP/DYN}(DA) = B_{ENK}(DA) = 1$; *b–g*, $B_{SP/DYN}(DA) = (DA)^2$; $B_{ENK}(DA) = 3(DA)/[(DA) + 0.25]$

and Strick (1993). This may explain data obtained by Mink and Thach (1991b) who reported that permanent lesions with injections of kainic acid in their second monkey *centered* in GPi did not produce RT effects but did result in marked increases in movement durations as well as reduced movement amplitudes. However, Baron et al. (1993) have found that lesions in the caudal and lateral GPi improve both RT and MT in PD subjects. Laitinen et al. (1992) found that lesions in posteroventral pallidum alleviate akinesia. Other recent lesion and neurophysiological data support pallidal involvement in motor initiation (Nambu et al. 1990; Alamy et al. 1994; Cheruel et al. 1994). Taken together, these data suggest there is functional segregation within the striatum and the globus pallidus that may be responsible for the apparent contradictory RT data.

5 Lesion studies

Increases in STN activity in the MPTP parkinsonian model of the monkey are thought to produce hypokinetic disorders because subthalamotomy reduces the rigidity commonly seen in PD (Bergman et al. 1990). Consistent with these observations, Kato and Kimura (1992) have suggested that high GPi activities are needed to maintain a limb at a particular position (a posture). The high GPi activity could be enhanced or maintained through the indirect excitatory input from STN. During movement,

the GPi activity is decreased through activation of putaminal cells.

In PD, GPi neurons are known to discharge at very high rates. STN lesions by injection of ibotenate reduce the spontaneous discharge rate of GPi neurons due, presumably, to decreased glutamatergic excitation from STN (Hamada and DeLong 1992). This suggests that lesioning the STN may help to alleviate PD symptoms by decreasing GPi activity levels. Studies have shown that subthalamotomy or blockade of STN output decreases rigidity (Guridi et al. 1993). Alternatively, lesioning the GPi neurons directly (either by pallidotomy or by injections of GABA agonists) produces disinhibition of thalamic cells (Baron et al. 1993). However, stereotaxic lesions in PD patients directed at the motor thalamus or globus pallidus, known to reduce rigidity and tremor, do not seem to influence hypokinesia, bradykinesia, or dyskinesias (Marsden and Obeso 1994).

Figure 6 stimulates stereotaxic interventions to alleviate PD. Pallidotomy reduced the pallidal output to about 24% of previous PD levels, while subthalamotomy suppressed totally the glutamatergic output to GPi. These simulations show that pallidotomy is more efficient in alleviating PD symptoms. In particular RT, MT, and hypometria are normalized (panels A and B). In contrast subthalamotomy does not improve MT or hypometria significantly, and does not improve RT at all. As expected, both lesions decrease the level of GPi activity (panel C) and therefore increase the disinhibition of thalamic neurons (panel D). The activity profiles shown in Fig. 6C may suggest side effects due to pallidotomy. Lesioning the GPi neurons effectively decreases further the dynamic range of the pallidal outputs, which could be reflected in more restricted motor repertoire or inflexibility in the pallidal modulation of movement (Kato and Kimura 1992). The differential effects of STN lesions and GPi lesions have been documented. In particular, injections of muscimol (a GABA agonist) that suppress GPi activity have stronger effects on behavior than kynurate injections (a glutamate antagonist blocking STN projections) in GPi cells. The null effect of subthalamotomy in RT in these simulations could be explained in terms of the direct and indirect pathways. Blocking STN excitatory projections to GPi would not have an immediate effect on the suppression of GPi activity by striatal stimulation if movement is triggered by direct striatopallidal activity, which in this case is smaller than normal.

It can be concluded from these simulations that stereotaxic surgery aimed at the pallidum or thalamus, which seems to reduce tremor and rigidity, may further impair on-line modulation of movement. It is predicted that patients would have a restricted movement repertoire because although such surgery may reduce the pathological level of activity in pallidal neurons, the modulation of cortical activity by striatopallidal projections is still disrupted. These observations suggest that in PD the neurons in GPi are saturated by excitatory activity from the subthalamic nucleus, and show small dynamic ranges of modulation by striatopallidal projections. Procedures aimed at improving PD should attack both (i.e. saturation and small dynamic range of pallidal activity) simultaneously.

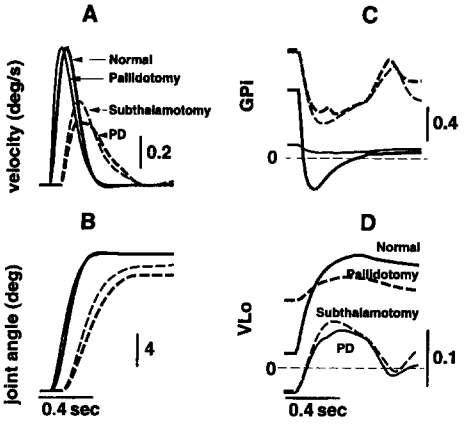

Fig. 6A–D. Simulated lesion studies. **A, B** joint velocity and position for a normal, PD, subthalamotomy, and pallidotomy networks; **C** GPi activities; **D** thalamic activities. Pallidotomy produces the most improvement in terms of reaction time (RT), movement time (MT), and movement amplitude. The effects of subthalamotomy are more subtle, and it does not improve RT. Therefore pallidotomy is more efficient in improving PD. Subthalamotomy was total, while pallidotomy destroyed 70% of pallidal output

6 Handwriting movements

Handwriting, a highly refined motor act that has both sequential and simultaneous components, is also affected by PD (McLennan et al. 1972; Margolin and Wing 1983). Known as micrographia, this deficit is characterized by a progressive decrease in letter size, fluctuating changes in writing baseline, and slowness. Because PD is associated with basal ganglia disease, micrographia has been attributed to basal ganglia dysfunction.

6.1 The VITE-WRITE model of handwriting production

Bullock et al. (1993) have proposed a neural network of handwriting production called the VITE-WRITE model. The VITE-WRITE model is a hierarchical model for handwriting by a redundant hand with three degrees of freedom (DOF). The handwriting motor program (vector plan) is composed of a sequence of normalized, directional motor subprograms that code single strokes. Each subprogram (TPV) is processed by a trajectory formation network (VITE) that generates the desired kinematics (position and velocity) for each stroke. A first-input, first-output central controller reads in successive motor subprograms from the vector plan at times of zero or maximum peak velocities until the whole motor sequence has been generated. The order and timing of the motor commands for each DOF determine the curvature of the movement. The three DOF model of Bullock et al. (1993) uses a VITE model to control each DOF or synergy independently. This system models transverse movements of the pen by finger extension/retraction, while longitudinal movements are modeled by vertical wrist

rotation (small horizontal movements) and horizontal wrist rotation (mainly responsible for left-to-right progression movements within words).

In the VITE-WRITE system, descriptors of desired global speed (GO) and size (GRO) scale the handwriting in time and space. The independent specification of path (shape) descriptors and speed and size descriptors allows the storing of highly compressed motor programs in motor memory. The final output is a series of pentip strokes whose control may be governed with respect to extrinsic spatial kinematics, idealized time-varying force components and underlying muscle activity. One of the features of the Bullock et al. model is that it assumes that graphic output is represented in an effector-dependent fashion. Next, we show how this system can be extended to include basal ganglia interactions that account for normal and parkinsonian handwriting.

6.2 Basal ganglia external loops and handwriting control

In the BASAL GANGLIA-VITE-WRITE system, the (cortical) highest-level module defines the movement plan. Complex finger movements, such as in handwriting, have been associated with activity in SMA (Roland et al. 1980a, b). Therefore, SMA is a strong candidate for the planning of handwriting motor programs. Anatomical data also support the role of SMA in other complex movements (e.g. sequential and/or simultaneous movements). In particular, it is known from neurophysiological and anatomical data that the basal ganglia receive a major input from SMA (Kunzle 1975; Alexander and Crutcher 1990). Furthermore, inhibitory inputs from GPi are directed to the thalamic nuclei VA and VLo (DeVito and Anderson 1982). Schell and Strick (1984) have shown that the SMA is connected densely with the VLo closing the basal ganglia–thalamocortical loop (Alexander et al. 1986). In the model of Fig. 3, the thalamocortical projections to SMA trigger the read-in of the next motor subprogram from the movement plan. It is predicted that lesions or blockade of VLo projections to SMA will differentially impair the sequential aspect of complex movements producing distortions in the shape of the trajectories. In addition, lesions to thalamic projections to motor or premotor cortex would impair the production of individual components of the task as seen in previous sections.

Figure 7 depicts a simulation of the handwriting letter sequence *llllllll* for a normal (A) and a PD system with 20% DA depletion (B) using three DOF, each represented by a basal ganglia–thalamocortical motor loop. The joint velocities for each DOF are shown in Fig. 7C. Several differences can be observed between the normal and the PD handwriting simulations. In the PD simulation, the handwriting shows a progressive decrease in letter size (or recurrent hypometria), increase in movement time (bradykinesia), and changes in handwriting baseline. These handwriting deficits resemble those seen in micrographia (McLennan et al. 1972). The peak velocities at each DOF show a progressive decrease in peak amplitude in the PD simulation. This simulation shows that disruptions in basal ganglia output signals can cause

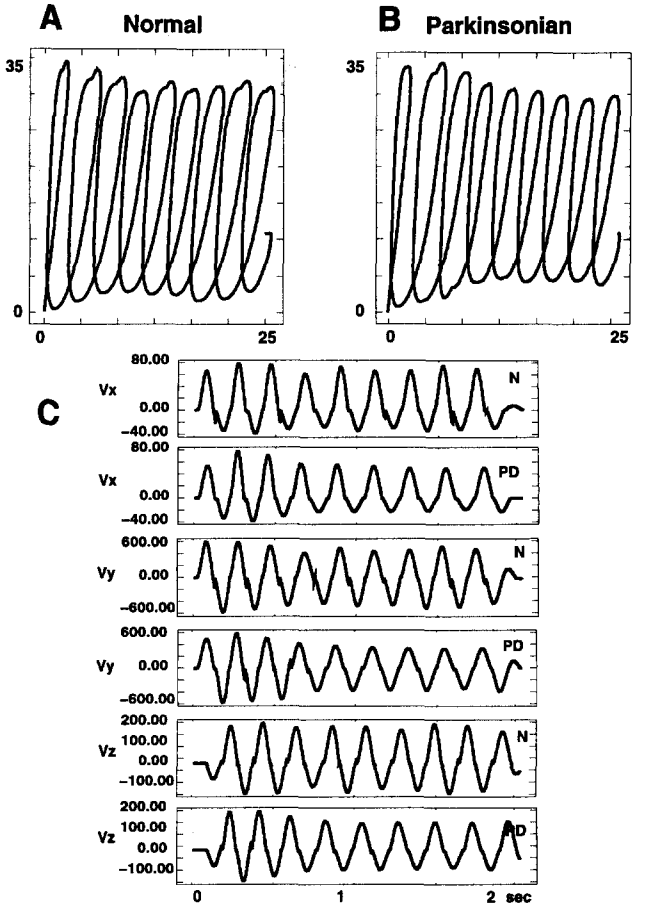

Fig. 7A–C. Handwriting simulation. **A** Normal (*N*) and **B** PD simulation of the sequence *llllllll* in arbitrary spatial units (*XY* plane). **C** Joint velocities for each degree of freedom (Bullock et al. 1993). $Vx(10^{-3}$ units/s), transverse movements (finger extension/retraction); Vy $(10^{-3}$ units/s), longitudinal hand movements by vertical wrist rotation; $Vz(10^{-6}$ units/s), transverse hand movements produced by horizontal wrist rotation. Micrographia is observed in the PD simulation (i.e. progressive decrease in letter size, increase in movement time, and changes in writing baseline) for 20% DA depletion. The motor sequence (temporal TPV) for each DOF was given by $\{\{25, 150, 0\}, \{0, 0, -3\}, \{-4, -150, 0\}, \{0, 0, 6\}\}$. This motor pattern was repeated nine times to obtain the motor sequence

deficits in movement speed and size. It suggests that micrographia is produced by abnormal pallidal output that produces slower rate of growth and premature resetting of pallidal-receiving thalamic outputs by increased subthalamic activity. These simulations support and extend the VITE-WRITE model of Bullock et al. (1993) to account for parkinsonian handwriting. In addition, these simulations suggest basal ganglia generation of GO signals (Bullock and Grossberg 1988). However, the network proposed here significantly suggests how neural structures cooperate to specify and generate simple and complex movements, and how deficits in neurochemical interactions can impair or degrade these movements. Furthermore, in these simulations the smaller-than-normal GO signal alone (e.g. Fig. 1) produces the spatio-temporal handwriting deficits seen in micrographia. This suggests that the GRO signal in the original VITE-WRITE model of Bullock et al., which spatially scales the

motor program to account for different global handwriting sizes, may not be impaired in PD.

7 Conclusions

Simulation studies support the hypothesis that pallidothalamic outputs provide gating signals that modulate phasically movement initiation and execution. Impairment of these signals in PD causes deficient modulation of movement speed and premature gating of movement components, which are caused by neurochemical imbalances in the opponently organized basal ganglia direct and indirect pathways. The opponent nature of these interactions suggests that in order to improve motor abnormalities resulting from PD, pharmacological approaches should aim to restore the balance in the activity of the direct and indirect pathways to improve not only the mean baseline rate of pallidal output, but also the dynamic range of striatopallidal modulation.

Appendix

The VITE circuit (Bullock and Grossberg 1988) computes the desired kinematics for a point-to-point movement as follows:

$$\frac{dV}{dt} = 30(-V + TPV - PPV)$$

where V is the difference vector; TPV and PPV are the target and present position vectors respectively; and $dPPV/dt = P[V]^+$, where P is the output from thalamic neurons, and $[x]^+ = x$ if $x > 0$ or zero otherwise.

The parameters for the basal ganglia network used in the simulations are: $A_s = 10.0$, $A_g = 3.0$, $A_h = 3.0$, $A_j = 10.0$, $A_p = 2.0$, $B_s = 1.0$, $B_g = 3.0$, $B_h = 2.0$, $B_j = 2.0$, $B_p = 2.0$, $D_s = 0.0$, $D_g = 0.8$, $D_h = 0.8$, $D_j = 0.8$, $D_p = 0.8$, $b = 2.0$, $c = 8.0$, $I_{\text{tonic}} = 0.2$, $I_s = 0.4$, $I_{\text{ACh}} = 0.5$, $I_k = 0$.

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References

Alamy M, Trouche E, Nieoullon A, Legallet E (1994) Globus pallidus and motor initiation: the bilateral effects of unilateral quisqualic acid-induced lesion on reaction times in monkeys. Exp Brain Res 99:247–258

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

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

Alexander GE, DeLong MR (1985) Microstimulation of the primate neostriatum. I. Physiological properties of striatal microexcitable zones. J Neurophysiol 53:1401–1416

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381

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

Baron M, Vitek J, Turner R, Kaneoke Y, Bakay R, DeLong M (1993) Lesions in the sensorimotor region of the internal segment of the globus pallidus (GPi) in Parkinsonian patients are effective in alleviating the cardinal signs of Parkinson's disease. Soc Neurosci Abstr 19:1584

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

Bullock D, Grossberg S (1988) Neural dynamics of planned arm movements: emergent invariants and speed–accuracy properties during trajectory formation. Psychol Rev 95:49–90

Bullock D, Grossberg S, Mannes C (1993) A neural network model for cursive script production. Biol Cybern 70:15–28

Cheruel F, Dormont JF, Amalric M, Schmied A, Farin D (1994) The role of putamen and pallidum in motor initiation in the cat. I. Timing of movement-related single-unit activity. Exp Brain Res 100:250–266

Chevalier G, Deniau JM (1990) Disinhibition as a basic process in the expression of striatal functions. Trends Neurosci 13:277–280

Contreras-Vidal JL, Teulings HL, Stelmach GE (1994) Understanding handwriting motor impairments in Parkinson's disease through neural networks. In: Proceedings of the World Congresss on Neural Networks, Vol II. INNS Press, pp 709–716

DeLong MR, Wichmann T (1993) Basal ganglia–thalamocortical circuits in Parkinsonian signs. Clin Neurosci 1:18–26

DeVito JL, Anderson ME (1982) An autoradiographic study of efferent connections of the globus pallidus. Exp Brain Res 46:107–117

Fink JS (1993) Neurobiology of basal ganglia receptors. Clin Neurosci 1:27–35

Flaherty AW, Graybiel AM (1993) Output architecture of the primate putamen. J Neurosci 13:3222–3237

Flaherty AW, Graybiel AM (1994) Input–output organization of the sensorimotor striatum in the squirrel monkey. J Neurosci 14: 599–610

Gerfen CR (1992) The neostriatal mosaic: multiple levels of compartmental organization in the basal ganglia. Annu Rev Neurosci 15:285–320

Gerfen CR (1993) Segregation of D1 and D2 dopamine receptor mRNA in separate populations of striatal neurons. Soc Neurosci Abstr. 19:133

Georgopoulos AP, DeLong MR, Cruther 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

Georgopoulos AP, Schwartz AB, Kettner RE (1986) Neuronal population coding of movement direction. Science 233:1416–1419

Golani I (1992) A mobility gradient in the organization of vertebrate movement: the perception of movement through symbolic language. Behav Brain Sci 15:249–308

Goldman PS, Nauta WSH (1977) An intricately patterned prefrontcaudate projection in the rhesus monkey. J Comp Neurol 171:369–386

Graybiel AM (1990) Neurotransmitters and neuromodulators in the basal ganglia. Trends Neurosci 13:244–254

Graybiel AM, Aosaki T, Flaherty AW, Kimura M (1994) The basal ganglia and adaptive motor control. Science 265:1826–1831

Grossberg S (1984) Some normal and abnormal behavioral syndromes due to transmitter gating of opponent processes. Biol Psychiatry 19:1075–1117

Guridi J, Luquin MR, Herrero MT, Obeso JA (1993) The subthalamic nucleus: a possible target for stereotaxic surgery in Parkinson's disease. Mov Disorders 8:421–429

Hamada L, DeLong MR (1992) Excitotoxic acid lesions of the primate subthalamic nucleus result in reduced pallidal neuronal activity during active holding. J Neurophysiol 68:1859–1866

Hoover JE, Strick PL (1993) Multiple output channels in the basal ganglia. Science 259:819–821

Horak FB, Anderson ME (1984) Influence of globus pallidus on arm movements in monkeys. I. Effects of lesions. J Neurophysiol 52:290–304

Jaeger D, Gilman S, Aldridge JW (1993) Primate basal ganglia activity in a precued reaching task: preparation for movement. Exp Brain Res 95:51–64

Jinnai K, Nambu A, Yoshida S (1989) Activity of thalamic neurons conveying the basal ganglia output to the motor cortex. In: Ito M (ed) Neural programming. Karger, Basel, pp 111–121

Kato M, Kimura M (1992) Effects of reversible blockade of basal ganglia on a voluntary arm movement. J Neurophysiol 68:1516–1534

Kish SJ, Shannak K, Hornykiewicz O (1988) Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. N Engl J Med 318:876–880

Kunzle H (1975) Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia: an autoradiographic study in *Macaca fascicularis*. Brain Res 88:195–209

Laitinen LV, Bergenheim AT, Hariz MI (1992) Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg 76:53

Margolin DI, Wing AM (1983) Agraphia and micrographia: clinical manifestations of motor programming and performance disorders. Acta Psychol 54:263–283

Marsden CD, Obeso JA (1994) The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. Brain 117:877–897

McLennan JE, Nakano K, Tyler HR, Schwab RS (1972) Micrographia in parkinson's disease. J Neurol Sci 15:141–152

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

Mink JW, Thach WT (1991b) Basal ganglia motor control. III. Pallidal ablation: normal reaction time, muscle cocontraction, and slow movement. J Neurophysiol 65:330–351

Montgomery EB, Buchholz SR (1991) The striatum and motor cortex in motor initiation and execution. Brain Res 549:222–229

Montgomery EB, Gorman DS, Nuessen J (1991) Motor initiation versus execution in normal and Parkinson's disease subjects. Neurology 41:1469–1475

Nambu A, Yoshida SI, Jinnai K (1990) Discharge patterns of pallidal neurons with input from various cortical areas during movement in the monkey. Brain Res 519:183–191

Neve KA, Neve RL, Fidel S, Janowsky A, Higgins GA (1991) Increased abundance of alternatively spliced forms of D2 dopamine receptor mRNA after denervation. Proc Natl Acad Sci USA 88:2802–2806

Penney JB, Young AB (1983) Speculations on the functional anatomy of basal ganglia disorders. Annu Rev Neurosci 6:73–94

Roland PE, Larsen B, Lassen NA, Skinhoj E (1980a) Supplementary motor area and other cortical areas in organization of voluntary movements in man. J Neurophysiol 43:118–136

Roland PE, Larsen B, Lassen NA, Skinhoj E (1980b) Different cortical areas in man in organization of voluntary movements in extrapersonal space. J Neurophysiol 43:137–150

Schell GR, Strick PL (1984) The origin of thalamic input to the arcuate premotor and supplementary motor areas. J Neurosci 4:539–560

Schneider JS (1987) Basal ganglia-motor influences: role of sensory gating. In: Schneider JS, Lidsky TI (eds) Basal ganglia: sensory aspects of motor functioning. Pitman, London, pp 103–121

Stelmach GE, Phillips JG (1991) Movement disorders: limb movement and the basal ganglia. Phys Ther 71:60–66

Stelmach GE, Teasdale N, Phillips J, Worringham CJ (1989) Force production characteristics in Parkinson's disease. Exp Brain Res 76:165–172