

# 기저핵 운동회로와 파킨슨 증상의 신경생리

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## Basal Ganglia Motor Circuit and Physiology of Parkinsonism

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The basal ganglia are a group of nuclei located in the deep portion of the brain. Along with the cerebellum, the basal ganglia have a major role in controlling human voluntary movements, and their dysfunction is apparently responsible for various involuntary movements. Although the exact mechanism of how the basal ganglia control movements has yet to be clarified, the model of focused selection (through the direct pathway) and tonic inhibition (via the indirect pathway) is proposed to be a principal functional model of the basal ganglia. Parkinson's disease (PD) is classically characterized by bradykinesia, rigidity and tremor-at-rest. All features seem to be associated with dopamine depletion resulting from the degeneration of the nigrostriatal pathway, which produces reduced activity of the direct pathway and a concurrent enhancement of excitatory output from STN. This change may result in increased tonic background inhibition and reduced focused selection via the direct pathway, causing difficulties in performing voluntary movements selectively. However, it has not been possible to define a single underlying pathophysiologic mechanism that explains all parkinsonian symptoms. Here the data that give separate understanding to each of the three classic features are discussed.

**Key Words:** Basal ganglia, Motor circuit, Parkinsonism

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### Basal Ganglia

The basal ganglia are a group of nuclei located in the deep portion of the brain. The term basal ganglia has no strict anatomical definition and includes the caudate nucleus, the lenticular nucleus including the putamen and the globus pallidus (GP), and other subcortical nuclei such as the subthalamic nucleus (STN), the substantia nigra [consisting of the pars compacta (SNc) and pars reticulata (SNr)], and more recently pedun-

culopontine nucleus (PPN). The caudate and putamen are together referred to as the striatum. The basal ganglia are part of complex network of neuronal circuits organized in parallel to integrate different cortical functions.<sup>1</sup> Five functionally different cortico-basal ganglia-thalamo-cortical loops have been defined: (1) motor, (2) oculomotor, (3) associative, (4) limbic, and (5) orbitofrontal. In addition, the basal ganglia have intimate connections with the various brainstem nuclei such as the locus ceruleus, the raphe nucleus and the reticular formation. The motor circuit is most relevant to the pathophysiology of various movement disorders including parkinsonism, although dysfunction of other circuits are also frequently associated with these disorders. Thus, in this chapter, we primarily focused on the motor circuits of the basal ganglia and its

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impairments in parkinsonism.

## 1. Afferent structures

### 1) Striatum

The striatum is the main afferent structure in the basal ganglia, which receives an excitatory, glutamatergic input from all of the cerebral cortex, except for primary visual and auditory areas.<sup>2-4</sup> The cortical input is arranged with a rough topography so that projections from each cortical area are connected to longitudinal bands in the striatum.<sup>5</sup> There is also convergence and divergence of cortical input to the striatum.<sup>6,7</sup> While the projection from a single cortical area terminates divergently in several patches in the striatum, there is also convergence of inputs from more than one cortical area such that the projections from one body part area of the motor and sensory cortex overlap.<sup>6</sup> The multiply convergent and divergent pattern of the corticostriatal projection provides an anatomical substrate in the striatum for the integration of information from several different areas of the cerebral cortex.<sup>7</sup> Other excitatory inputs to the striatum arise from the midline and intralaminar nuclei of the thalamus,<sup>8</sup> and from the limbic structures, particularly the amygdale.<sup>9</sup> The striatum also receives dopaminergic afferents from SNc and the ventral tegmental area, serotonergic afferents from the dorsal nucleus of the raphe, and a sparse noradrenergic innervation from the locus ceruleus.<sup>10</sup>

Medium spiny neurons are the major neuronal population in the striatum, accounting for almost 95% of total striatal cells and project to the globus pallidus and substantia nigra.<sup>11,12</sup> The remaining 5% of striatal neurons consists of aspiny interneurons, which contain acetylcholine, somatostatin, NADPH-diaphorase or GABA.<sup>13</sup> Medium spiny neurons, since they have radial dendritic trees spanning up to 500  $\mu\text{m}$ ,<sup>14</sup> may receive inputs from several cortical areas. In addition, medium spiny neurons also receive a number of other inputs, including (1) an excitatory input from the thalamus<sup>15</sup>; (2) cholinergic input from the large aspiny striatal neurons<sup>16</sup>; (3)  $\gamma$ -aminobutyric acid (GABA), substance P/dynorphin, and enkephalin input from adjacent medium

spiny neurons<sup>17</sup>; (4) dopaminergic input from SNc.<sup>18</sup> Medium spiny neurons contain the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA) and colocalized peptide neurotransmitters such as enkephalin and substance P/dynorphin.<sup>17,19</sup> Medium spiny neurons can be divided based on their neurotransmitter content and post-synaptic target. One population contains GABA and substance P/dynorphin and projects to the internal segment of the globus pallidus (GPi) and SNr, while the second population containing GABA and enkephalin, sends their axons to the external segment of the globus pallidus (GPe).<sup>20-22</sup> There is other anatomically segregated population of medium spiny neurons containing GABA and substance P/dynorphin, which projects to SNc.<sup>20</sup>

Striatal neurons express both D1 and D2 dopamine receptors, which mediate the modulatory effect of dopamine released from nigrostriatal nerve terminals. D1 and D2 receptors are supposed to be functionally segregated to different subsets of striatal neurons. Accordingly, D1 receptors are expressed by neurons projecting to GPi and SNr, while D2 receptors are expressed by neurons projecting to GPe.<sup>22,23</sup> A small population of striatal neurons expresses both D1 and D2 receptors.<sup>24</sup> Dopaminergic transmission modulates the striatal responses to incoming inputs, particularly those mediated by glutamate.<sup>25,26</sup>

### 2) Subthalamus

STN is the only glutamatergic nucleus of the basal ganglia circuit.<sup>27</sup> STN receives an important inhibitory GABA input from GPe. Other inhibitory projections arise from GPi and the striatum.<sup>28</sup> STN also receives a short-latency, excitatory, glutamatergic input from motor areas of ipsilateral cerebral cortex, including the primary motor, premotor, supplementary motor cortex and the frontal eye field.<sup>29,30</sup> Although the cortico-subthalamic projection appears to be topographically organized,<sup>29</sup> there may be a certain degree of convergence of inputs from the different cortical areas onto an individual STN neuron, considering the length of dendrites of STN neurons (up to 1200  $\mu\text{m}$ ).<sup>31</sup> The STN output is excitatory and glutamatergic, and projects mainly to the basal gan-

glia output nuclei, GPi and SNr, and also to GPe.<sup>32</sup> The projections from STN to the output nuclei show a rough topography.<sup>33</sup> The majority of STN projections to GPi and to SNr arise from a separate population of neurons.<sup>34</sup> The STN to GPi projection appears to be highly divergent so that each STN neuron is connected to many GPi neurons.<sup>35</sup> In summary, STN sends a fast, divergent, excitatory signal to GPi and SNr, while the striatum sends a slower, more focused, inhibitory signal.<sup>36</sup>

## 2. Efferent structures

The internal segment of the globus pallidus and SNr are the main output structures of the basal ganglia, and are composed of large neurons that receive similar patterns of input. Because of histological and connectional similarities between GPi and SNr, these two nuclei are considered to be one structure that is divided by the internal capsule during development.<sup>18</sup>

### 1) Internal segment of the globus pallidus (GPi)

In primates, the globus pallidus is divided into internal (GPi) and external segments (GPe) by the internal medullary lamina. In rodents, GPi is located within the internal capsule, and called entopeduncular nucleus. GPi is primarily composed of large neurons projecting outside of the basal ganglia, which are inhibitory and GABAergic.<sup>37</sup> GPi projects primarily to the motor thalamus, particularly the ventral anterior and ventral lateral thalamic nuclei that, in turn, project widely to the motor, premotor, supplementary motor, and possibly prefrontal cortex.<sup>38</sup> An individual GPi neuron sends output via the thalamus to only one area of the cerebral cortex.<sup>39</sup> GPi neurons projecting to the motor cortex are separate from those projecting to the premotor cortex. This arrangement of GPi projection suggests functionally segregated parallel outputs of the basal ganglia.<sup>1,39</sup> Other projections of GPi are connected to the parafascicular nucleus of the thalamus, lateral habenula and pedunculopontine nucleus (PPN).<sup>40,41</sup> GPi neurons receive a combination of inhibitory (GABAergic) and excitatory (glutamatergic) projections. The main source of

GABAergic inputs arise from the striatum and GPe,<sup>32</sup> while most excitatory innervation is provided by STN,<sup>32</sup> with a small contribution from the frontal cortex.<sup>42</sup> The balance between these two opposite systems determines the functional activity of GPi.

### 2) Substantia nigra pars reticulata (SNr)

Like the globus pallidus, the substantia nigra is divided into two segments. One is densely cellular region called pars compacta, while the other is sparsely cellular and called pars reticulata.<sup>18</sup> SNr lies ventral to SNc, and contains GABAergic neurons,<sup>43</sup> while SNc contains mainly dopaminergic cells. Like GPi, SNr sends its inhibitory GABAergic projections mainly to the ventral anterior and ventral lateral nuclei of the thalamus.<sup>38,43</sup> These thalamic areas in turn project to the premotor and prefrontal cortex.<sup>44</sup> Other targets of nigral projections include the centromedian-parafascicular complex of the thalamus and PPN.<sup>38,45</sup> The primary difference between the output of GPi and SNr is that the lateral portion of SNr is connected with cortical and brainstem areas related to eye movements. This lateral part of SNr sends an inhibitory projection to the superior colliculus and the paramedian part of the dorsal medial thalamus that project in turn to the frontal eye field.<sup>46,47</sup> Afferent inputs to SNr are similar to those to GPi, which are composed of both GABAergic and glutamatergic inputs from diverse structures.<sup>38</sup>

## 3. Intrinsic nuclei

GPe and SNc are considered as intrinsic nuclei of the basal ganglia. They receive most of their inputs from and send most of their outputs to the other basal ganglia nuclei.

### 1) External segment of the globus pallidus

The main sources of inputs to GPe are the striatum (GABAergic) and STN (glutamatergic).<sup>32</sup> The pattern of termination of the striatal and STN afferents in GPe is similar to GPi: the striatal input is focused and relatively discrete, while the STN input is divergent.<sup>35</sup> The GPe output is GABAergic (co-localized with enkephalin) and

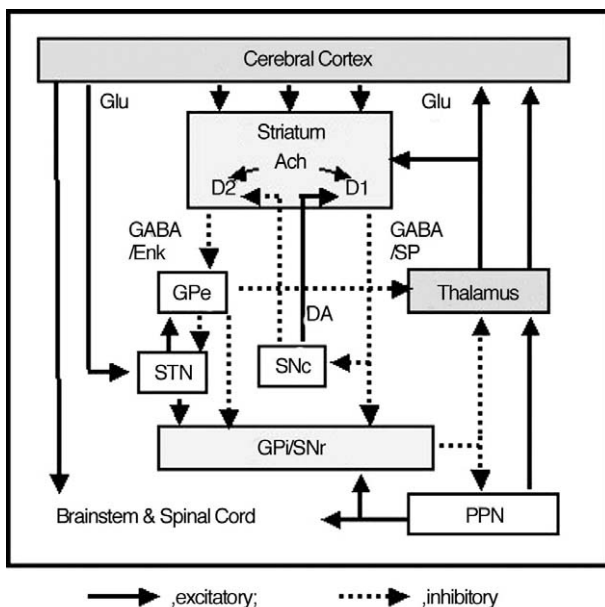
mainly to STN.<sup>32</sup> In addition, other GABAergic GPe outputs to GPi and SNr have been described.<sup>32,48</sup> Since GPe and GPi get input from anatomically intermixed striatal neurons, they presumably receive similar information. Considering the fact that GPe inhibits GPi directly or via STN, GPe may act to oppose, limit, or focus the effect of striatal projection to GPi.<sup>49</sup>

2) Substantia nigra pars compacta

SNc is mainly composed of large dopamine-containing cells. SNc receives GABAergic inputs from the striatum.<sup>50</sup> SNc dopamine neurons project to all of the striatum, both the caudate and putamen, in a topographical manner.<sup>51</sup>

Motor Control

Along with the cerebellum, the basal ganglia have a major role in controlling human voluntary movements, and their dysfunction is apparently responsible for various involuntary movements.



**Figure 1.** Schematic representation of basal ganglia functional circuitry, according to the direct and indirect pathway model. Ach, acetylcholine; Enk, enkephalin; D1 & D2, D1 & D2 dopamine receptor; DA, dopamine; Glu, glutamate; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; PPN, pedunculopontine nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; SP, substance P; STN, subthalamic nucleus.

Although the exact mechanism of how the basal ganglia control movements has yet to be clarified, several models of basal ganglia functioning have been proposed.<sup>21,23,36,49,50,52</sup>

1. Direct and indirect pathway

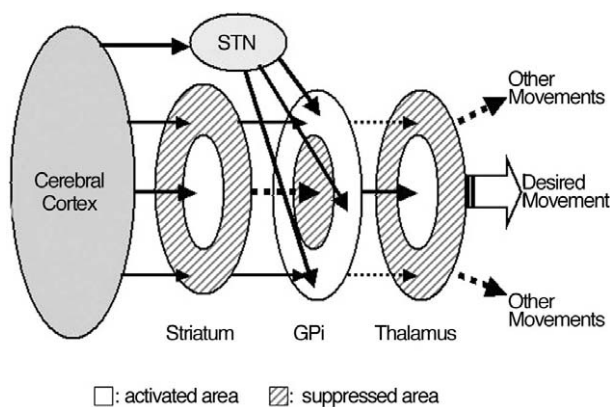
The striatum—the main afferent nucleus of the basal ganglia—transmits the flow of information received from the cerebral cortex to the basal ganglia output nuclei, GPi and SNr, via the direct and the indirect pathway. These two pathways originate from different subsets of striatal neurons and remain functionally segregated. In the direct pathway, striatal GABAergic neurons that contain substance P and dynorphin as co-transmitters and express D1 dopamine receptors, project monosynaptically to GPi and SNr. In the indirect pathway, a different subset of striatal GABAergic neurons containing enkephalin and expressing D2 dopamine receptor, projects to GPe, which sends GABAergic projection to STN. STN, in turn, sends its glutamatergic efferents to GPi and SNr. From GPi and SNr, inhibitory GABAergic projections reach the ventral anterior and ventral lateral nuclei of the thalamus. Thalamic nuclei then send excitatory glutamatergic projection to the motor cortex, thus completing the cortico-basal ganglial-thalamo-cortical loop (Fig. 1).

According to this scheme, the functional consequence of such organization is that activation of the direct and the indirect pathway leads to opposite changes in the net output of the basal ganglia circuit. In fact, activation of the striatal neurons giving rise to the direct pathway produces inhibition of GABAergic neurons of the output nuclei, which, in turn, leads to disinhibition of the thalamic nuclei. In contrast, activation of the striatal neurons projecting to GPe in the indirect pathway causes inhibition of GPe and subsequent disinhibition of STN, which, in turn, increase the inhibitory activity of the output neurons from GPi and SNr to the thalamus. In this functional model of the basal ganglia, the balance of activity between the direct and indirect pathway is supposed to have an important role in controlling human voluntary movement, and its

imbalance is assumed to be responsible for various involuntary movements on one hand and bradykinesia on the other hand.

## 2. Focused selection and tonic inhibition

Mink<sup>36</sup> expanded the direct and indirect pathway model of the basal ganglia function, and proposed 'focused selection and tonic inhibition' concept as a functional model of the basal ganglia, based on several previous observations about the characteristics of the basal ganglia nuclei during voluntary movements. These include: (1) Movement-related neurons in the striatum, STN, GPi and SNr are somatotopically arranged.<sup>53-55</sup> (2) Striatal neurons are quiet at rest and activated during movements,<sup>54,56</sup> while STN neurons are tonically active and more activated during movements.<sup>55,57,58</sup> Considering the anatomical connections, these facts indicate that GPi/SNr neurons receive a widespread, tonically active excitatory input with phasic increases from STN and a focused, intermittent phasic inhibitory input from the striatum. (3) Some neurons in the basal ganglia discharge in relation to movement in a context-dependent manner,<sup>59-61</sup> but code neither parameters of movement nor muscle activity patterns. (4) The basal ganglia neurons with set-and movement-related discharge are active after those neurons in the motor and supplementary motor cortex,<sup>62-64</sup> suggesting that set-and movement-related activity does not originate in the basal



**Figure 2.** Functional organization of the basal ganglia, according to the focused selection and tonic inhibition model. GPi, internal segment of the globus pallidus; STN, subthalamic nucleus.

ganglia. In this model, during voluntary movements, enhanced corticosubthalamopallidal activity inhibits thalamic excitatory output to the motor cortex, providing tonic suppression of the motor cortex. Simultaneously other pallidal neurons projecting to the thalamus act to generate desired movements by decreasing their discharge through focused striatal output via the direct pathway, thereby removing tonic inhibition to the thalamus and releasing the 'brake' from the desired cortical generators (Fig. 2).

## 3. Surround inhibition as a principle mechanism to select desired movement

Surround inhibition, suppression of excitability in an area surrounding an activated neural network, is a physiologic mechanism to focus neuronal activity and to select neuronal responses. In the sensory system, surround inhibition is proved to be an essential mechanism for spatiotemporal discrimination of various sensory inputs.<sup>65</sup> In the motor cortex, although a somatotopic representation is relatively well preserved between the major subdivisions of the body musculature (such as face, arm and leg), zones related to a single muscle are intermixed with zones related to different muscles within each of these divisions.<sup>66</sup> In addition, a single muscle is often activated by several spatially segregated zones,<sup>66,67</sup> and stimulation of a single pyramidal neuron usually produces responses from multiple muscles.<sup>68-70</sup> In this setting, the execution of a desired movement certainly requires coordination of spatially separated neural elements through intracortical connectivity, i.e., a neural network.<sup>71,72</sup> Thus, any surround inhibition in the motor cortex may not be anatomically wired, but presumably exists between representation zones of unrelated or reciprocally interfering movement patterns. Pyramidal neurons in the motor cortex that exert excitatory influences on their postsynaptic targets have horizontal axon collaterals that are connected locally to other pyramidal neurons as well as to inhibitory interneurons.<sup>73,74</sup> The connections between pyramidal neurons presumably provide feedforward excitatory interactions between groups of cells related to the same

movement, whereas the connections with inhibitory interneurons may form a basis for surround inhibition between representation zones related to the activation of different muscles.<sup>72</sup> The arrangement of the basal ganglia–thalamo–cortical output in ‘focused selection and tonic inhibition’ model could regulate neural networks in the motor cortex resulting in a recruitment of cells related to a desired movement, and a concurrent suppression of cells related to other unwanted movements, i.e., surround inhibition.

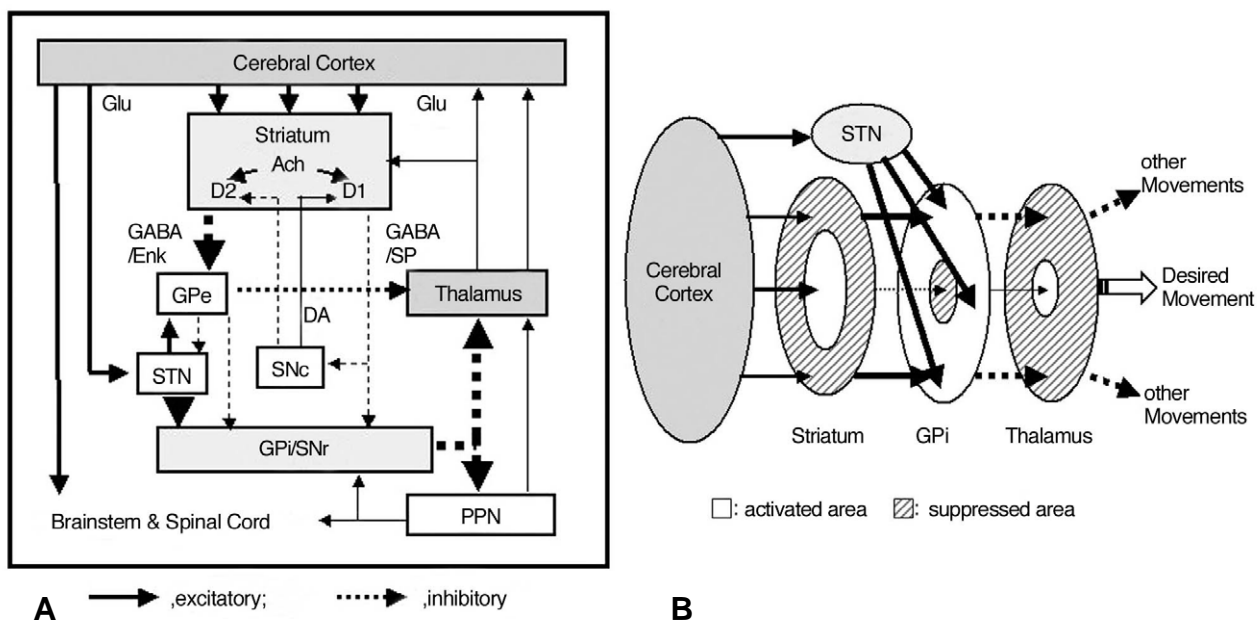
### Parkinsonism

Parkinson’s disease (PD) is classically characterized by bradykinesia, rigidity and tremor-at-rest. All features seem to be associated with dopamine depletion resulting from the degeneration of the nigrostriatal pathway, which produces reduced activity of the direct pathway and a con-

current enhancement of excitatory output from STN (Fig. 3A). This change may result in increased tonic background inhibition and reduced focused selection via the direct pathway, causing difficulties in performing voluntary movements selectively (Fig. 3B). However, it has not been possible to define a single underlying pathophysiologic mechanism that explains all parkinsonian symptoms. Nevertheless, there are considerable data that give separate understanding to each of the three classic features.

#### 1. Bradykinesia

The most important functional disturbance in patients with PD is a disorder of voluntary movement prominently characterized by slowness. This phenomenon is generally called bradykinesia, although it has at least two components, which can be designated as bradykinesia and akinesia.<sup>75</sup> Bradykinesia refers to slowness of move-



**Figure 3.** (A) Alteration of the basal ganglia functional circuitry in Parkinson’s disease. Through the direct and indirect pathway, reduced nigrostriatal dopaminergic activity results in enhancement of basal ganglia inhibitory output to the thalamus, thereby causing reduction in thalamocortical excitation. Ach, acetylcholine; Enk, enkephalin; D1 & D2, D1 & D2 dopamine receptor; DA, dopamine; Glu, glutamate; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; PPN, pedunculopontine nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; SP, substance P; STN, subthalamic nucleus. (B) Changes in focused selection and tonic inhibition function of the basal ganglia in Parkinson’s disease. While enhanced activity of the indirect pathway results in increased suppression of other unwanted movements, reduced direct pathway activity causes reduction in thalamic disinhibition, producing impaired release of desired action from tonically suppressed motor cortex. GPi, internal segment of the globus pallidus; STN, subthalamic nucleus.

ment that is ongoing. Akinesia refers to failure of willed movement to occur. There are two possible reasons for the absence of expected movement. One is that the movement is so slow (and small) that it cannot be seen. A second is that the time needed to initiate the movement becomes excessively long.

While self-paced movements can give information about bradykinesia, the study of reaction time movements can give information about both akinesia and bradykinesia. In the reaction time situation, a stimulus is presented to a subject, and the subject must make a movement as rapidly as possible. The time between the stimulus and the start of movement is the reaction time, and the time from initiation to completion of movement is the movement time. Using this logic, prolongation of reaction time is akinesia, and prolongation of movement time is bradykinesia. Studies of patients with PD confirm that both reaction time and movement time are prolonged. However, the extent of abnormality of one does not necessarily correlate with the extent of abnormality of the other.<sup>76</sup> This suggests that they may be impaired by separable physiological mechanisms. In general, prolongation of movement time (bradykinesia) is better correlated with the clinical impression of slowness than is prolongation of reaction time (akinesia).

Some contributing features of bradykinesia are established. One is that there is a failure to energize muscles up to the level necessary to complete a movement in a standard amount of time. This has been demonstrated clearly with attempted rapid, monophasic movements at a single joint.<sup>77</sup> In this circumstance, movements of different angular distances are accomplished in approximately the same time by making longer movements faster. The EMG activity underlying the movement begins with a burst of activity in the agonist muscle of 50 to 100 ms, followed by a burst of activity in the antagonist muscle of 50 to 100 ms, followed variably by a third burst of activity in the agonist. This "triphasic" pattern has relatively fixed timing with movements of different distance, correlating with the fact of similar total time for movements of different dis-

tance. Different distances are accomplished by altering the magnitude of the EMG within the fixed duration burst. The pattern is correct in patients with PD, but there is insufficient EMG activity in the burst to accomplish the movement. These patients often must go through two or more cycles of the triphasic pattern to accomplish the movement. Interestingly, such activity looks virtually identical to the tremor-at-rest seen in these patients. The longer the desired movement, the more likely it is to require additional cycles. These findings were reproduced by Baroni et al<sup>78</sup> who also showed that L-DOPA normalized the pattern and reduced the number of bursts.

Berardelli and colleagues<sup>79</sup> showed that PD patients could vary the size and duration of the first agonist EMG burst with movement size and added load in the normal way. However, there was a failure to match these parameters appropriately to the size of movement required. This suggests an additional problem in scaling of actual movement to the required movement. A problem in sensory scaling of kinesthesia was demonstrated by Demirci et al.<sup>80</sup> PD patients used kinesthetic perception to estimate the amplitude of passive angular displacements of the index finger about the metacarpophalangeal joint and to scale them as a percentage of a reference stimulus. The reference stimulus was either a standard kinesthetic stimulus preceding each test stimulus (task K) or a visual representation of the standard kinesthetic stimulus (task V). The PD patients' underestimation of the amplitudes of finger perturbations was significantly greater in task V than in task K. Thus, when kinesthesia is used to match a visual target, distances are perceived to be shorter by the PD patients. Assuming that visual perception is normal, kinesthesia must be "reduced" in PD patients. This reduced kinesthesia, when combined with the well-known reduced motor output and probably reduced corollary discharges, implies that the sensorimotor apparatus is "set" smaller in PD patients than in normal subjects.

In a slower, multijoint movement task PD patients show a reduced rate of rise of muscle activity that also implies deficient activation.<sup>81</sup>

On the other hand, Jordan, Sagar and Cooper<sup>82</sup> showed that release of force was just as slowed as increase of force suggesting that slowness to change and not deficient energization was the main problem. If termination of activity is an active process, then this finding really does not argue against deficient energization.

A second physiologic mechanism of bradykinesia is that there is difficulty with simultaneous and sequential movements.<sup>83</sup> That PD patients have more difficulty with simultaneous movements than with isolated movements was first pointed out by Schwab, Chafetz and Walker.<sup>84</sup> Quantitative studies show that slowness in accomplishing simultaneous or sequential movements is more than would be predicted from the slowness of each individual movement. With sequential movements, there is another parameter of interest, the time between the two movements designated the interonset latency (IOL) by Benecke and colleagues.<sup>83</sup> The IOL is also prolonged in patients with PD. This problem, similar to the problem with simple movements, can also be interpreted as insufficient motor energy.

Akinesia would seem to be multifactorial, and a number of contributing factors are already known. As noted above, one type of akinesia is the limit of bradykinesia from the point of view of energizing muscles. If the muscle is selected but not energized, then there will be no movement. Such phenomena can be recognized on some occasions with EMG studies where EMG activity will be initiated but will be insufficient to move the body part. Another type of akinesia, again as noted above, is prolongation of reaction time; the patient is preparing to move, but the movement has not yet occurred. Considerable attention has been paid to mechanisms of prolongation of reaction time. One factor is easily demonstrable in patients with rest tremor, who appear to have to wait to initiate the movement together with a beat of tremor in the agonist muscle of the willed movement.<sup>85,86</sup>

Another mechanism of prolongation of reaction time can be seen in those circumstances where eye movement must be coordinated with limb movement.<sup>87</sup> In this situation, there is a visual

target that moves into the periphery of the visual field. Normally, there is a coordinated movement of eyes and limb, the eyes beginning slightly earlier. In PD, some patients do not begin to move the limb until the eye movement is completed. This might be due to a problem with simultaneous movements, as noted above. Alternatively, it might be that PD patients need to foveate a target before they are able to move to it.

Many studies have evaluated reaction time quantitatively with neuropsychological methods.<sup>88</sup> The goal of these studies is to determine the abnormalities in the motor processes that must occur before a movement can be initiated. In order to understand reaction time studies, it is useful to consider from a theoretical point of view the tasks that the brain must accomplish. The starting point is the "set" for the movement. This includes the environmental conditions, initial positions of body parts, understanding the nature of the experiment and, in particular, some understanding of the expected movement. In some circumstances, the expected movement is described completely, without ambiguity. This is the "simple reaction time" condition. The movement can be fully planned. It then needs to be held in store until the stimulus comes to initiate the execution of the movement. In other circumstances, the set does not include a complete description of the required movement. It is intended that the description be completed at the time of the stimulus that calls for the movement initiation. This is the "choice reaction time" condition. In this circumstance, the programming of the movement occurs between the stimulus and the response. Choice reaction time is always longer than simple reaction, and the time difference is due to this movement programming.

In most studies, simple reaction time is significantly prolonged in patients compared with normals.<sup>88</sup> On the other hand, patients appear to have normal choice reaction times or the increase of choice reaction time over simple reaction time is the same in patients and normal subjects. Many studies in which cognitive activity was required for a decision on the correct motor response have shown that PD patients do not



have apparent slowing of thinking, called bradyphrenia. We extended the study of choice reaction times by considering three different choice reaction time tasks that required the same simple movement, but differed in the difficulty of the decision of which movement to make.<sup>89</sup> Comparing PD patients to normal subjects, the patients had a longer reaction time in all three conditions, but the difference was largest when the task was the easiest and smallest when the task was the most difficult. Thus, the greater the proportion of time there is in the reaction time devoted to motor program selection, the closer to normal are the PD results. Labutta et al.<sup>90</sup> have shown that PD patients have no difficulty holding a motor program in store. Hence, the difficulty must be executing the motor program. Execution of the movement, however, lies at the end of choice reaction time, just as it does for simple reaction time. How then can it be abnormal and choice reaction time be normal? The answer may be that in the choice reaction time situation both the motor programming and the motor execution can proceed in parallel.

Transcranial magnetic stimulation (TMS) can be used to study the initiation of execution. With low levels of TMS, it is possible to find a level that will not produce any motor evoked potentials (MEPs) at rest, but will produce an MEP when there is voluntary activation. Using such a stimulus in a reaction time situation between the stimulus to move and the response, Starr et al.<sup>91</sup> showed that stimulation close to movement onset would produce a response even though there was still no voluntary EMG activity. A small response first appeared about 80 ms before EMG onset and grew in magnitude closer to onset. This method divides the reaction time into two periods. In the first period, the motor cortex remains "unexcitable." In the second period, the cortex becomes increasingly "excitable" as it prepares to trigger the movement. We found that most of the prolongation of the reaction time was due to prolongation of the later period of rising excitability.<sup>92</sup> This result has been confirmed.<sup>93</sup> Our finding of prolonged initiation time in PD patients is supported by studies of motor cortex neuronal activi-

ty in reaction time movements in monkeys rendered parkinsonian with MPTP.<sup>94</sup> In these investigations, there was a prolonged time between initial activation of motor cortex neurons and movement onset.

Thus, an important component of akinesia is the difficulty in initiating a planned movement. This statement would not be a surprise to PD patients, who often say that they know what they want to do, but they just can't do it. A major problem in bradykinesia is a deficiency in activation of muscles, whereas the problem in akinesia seems to be a deficiency in activation of motor cortex. The dopaminergic system apparently provides energy to many different motor tasks, and the deficiency of this system in PD leads to both bradykinesia and akinesia.

Another factor that should be kept in mind is that patients appear to have much more difficulty initiating internally triggered movements than externally triggered movements. This is clear clinically in that external clues are often helpful in movement initiation. Examples include improving walking by providing an object to step over or playing march music. This can also be demonstrated in the laboratory with a variety of paradigms.<sup>95,96</sup>

#### 1) Additional human evidence for decreased cortical activation in PD

Rossini et al.<sup>97</sup> showed that the amplitude of the N30 of the median nerve somatosensory evoked potential (SEP) was diminished in PD. Other peaks of the SEP were normal and the N30 had normal latency and topography. The origin of the N30 (as most of the waves of the SEP) is debated, but its decrease does suggest deficient cortical activation.

Studies of movement related cortical potentials (MRCPs) in patients with PD are controversial, but many studies show a decreased Bereitschaftspotential (BP), a slowly rising negativity appearing during the 1 second before self-paced voluntary movements.<sup>98-100</sup> In the study by Jahanshahi et al.,<sup>100</sup> the BP was deficient with self-paced movements, but not externally triggered movements suggesting a particular diffi-

culty with internally triggered actions.

Neuroimaging studies show a decreased blood flow response in the supplementary motor area, and sometimes the sensorimotor area, with voluntary movement in PD patients.<sup>100-103</sup> This can be reversed with dopaminergic therapy. In the study by Jahanshahi et al.,<sup>100</sup> where the neuroimaging was done together with EEG recording, it was found that there was a deficiency of activation of the supplementary motor area in self-paced movements, but not in externally triggered movement.

The excitability of the motor cortex in PD patients has been assessed using TMS.<sup>104</sup> The threshold for a response was the same in normals and patients, there was a trend for the increase in MEP amplitude with stimulus intensity to be greater than normal, but the increase of the MEP amplitude with voluntary contraction was statistically less than normal. These results suggest that control of the excitability of the motor system is abnormal in PD patients, with enhanced excitability at rest and weak energization during voluntary muscle activation.

There also appears to be slightly less intracortical inhibition in patients with PD. One study found reduced intracortical inhibition,<sup>105</sup> while another did not.<sup>106</sup> On the other hand, both studies found shortening of the TMS provoked silent period that lengthened with dopaminergic treatment.

## 2. Rigidity

Tone is defined as the resistance to passive stretch. Rigidity is one form of increased tone, that is seen in disorders of the basal ganglia ("extrapyramidal disorders"), and is particularly prominent in PD. Increased tone can result from changes in (1) muscle properties or joint characteristics, (2) amount of background contraction of the muscle, and (3) magnitude of stretch reflexes. There is evidence for all three of these aspects contributing to rigidity. For quantitative purposes, responses can be measured to controlled stretches delivered by devices that contain torque motors. The stretch can be produced by altering the torque of the motor or by altering the position

of the shaft of the motor. The perturbation can be a single step or more complex, such as a sinusoid. The mechanical response of the limb can be measured: the positional change if the motor alters force, or the force change if the motor alters position. Such mechanical measurements can directly mimic and quantify the clinical impression.<sup>107,108</sup>

There are changes in the passive mechanical properties of muscle in patients with PD. The first suggestion that this might be true came from gait studies that showed reduced dorsiflexion movement of the ankle despite strong tibialis anterior activity and silent triceps surae.<sup>109</sup> Subsequently, using a quantitative measure, it was determined that the upper limb of patients was stiffer than normals in the totally relaxed state with no electromyographic activity present.<sup>110</sup> This phenomenon has been called into question by findings of another group that studied the lower leg and found normal contraction parameters (time-to-peak and half relaxation time), responses to short tetani and resistance to stretch.<sup>111</sup> However, they found an increased resistance to passive stretch under static conditions, presumably elastic in origin. The results may be evidence against a contribution of altered muscle contractile properties to rigidity in PD, but still reveal an increased totally passive component.

Patients with PD do not relax well and often have slight contraction at rest. This is a standard clinical as well as electrophysiological observation, and it is clear that this mechanism plays a significant part in rigidity.

There are increases in long latency reflexes in PD patients. Generally, this is neurophysiologically distinct from the increases in the short latency reflexes seen in spasticity, increase in tone of "pyramidal" type. The short-latency reflex is the monosynaptic reflex. Reflexes occurring at a longer latency than this are designated long latency. When a relaxed muscle is stretched, in general only a short-latency reflex is produced. When a muscle is stretched while it is active, one or more distinct long-latency reflexes are produced following the short-latency reflex

and prior to the time needed to produce a voluntary response to the stretch. These reflexes are recognized as separate because of brief time gaps between them, giving rise to the appearance of distinct "humps" on a rectified EMG trace. Each component reflex, either short or long in latency, has about the same duration, approximately 20 to 40 msec. They appear to be true reflexes in that their appearance and magnitude depend primarily on the amount of background force that the muscle was exerting at the time of the stretch and the mechanical parameters of the stretch; they do not vary much with whatever the subject might want to do after experiencing the muscle stretch. By contrast, the voluntary response that occurs after a reaction time from the stretch stimulus is strongly dependent on the will of the subject.

The short latency stretch reflex can be easily measured with the tendon jerk or H reflex. To obtain a meaningful measure of the response, the amplitude of the maximal reflex must be compared with the amplitude of the EMG in maximum voluntary effort or the amplitude of the EMG produced by supramaximal stimulation of the nerve to that muscle (H/M ratio).<sup>107,108</sup> Unfortunately, there is a large interindividual variability that makes the measurement less useful than it might be. The H/M ratio is enhanced in spasticity, but not in parkinsonian rigidity. Another clinically useful test is vibratory inhibition of the H reflex.<sup>112</sup> In normal subjects, the amplitude of the H reflex is markedly inhibited by vibration of the muscle. Vibratory inhibition is often dramatically reduced in spasticity, but it is normal in parkinsonian rigidity.

Long latency reflexes are best brought out with controlled stretches with a device such as a torque motor. While long latency reflexes are normally absent at rest, they are prominent in PD patients.<sup>107,108,113,114</sup> Long latency reflexes are also enhanced in PD with background contraction. Since some long latency stretch reflexes appear to be mediated by a loop through the sensory and motor cortices, the enhancement of long latency reflexes has been generally believed to indicate increased excitability of this central loop.

There is some evidence that at least one com-

ponent of the increased long latency stretch reflex in PD is a group II mediated reflex. This suggestion was first made by Berardelli et al.<sup>115</sup> on the basis of physiologic features including insensitivity to vibration. It was subsequently supported by the observation that an enhanced late stretch reflex response could not be duplicated with a vibration stimulus.<sup>116</sup>

Some studies show a correlation between clinically measured increased tone and the magnitude of long latency reflexes,<sup>115</sup> while others do not.<sup>117,118</sup> Long latency reflexes contribute significantly to rigidity, but are apparently not completely responsible for it.

The enhancement of long-latency reflexes can also be brought out by electrical stimulation of a mixed nerve. Such stimulation while the limb is at rest will produce only an M wave and F response in the muscles innervated by that nerve. If a mixed nerve is stimulated while the muscles are active, however, additional responses will be produced.<sup>107,108</sup> With mixed nerve stimulation, there is a short-latency response that seems analogous to the H reflex (HR) and one or more long-latency responses. One of these long-latency responses, called LLRII by Deuschl and associates,<sup>119</sup> may have a transcortical pathway similar to some of the long-latency reflexes to stretch. A long-latency response, the LLRI, intermediate in latency between the HR and LLRII, is enhanced in about half of patients with PD.

Some spinal inhibitory reflexes such as reciprocal inhibition and Ib inhibition are deficient, and these mechanisms may also play a role. If inhibition is lacking, there will be excessive activity that could contribute to rigidity or failure to relax.

Reciprocal inhibition is a fundamental mechanism of motor control. There are multiple pathways for reciprocal inhibition, the simplest of which is the disynaptic pathway via the Ia inhibitory interneuron. In the arm, reciprocal inhibition has been studied looking at the effects of radial nerve stimulation upon the H reflex of the flexor carpi radialis (FCR).<sup>120,121</sup> Via various pathways, and therefore at various time intervals after the radial nerve stimulus, the radial affer-

ent traffic can inhibit the motoneuron pools of the FCR. Normal subjects showed three periods of inhibition, reaching a peak at delays of 0 ms, 10 ms, and 75 ms. The first period of inhibition is caused by disynaptic Ia inhibition, the second period of inhibition is explained as a presynaptic inhibition, and, unfortunately, very little is known about the third period of inhibition, but the long latency (75~200 ms) appears to be compatible with a polysynaptic pathway. The first relative facilitation (at about 2 ms delay) is a function of Ib fiber actions, and indirect evidence indicates that the second facilitation (at about 50 ms delay) can be a function of cutaneous group II action.

Reciprocal inhibition is reduced in patients with dystonia, including those with generalized dystonia, writer's cramp, spasmodic torticollis, and blepharospasm.<sup>121,122</sup> Reciprocal inhibition is also abnormally reduced in PD patients.<sup>123</sup> On the other hand, short latency reciprocal inhibition is increased in the lower extremities, the opposite to what is found in the upper extremities.<sup>124</sup>

That Ib inhibition can be demonstrated in the human was first demonstrated by the clever experiments of Pierrot-Deseilligny and colleagues.<sup>125</sup> They showed that stimulation of the nerve to the medial head of gastrocnemius (GM) provoked short latency inhibition of the H reflex in soleus that was most consistent with Ib effects. Presumably this is apparent because there are very few heteronymous Ia projections from the medial head of gastrocnemius onto soleus motoneurons. In patients with spasticity, Ib inhibition is absent and is replaced by facilitation.<sup>126</sup> The explanation for this inversion is not clear. Similarly, the Ib inhibition is diminished in PD and when rigidity is more severe, the inhibition is replaced by facilitation. The authors explain this on the hypothesis of increased activity of the nucleus gigantocellularis of the brainstem.

Reduction of Ib inhibition was confirmed using a different method, electrical stimulation via skin electrodes placed over human tendons resulting in a reflex inhibition of voluntary activity in the stimulated muscle.<sup>127</sup> The threshold of the inhibitory response was significantly increased in

PD compared with controls. Also, the latency of the inhibitory wave was increased, and the duration of inhibition was increased in patients.

Inhibitory and excitatory reflex effects from stimulation of cutaneous nerves can be detected by recording changes in levels of tonic voluntary EMG activity of various hand muscles.<sup>107,108</sup> These reflexes consist of a series of bursts of EMG activity separated by periods of inhibition. The first excitatory component is generally agreed to be of spinal origin while there is debate about a supraspinal or even a transcortical loop of the later reflex components. The first inhibitory component is produced by inhibition above the level of the alpha motoneuron, but below the level of the cortex, and is diminished in PD.<sup>128</sup>

Recurrent inhibition can be studied using the complicated method developed by Pierrot-Deseilligny and colleagues.<sup>129</sup> While in spasticity some patients show loss of inhibition, there is no loss of inhibition in PD.<sup>123</sup>

Delwaide et al.<sup>130</sup> have suggested that the magnitude of audiospinal facilitation correlates with rigidity. They compared audiospinal facilitation using the soleus H-reflex in control subjects and PD patients. In the patients, facilitation was significantly reduced during the 75 to 150 msec after the conditioning stimulation. This reduction was seen bilaterally even in patients with a hemisyndrome. It was corrected by L-dopa but not by anticholinergic agents. Facilitation at the 75-msec delay showed an inverse linear correlation with the bradykinesia intensity. The authors explain the results as a reduced excitability of the nucleus reticularis pontis caudalis from which a reticulospinal tract emanates as effector of audiospinal facilitation.

### 3. Tremor-at-rest

The so called "tremor-at-rest" is the classic tremor of PD and other parkinsonian states such as those produced by neuroleptics or other dopamine-blocking agents such as prochlorperazine and metoclopramide.<sup>108,131-133</sup> It is present at rest, disappears with action, but may resume with static posture. That the tremor may also be present during postural maintenance is a significant

point of confusion in regard to naming this tremor “tremor-at-rest”. It can involve all parts of the body and can be markedly asymmetrical, but it is most typical with a flexion-extension movement at the elbow, pronation and supination of the forearm, and movements of the thumb across the fingers (“pill-rolling”). Its frequency is 3 to 7 Hz, but is most commonly 4 or 5 Hz; and EMG studies show alternating activity in antagonist muscles. PD is sometimes divided into two types, the akinetic-rigid form and the tremor-predominant form; the latter has a better prognosis.

Tremor-at-rest can also be seen in the parkinson plus disorders, but it is not as common as in PD itself. For example, rest tremor was seen in 29 of 100 patients thought to have multiple system atrophy, but only 9 had a “classic appearance”.<sup>134</sup>

Some patients have rest tremor for a number of years without any other evidence of PD, and it has not been clear whether they really have PD. Eleven of these patients underwent 18F-dopa PET scan studies, and all showed reduced putaminal uptake, an abnormality characteristic of PD.<sup>135</sup> This result has been replicated in a double-blind fashion on 5 patients using MRI scanning. All 5 showed typical findings of PD with smudging or decreased distance between the substantia nigra and red nucleus.<sup>136</sup>

The anatomical basis of the tremor-at-rest may well differ from the classic neuropathology of PD, that of degeneration of the nigrostriatal pathway. For example, 18F-dopa uptake in the caudate and putamen declines with bradykinesia and rigidity, but is unassociated with degree of tremor.<sup>137</sup> Another point in favor of this idea is that the tremor may be successfully treated with a stereotaxic lesion or deep brain stimulation of the ventral intermediate (VIM) nucleus of the thalamus, a cerebellar relay nucleus.<sup>138,139</sup>

In parkinsonian tremor-at-rest, there may be some mechanical-reflex component and some 8–12 Hz component, but the most significant component comes from a pathological central oscillator at 3 to 5 Hz. This tremor component is unaffected by loading. Evidence for the central oscil-

lator includes the facts that the accelerometric record and the EMG are not affected by weighting, and small mechanical perturbations do not affect it. On the other hand, it can be reset by strong peripheral stimuli such as an electrical stimulus that produces a movement of the body part five times more than the amplitude of the tremor itself.<sup>140</sup> Where this strong stimulus acts is not clear, but does not have to be on the peripheral loop. Additionally, the tremor can be reset by TMS,<sup>141,142</sup> presumably indicating a role of the motor cortex in the central processes that generate the tremor. In the studies of Pascual-Leone et al.,<sup>142</sup> using a relatively small stimulus, the tremor was reset with TMS, but not with transcranial electrical stimulation. Since TMS affects the intracortical circuitry more, this seems to be further evidence for a role of the motor cortex.

While cells in the globus pallidus many have oscillatory activity, they are not as well related to the tremor as the cells in the VIM of the thalamus.<sup>143,144</sup> Lenz and colleagues have been studying the physiological properties of cells in the VIM in relation to tremor production.<sup>145</sup> They have tried to see if the pattern of spike activity is consistent with specific hypotheses. They examined whether parkinsonian tremor might be produced by the activity of an intrinsic thalamic pacemaker or by the oscillation of an unstable long loop reflex arc. In one study of 42 cells, they found 11 with a sensory feedback pattern, 1 with a pacemaker pattern, 21 with a completely random pattern, and 9 that did not fit any pattern.<sup>145</sup> In another study of thalamic neuron activity, some cells with a pacemaker pattern were seen, but these did not participate in the rhythmic activity correlating with tremor.<sup>146</sup> These results confirm those of Lenz et al, suggesting that the thalamic cells are not the pacemaker.

Wherever the pacemaker for the tremor, it is important to note while the tremor is synchronous within a limb, it is not synchronous between limbs.<sup>147</sup> Hence a single pacemaker does not influence the whole body.

There are other types of tremor in PD including an action tremor looking like essential tremor, but these have not been extensively studied.

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