

# Pathophysiology of Parkinson's Disease: From Clinical Neurology to Basic Neuroscience and Back

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**Abstract:** Parkinson's disease (PD) is characterized by motor and nonmotor (cognitive and limbic) deficits. The motor signs of PD include hypokinetic signs such as akinesia/bradykinesia, rigidity and loss of normal postural reflexes, and hyperkinetic signs such as tremor. Dopamine depletion in the striatum is the hallmark of PD and of its animal models, still the pathophysiology of the parkinsonian symptoms and especially of parkinsonian tremor are under debate. The most extreme hypotheses argue about peripheral versus central nervous system origin, intrinsic cellular oscillator versus network oscillators, and basal ganglia-based pathophysiology versus cerebellar–thalamic based pathophysiology. Recent studies support the view that parkinsonian symptoms are most likely due to abnormal synchronized oscillating neuronal activity within the basal ganglia. Peripheral factors do only play a minor role for the generation, maintenance, and modulation of PD tremor and other signs.

The most likely candidates producing these neuronal oscillations are the weakly coupled neural networks of the basal ganglia–thalamo–cortical loops. However, the present evidence supports the view that the basal ganglia loops are influenced by other neuronal structures and systems and that the tuning of these loops by cerebello–thalamic mechanisms and by other modulator neurotransmitter systems entrain the abnormal synchronized oscillations. Neurosurgical procedures, such as lesions or high-frequency stimulation of different parts of the loop, might resume the normal unsynchronized activity of the basal ganglia circuitry, and, therefore, ameliorate the clinical symptoms of Parkinson's disease. © 2002 Movement Disorder Society

**Key words:** Parkinsonism; MPTP; human; primates; oscillations; synchronization

The understanding of the pathophysiology of Parkinson's disease (PD) is a major precondition for developing new treatment and diagnosis strategies for this common disease. Although significant progress has been made in our understanding of the clinical deficits of PD, the detailed pathophysiology of PD is still a problem that is not yet solved. Because of its rhythmic nature, and because of the recent advances in our methodology for study and analysis of periodic phenomena, much of the basic research is oriented toward the study of tremor. In this review, we use the PD tremor as our main tool to investigate the pathophysiology of PD and tremor in general; however, we also cover the other clinical symptoms

of PD and other types of clinical tremor. This review is based on earlier reviews regarding the pathophysiology of Parkinson's disease<sup>1–4</sup> and of tremor<sup>5–11</sup> and the recent literature on this topic. We will compare the physiological studies in the primate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP) model of Parkinsonism with the human data and will try to arrive at some hypotheses how parkinsonian symptoms and tremor might be generated.

## **PATHOLOGY AND CLINICAL SUBTYPES OF PARKINSON'S DISEASE**

The pathological hallmark of Parkinson's disease<sup>12</sup> and MPTP-induced Parkinsonism<sup>13</sup> is the degeneration of dopaminergic cells within the substantia nigra and the subsequent dopamine depletion of the striatum. Rest tremor is the most specific sign for idiopathic PD.<sup>14–16</sup> Patients with tremor-dominant PD have a better prognosis concerning disease progression than those with the

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akinetic/rigid variant.<sup>17,18</sup> Several studies have indicated that the pathology of human tremor-dominant PD differs from the one of akinesia/rigidity-dominant PD. The medial substantia nigra, especially the retrorubral area A8 is more severely affected by dopaminergic cell degeneration in the tremor dominant form in contrast to more severe damage of the lateral substantia nigra (A9) in the akinetic/rigid variant.<sup>15,19,20</sup>

If a strict definition of rest tremor is applied, it is noteworthy that only two forms of tremor, parkinsonian tremor and Holmes' tremor (formerly called rubral or midbrain tremor) display a rest tremor. Both of these patient groups show a dopaminergic deficit in the striatum on positron emission tomography (PET).<sup>21,22</sup> This finding is a strong argument for rest tremor to be a consequence of a striatal dopamine deficit. However, there is no correlation between the severity of the dopaminergic deficit in the striatum and the severity of tremor.<sup>23-26</sup> The clinical severity of PD tremor is also uncorrelated with the clinical disease progression in contrast with rigidity and akinesia.<sup>17,18,27</sup>

Thus human PD tremor is depending on the nigrostriatal deficit but once this is present, the tremor does not depend on the severity of this deficit. Moreover, in the MPTP primates, there is no correlation between midbrain dopamine pathology and tremor. Therefore, it is possible that, transmitter systems other than dopamine (e.g., cholinergic, serotonergic) or neural circuits other than the basal ganglia do play a critical additive role for this symptom.

## CLINICAL PHYSIOLOGICAL STUDIES OF PARKINSON'S DISEASE AND ITS ANIMAL MODELS

### Tremor in Human Idiopathic Parkinson's Disease

The clinical presentation of tremor in PD is not uniform and, although rest tremor is typical, there are other manifestations that present with mainly postural tremors. Classical parkinsonian tremor is defined as a rest tremor or rest and postural/kinetic tremor with the same frequency.<sup>28</sup> Mostly this tremor is inhibited during movement and may reoccur with the same frequency when adopting a posture or even when moving.<sup>28,29</sup> The frequency of rest tremor is between 4 and 9 Hz.<sup>30</sup> A low-amplitude and high-frequency (8–12 Hz) kinetic tremor is present in many parkinsonian patients.<sup>31,32</sup> In any case, the tremor frequency or amplitude alone are poor criteria for separating PD tremor from other tremors.<sup>33</sup> The pattern of activation in antagonistic muscles is mostly reciprocal alternating but this finding is also not a reliable discriminator between PD and other tremors.<sup>34,35</sup>

It has long been observed that the frequency of tremor in a given patient is often admirably similar between different muscles of the extremities and trunk. These observations led to the assumption that a common single oscillator is controlling all tremulous muscles.<sup>36</sup> Coherence analysis<sup>37-39</sup> applied to accelerometer or electromyographic recordings of tremor of PD patients revealed that the tremor on the right and left arm are not coherent.<sup>40,41</sup> A more detailed analysis of this phenomenon (Fig. 1) has shown that the muscles within one body part (arm, leg, head) are mostly coherent but the rhythms in different extremities are almost never coherent.<sup>42</sup> We concluded that these differences are indicating that different oscillators are underlying parkinsonian tremor in the different extremities.

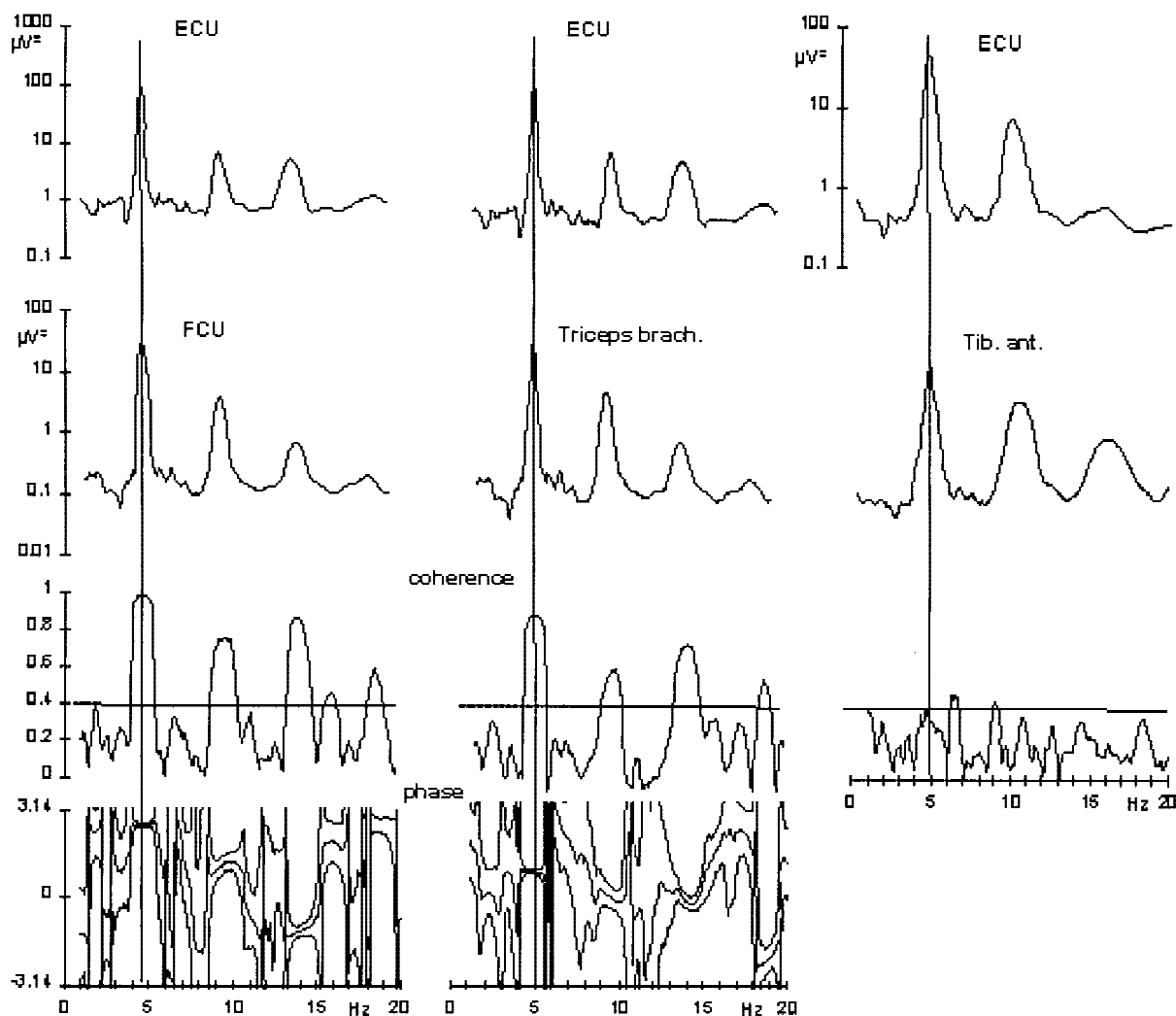
### Human and Primate MPTP-Induced Parkinsonism

A breakthrough of our understating of PD came with the discovery of the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP) neurotoxin.<sup>43,44</sup> MPTP-affected human patients develop akinesia and rigidity. However, only four of seven human patients with MPTP-induced parkinsonism had rest tremor with a frequency of 4 to 6 Hz.<sup>45</sup>

The best animal model of PD seems to be the MPTP primate model.<sup>2,46</sup> Systemic or intracarotid treatments with MPTP rendered the monkeys with severe parkinsonian symptoms, including akinesia, rigidity, and abnormal postural reflexes. However, not all primate species develop tremor, and if they do, the animals only rarely have classical resting tremor.<sup>47</sup> Previous studies in the rhesus and vervet monkey<sup>48-50</sup> demonstrated that the rhesus monkey develops a low-amplitude high-frequency (~10–12 Hz) action tremor, resembling the "rippling" or kinetic tremor in PD, whereas the vervet monkey can develop a high-amplitude, low-frequency (~5–7 Hz) tremor resembling resting tremor of PD.<sup>50,51</sup> Finally, as with the human studies, coherence analysis of accelerometers attached to different limbs of the tremulous vervet monkeys revealed very low level of correlation between the limbs.<sup>52</sup>

### Non-MPTP In Vivo Models of Parkinsonian Tremor

A variety of animal models of tremors exist.<sup>47</sup> It transpires from these studies that akinesia, rigidity, and postural and action tremors are much easier to produce in animals than resting tremor. Many attempts have been undertaken to produce resting tremor in animals (especially monkeys; for review see Wilms et al., 1999<sup>47</sup>). Early primate models of Parkinson's disease and tremor found that lesions of the ventral tegmentum produce hypokinesia and tremor.<sup>53,54</sup> The tremor of these models



**FIG. 1.** Cross-spectral analysis of three muscle combinations in a Parkinson's disease (PD) patient. The upper two traces show the power spectra for both muscles. The coherence and phase spectra are demonstrated in the third and fourth row. The thin lines indicate the upper and lower limits of the 95% confidence interval of the spectra. The antagonistic and nonantagonistic muscle combinations within the same arm show highly significant coherence findings (see columns 1 and 2). The coherence is near 1, and the phase is around  $\pi$  for the extensor carpi ulnaris–flexor carpi ulnaris (ECU–FCU) muscle pair and near 0 for the ECU–triceps combination. The coherence and phase plots show narrow confidence limits for the peak frequencies and the higher harmonics with the latter being a mathematical artefact. In contrast the forearm extensor and the anterior tibial muscle of the same side (C) oscillate independently from each other, although they share exactly the same frequency. (Modified from references 40 and 42.)

has frequently been described as “postural or rest tremor”; however, it is difficult to assess whether these tremors were really compiling with the strict definitions of rest tremor. Especially the destruction of three structures seems to be crucial the induction of rest and intention tremor in the primate model: the parvocellular division of the red nucleus, cerebellothalamic fibers, and nigrostriatal fibers.<sup>55–57</sup> In these tremor models, rhythmic discharges could be recorded at the thalamocortical and corticospinal level.<sup>58</sup>

Numerous cholinergic substances have been shown to induce tremor in animals<sup>47</sup> that, however, did not very well match with rest tremor. The frequency of this tremor

is mostly above 8 Hz. The striatum might play an important role for the development of this form of tremor, because of the significant role of striatal cholinergic innervation.<sup>59</sup> It is tempting to speculate that this form of tremor is related to the action tremor seen in some patients with Parkinson's disease that has a frequency indistinguishable from enhanced physiologic tremor.

#### PERIPHERAL VERSUS THE CENTRAL PATHOPHYSIOLOGICAL MODELS OF PD

Although the critical role of nigrostriatal dopamine depletion in generation of PD symptoms is well accepted, the physiological origin of parkinsonian rigidity

and rest tremor is still disputed. Two apparently contradictory mechanisms (oscillatory spinal reflex mechanisms vs. central pathophysiology) were proposed for the tremor. However, the two mechanisms are not mutually exclusive, and a synthesis at different level seems appropriate.

### Contribution of Reflex Pathways

Mechanical factors do always contribute to the generation of tremor but their contribution is almost negligible for large-amplitude PD tremors. Spinal reflexes play only a minor role for the generation of parkinsonian tremor.<sup>60,61</sup> The removal of the dorsal roots in a patient with parkinsonian tremor did reduce the tremor amplitude but did only slightly change the frequency and did not stop the tremor.<sup>62</sup> Similarly, infiltration of the muscles with local anesthetic until rigidity and stretch reflexes were diminished has no effect on tremor.<sup>63</sup> Several studies demonstrated absent frequency reduction after loading of the trembling limb in PD patients.<sup>33,64</sup>

Another series of studies has dealt with resetting of the rhythm of parkinsonian tremor after different stimuli as mechanical perturbations,<sup>65</sup> electrical stimulation of the median nerve,<sup>66,67</sup> or transcranial magnetic stimulation of the motor cortex.<sup>68</sup> The results did not show a consistent resetting of the tremor rhythm when stimulating the periphery but a complete resetting when the cortex was stimulated.

In summary, most studies do not support a critical role of peripheral mechanisms in the generation of parkinsonian tremor. There are indications that PD tremor may be modulated (reset) by peripheral manipulation; however, central oscillator(s) could be modulated by peripheral inputs.<sup>69</sup> The role of the central generators seems to be much more important.

### Clinical Data Suggesting a Major Role of Central Origin of Parkinsonian Tremor

The observation that deafferentation changes the frequency of parkinsonian tremor but does not suppress it<sup>62</sup> strongly supports a central origin of parkinsonian tremor. Coherence studies linking brain and muscle rhythms in PD provide another piece of supportive evidence for the role of central mechanisms in PD tremor. In PD patients, the normal  $\mu$ -rhythm<sup>70</sup> is suppressed during tremor periods. Furthermore, a 10 Hz neuromagnetic activity coherent with the tremor can be recorded over wide cortical areas.<sup>71</sup> Many studies of neuronal activity have revealed a correlation between electrical activity of neurons in the central nervous system and tremor. However, correlation studies cannot prove causal relationships, and central

nervous system activation could be the result of abnormal feedback from the periphery.

It has been long known that different lesions within the central nervous system can suppress parkinsonian tremor. Early attempts removing parts of the motor cortex or lesioning of the internal capsule have been successful in suppressing tremor but have produced other unacceptable side effects.<sup>72</sup> The thalamus or the zona incerta have been successful targets during stereotactic procedures,<sup>73,74</sup> and recently it has been demonstrated that chronic stimulation of these same thalamic targets and also of the subthalamic nucleus and the pallidum are all able to efficiently suppress parkinsonian tremor.<sup>75-80</sup> We can conclude that the preservation of some loops within the nervous system is critical for the occurrence of PD symptoms, including tremor. We discuss the question of where this abnormal activity is located.

### CEREBELLOTHALAMIC PATHOPHYSIOLOGICAL MODELS OF PARKINSONIAN TREMOR

There are many lines of evidence supporting a critical role of the thalamus, or cerebellothalamic pathways, in the generation of parkinsonian symptoms.<sup>81</sup> Lesions that can effectively suppress rigidity or tremor of various origins are located in the ventrolateral thalamus, in the area that receives mainly cerebellar output.<sup>82-86</sup> Lenz and colleagues<sup>87</sup> could demonstrate that some thalamic neurons advance the tremor, suggesting an efferent role for this firing. The percentage of tremor cells among the different groups seems to be higher than for the subthalamic nucleus (STN) and globus pallidus pars interna (GPi).<sup>82</sup>

Fluorodeoxyglucose PET study has demonstrated that effective thalamic stimulation reduced the cerebellar regional blood flow compared to ineffective stimulation, whereas the cortical blood flow was not significantly influenced.<sup>88</sup> However, as this paradigm cannot exclude the possibility that peripheral afferents may activate the cerebellum preferentially, this finding may only reflect the somatosensory input of rhythmic muscle activity. This interpretation is further supported by the finding that almost all tremors show such a cerebellar hyperactivity.<sup>89,90</sup>

The specific oscillating properties of thalamic cells<sup>91-94</sup> might provide the basic mechanism of central tremors.<sup>95</sup> The oscillatory mode of the thalamic cells is driven by hyperpolarization of thalamic cells. As the GPi and SNr are overactive in Parkinson's disease,<sup>96-98</sup> the inhibitory input to the thalamus might hyperpolarize the thalamic cells, thereby causing this mechanism to be activated.<sup>99,100</sup>

Another hypothesis for how the 4 to 6 Hz pattern of parkinsonian tremor could be generated within the thalamus was driven by the early findings of high (>10 Hz) oscillations in the GP of dopamine-depleted rhesus monkeys.<sup>96,101</sup> Pare and associates<sup>102</sup> have shown that a 12 to 15 Hz pattern of pallidal cells can be transformed into a 4 to 6 Hz pattern due to specific membrane properties of the thalamic cells. However, recent data from MPTP-treated vervet monkeys<sup>48,50</sup> and from human patients<sup>103–106</sup> indicate that many of the tremor cells in the GPi are already firing at a low frequency and the 12 to 15 Hz range for the single cell oscillations seems to be not specifically more frequent in these parkinsonian monkeys and human patients.

#### **CLASSICAL (DIRECT/INDIRECT CLOSED LOOP) MODEL OF THE BASAL GANGLIA AND THE CHANGES OF DISCHARGE RATE AND PATTERN IN PD**

The basal ganglia are the primary locus of pathology in PD. Therefore, it is natural to assume that PD symptoms are due to abnormalities within these circuits. It is now clear that most parkinsonian symptoms can be effectively suppressed by stimulation of the pallidum (or pallidotomy)<sup>107–109</sup> and the subthalamic nucleus.<sup>76</sup> Thus, parkinsonian symptoms can also be effectively treated by the blockade of nuclei upstream the thalamus within the basal ganglia–thalamic loop.

#### **Basic Anatomy and Models of the Basal Ganglia**

The basal ganglia are classically viewed as part of a neural circuit that arise from the cortex; pass through striatum, pallidum, and the thalamus; and project back to the frontal cortex.<sup>1,110</sup> A comprehensive description of the cellular organization and anatomical connectivity of the basal ganglia have been published recently.<sup>111–113</sup> Moreover, each of the structures in the basal ganglia–thalamocortical circuitry is composed of many neurons and is characterized by complex spatiotemporal interactions. Therefore, here we will only highlight the most basic aspects of this model of basal ganglia anatomy.

The striatum serves as the recipient of efferents from most cortical areas, and projects by means of intrinsic pathways to both basal ganglia output nuclei, the internal segment of the globus pallidus (GPi), and to the substantia nigra–pars reticulata (SNr). Neurons from GPi and SNr project to the ventral motor nuclei of the thalamus that, in turn, project back to the frontal cortex. Dopamine, released from endings of neurons located in the substantia nigra–pars compacta (SNc), modulates the activity of striatal cells and, therefore, of the whole circuit. A major assumption of the model is that different dopa-

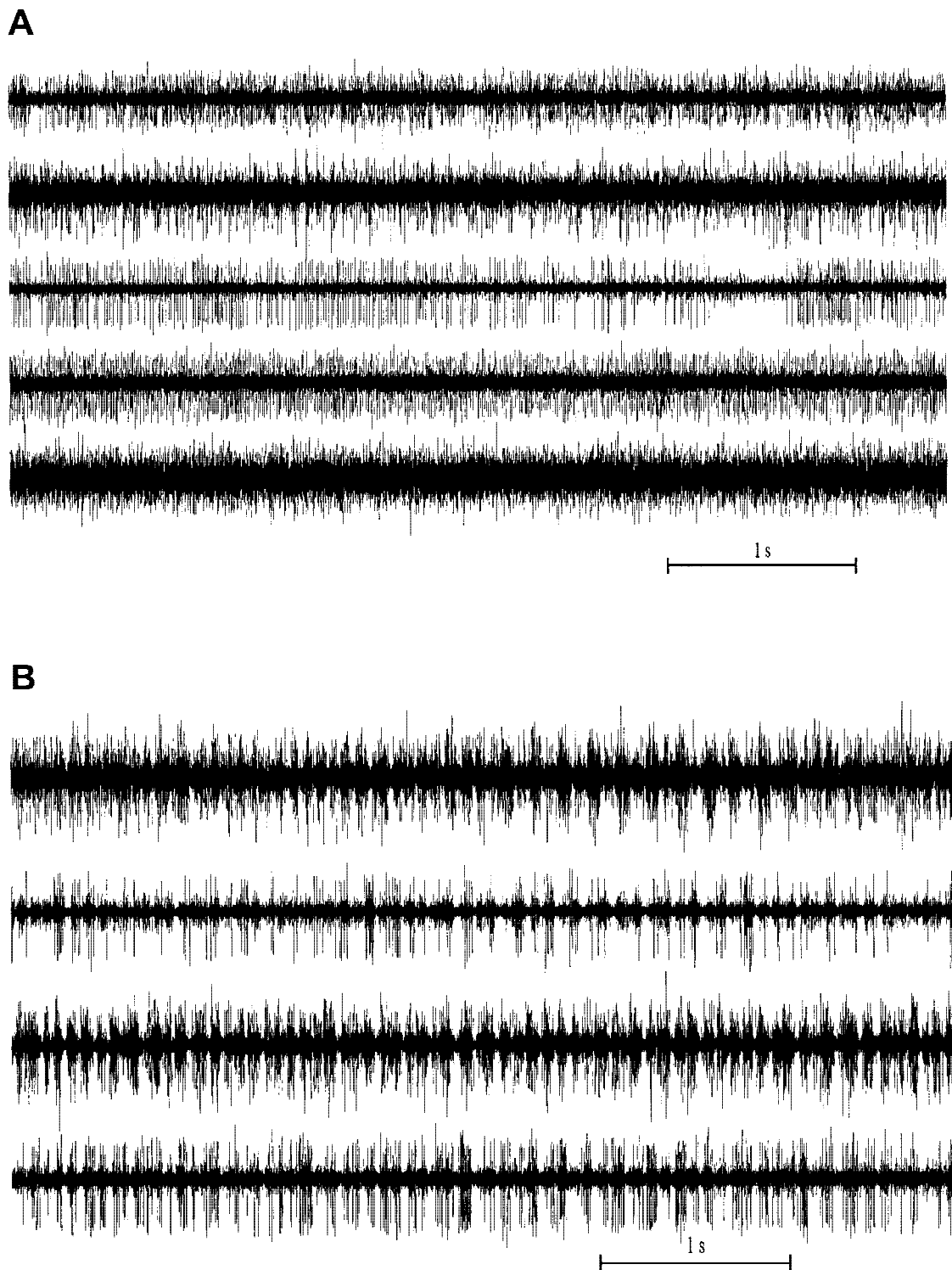
mine receptors (D1 or D2) are localized on the different striatal populations that give rise to direct (to GPi) and indirect (to GPe) pathways.<sup>114</sup>

#### **Discharge Rate and Pattern of Basal Ganglia Neurons and the Pathophysiology of PD**

Electrophysiological<sup>96,97</sup> and metabolic<sup>115–117</sup> studies of the basal ganglia of MPTP-treated monkeys have demonstrated that the discharge rate in the STN and GPi is increased and that the activity in GPe is decreased. The firing rate of GPi neurons of human patients with advanced PD seems to be high compared to the normal monkey and to GPe.<sup>118,119</sup> Moreover, dopamine therapy reduces the firing rate of those neurons.<sup>120–124</sup> These and other studies are in agreement with the classical model,<sup>1,2</sup> where the net action of dopamine is different on two subpopulations of striatal neurons.<sup>114</sup> Under normal condition, striatal neurons projecting directly to GPi appear to be facilitated by dopamine actions on D1 receptors, whereas neurons projecting to GPe are inhibited by dopamine actions on D2 receptors. Dopamine depletion in the striatum, therefore, leads to both a reduction of activity of the direct inhibitory pathway, and an increase of the activity in the indirect excitatory pathway, synergistically leading to an increase GPi activity. Because the GPi–thalamic projection is inhibitory, increased GPi discharge leads to inhibition of thalamocortical neurons. The resulting reduction of cortical activation would then account for the hypokinetic signs of PD.

In the pallidum of human patients with PD tremor, 12.3% of the cells were found to fire at the tremor frequency of the respective patient.<sup>103,125</sup> The rhythm of tremor cells within the pallidum is correlated with the tremor frequency of the tremor in the periphery. However, when GPi tremor cells were studied for their relation with the peripheral tremor only, one of them exhibited significant coherence with the peripheral tremor.<sup>106</sup> A recent study of pallidal cells in a single patient undergoing pallidotomy found that a single tremor cell showed coherent activity with a peripheral muscle for some time and desynchronized later from the ongoing peripheral tremor.<sup>105</sup>

The human pallidal data are in line with the early reports of pallidal activity in the healthy and MPTP-treated primates. In the normal primate, only few pallidal cells display significant oscillations. After MPTP treatment, ~40% of pallidal cells of the developed significant oscillations<sup>49,50</sup> (see Fig. 2). The oscillation frequencies of the single cells were bimodally distributed around 7 and 13 Hz, in parallel with the tremor frequencies of these monkeys. For 10% of the oscillatory cells, there was a significant tendency for the tremor and the neuro-



**FIG. 2.** An example of multiple-electrode recordings in the globus pallidus of (A) normal and (B) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP)-treated parkinsonian monkey. **A:** An example of 5 seconds of the simultaneous output of five electrodes positioned in the globus pallidus of a normal monkey. **B:** An example of the simultaneous recording of four electrodes in the globus pallidus of an MPTP-treated (parkinsonian) monkey. Time scale as in A. Intermittent episodes of synchronous bursting are seen. (Modified from Raz et al., 2000.)

nal oscillations to appear together. However, the coherence between the cell's activity and the tremor was dynamic and could be high at some periods of the recordings and low at other period. Finally, low-frequency oscillations were observed in pallidal cells after amelioration of the tremor by subthalamic lesion in the MPTP monkey.<sup>126</sup>

The tonic changes in the firing rate of the subthalamic nucleus (STN) have been strongly emphasized.<sup>96,126,127</sup> The percentage of cells with low-frequency oscillations increased also in the STN after MPTP treatment.<sup>48</sup> Tremor cells with 4 to 5 Hz bursting have been described for the STN in human patients with Parkinson's disease<sup>128,129</sup>; however, these cells are mostly sensitive to kinesthetic stimulation.

Cells in the striatum are only rarely recorded in human because the region interesting for functional stereotactic procedures is far from this nucleus. To the best of our knowledge, there are no tremor cells reported from the striatum of patients with Parkinson's disease. Recordings of striatal tonically active neurons (TANs, presumably the cholinergic interneurons of the striatum<sup>59,130</sup>) showed significant high (10–15 Hz) oscillations of these cells after MPTP.

#### **On the Problems of the Rate Models of the Basal Ganglia and PD**

Like any model, the classical Albin-DeLong model of the basal ganglia is limited, because it is trying to simplify the complex reality. The main advantages of the model were the predictions that lesions of the STN and the GPi should ameliorate parkinsonian symptoms.<sup>131,132</sup> However, multiple recent studies have revealed significant deviations from the main assumptions and the predictions of the classical model.<sup>133</sup>

Anatomical studies have revealed that the D1 and D2 receptors are colocalized on striatal projection neurons.<sup>134</sup> Moreover, single neuron labeling failed to identify direct-pathway striatal neurons that project only to the GPi.<sup>113</sup> The anatomy of the basal ganglia seems to be more complex than the description of the model because of the back projections GPe to the striatum,<sup>135,136</sup> and the feed-forward projections from the cortex to the GABAergic interneurons of the striatum.<sup>113</sup> The output projections from the basal ganglia to the brainstem, and especially to the PPN, might play a major role in the physiology of PD symptoms.<sup>137,138</sup>

Physiological and metabolic studies have questioned the predicted decrease in firing rate in GPe.<sup>133,139</sup> The final prediction of the classical models of PD is that increased inhibitory pallidal output reduces the activity of frontal cortex, including the primary motor cortex

(MI), resulting in the hypokinetic motor disorders of PD. However, our preliminary studies of the spontaneous discharge of neurons in the primary motor cortex revealed that the mean spontaneous discharge rate in M1 did not change following MPTP.<sup>140</sup>

Finally, the physiological findings of human neurosurgery are different from the model. First, pallidotomy and STN lesions are also effective for the treatment of the hyperkinetic movement disorders of PD, such as levodopa-induced dyskinesia.<sup>3,133</sup> Second, the firing rate in the GPi is not reduced in patients with hyperkinetic movement disorders, such as hemiballismus and dystonia.<sup>141–144</sup>

#### **SYNCHRONIZATION WITHIN THE BASAL GANGLIA AND THE PATHOPHYSIOLOGY OF PD**

Despite the problems with the classical model of the basal ganglia and PD, the basal ganglia are the primary locus of pathology in Parkinson's disease. Therefore, it is natural to assume that PD symptoms are due to abnormalities within these circuits; however, these abnormalities might be beyond changes in discharge rate and pattern. Recent experiences with multiple electrode recording (Fig 2) and with recording in behaving and MPTP primates have significantly expanded our view. Cross-correlation analysis of simultaneously recorded pallidal cells showed a very low level of correlated activity in the normal state. After MPTP, 40% of the cross-correlation functions showed significant oscillations mainly around 13 to 14 Hz.<sup>145</sup> Finally, our preliminary results indicate that dopamine replacement therapy restores the normal correlation level at the GP of these MPTP monkeys.<sup>146</sup> In the normal monkeys, only few TAN–pallidal pairs have shown correlated activity. After MPTP treatment, most of the cross-correlograms displayed significant high periodic oscillations. The frequency content of the coherent oscillations matched the frequency content of the individual TANs high-frequency activity but was only weakly related to that of individual pallidal cells.<sup>147</sup>

#### **Parallel Versus Funneling in the Basal Ganglia**

The neural networks of the basal ganglia are organized as single-layered elements connected by sequential feed-forward connections. Most neurons in the basal ganglia nuclei are projection neurons, with interneurons forming only a small fraction of the total neuronal population. Even the numerous lateral interconnections in the striatum are functionally weak.<sup>148</sup> The degree of segregation between the different circuits passing through the basal ganglia is still a matter of debate.<sup>149–154</sup> There are two extreme views: the first holds that neurons in the output

stage of the basal ganglia receive many common inputs (information funneling), whereas the second views the basal ganglia as segregated parallel circuits with minimal interactions between the parallel pathways.

The independent firing of neurons in the basal ganglia suggests that normal functioning of the basal ganglia is characterized by uncorrelated activity of their functional subcircuits. It can be further postulated that dynamic reorganization of these functional subcircuits represents part of the neural substrate of innate motor learning. After the development of parkinsonian symptoms, the basal ganglia networks probably lose their ability to keep the activity of pallidal neurons independent, and the previously inhibited cross-connections between "parallel" subcircuits become more active, resulting in abnormal synchronized activity within the basal ganglia.

### Competitive Neural Network Models of Basal Ganglia

One of the most attractive hypotheses regarding the role of the basal ganglia in normal brain functioning is the "action selection" model.<sup>155</sup> According to this model, when voluntary movement is generated by cortical or cerebellar networks, the basal ganglia act to inhibit competing motor actions that would otherwise interfere with the desired movement. Simultaneously, inhibition is removed focally from the desired motor actions to allow that movement to proceed. The single unit studies showing that the majority of neuronal responses in the pallidum are increases in firing rates<sup>156-158</sup> are in line with this model. Striatal dopamine depletion eventually resulted in inability to inhibit competing motor programs and, therefore, results in slow movements, abnormal postures, and involuntary muscle activity. Indeed, in the MPTP-treated monkey, the number of movement-related neurons increased, number of neurons that respond with suppression of firing rate dropped significantly,<sup>159</sup> and most responding cells were linked to several joints.<sup>159,160</sup>

There are many subsidiary closed loops within the basal ganglia circuitry. Instabilities within one or several of these loops might entrain an abnormal state in the whole basal ganglia circuitry. Thus studies of *in vitro* preparation suggested that STN and GPe are forming a pacemaker at frequencies between 0.4 and 1.8 Hz.<sup>161</sup> Like thalamic cells, many cells in the GP<sup>162,163</sup> and the STN<sup>164</sup> have intrinsic oscillatory properties, which might explain the tendency of these circuits for synchronous oscillatory behavior under pathological conditions.

However, recent models of the basal ganglia circuitry show that the instability and oscillations might be the result of abnormal dynamics within the full loop of the basal ganglia.<sup>165-167</sup> The normal uncorrelated activity

within the basal ganglia might be explained with a model in which the main role of the striatopallidal axis is to reduce the dimensionality of the cortical input to the basal ganglia circuitry. This reduction can be achieved through reinforcement-driven and local competitive rules within the basal ganglia circuitry.<sup>168</sup> PD can be characterized as a persistent state of negative reinforcement signal (due to the striatal dopamine depletion), leading to inefficient dimensionality reduction and abnormal synchronized activity in the basal ganglia.

### CONCLUSIONS

The available data strongly support the hypothesis that parkinsonian symptoms are related to abnormal activity within the basal ganglia. The cerebello-thalamo-cortical loop does play a role for the frequency of the PD tremor and is probably involved in the suppression of resting tremor during voluntary movements. Spinal reflex mechanisms are unlikely to play a major role for the generation of parkinsonian symptoms, but they are believed to modify the frequency and amplitude characteristics of the parkinsonian tremor.

Several studies have demonstrated that each limb of the parkinsonian patient or MPTP-treated primate trembles independently of the other but at a similar frequency. Spinal mechanisms might account for these observations but in this case, strong reflex effects would be expected on the rhythm and amplitude of parkinsonian tremor. It is now well established both with anatomical studies and cell recordings that the basal ganglia loop is topographically organized and that the loops of the basal ganglia cortical circuitry can be coupled. Under normal conditions, the topographic compartments of this circuit are highly separated but this segregation seems to be abolished under pathological conditions. This finding could provide the anatomical background for the development of parkinsonian symptoms, and this becomes even more likely as the major pathology of PD, the nigrostriatal dopaminergic deficit, affects this loop.

In patients and animal models, tremor cells were found in the subthalamic nucleus, the internal pallidum, and the thalamus. They could either be the generators themselves or they may be an integral part of an unstable oscillating network. In this case, not a single nucleus by itself is responsible but synchronized action of the cells regulating one functional region, or even from different regions, get synchronized because the dopaminergic input is believed to keep these cells separated under normal conditions. The excellent response of parkinsonian patients to lesions or stimulation within the GPi and the STN might be due to a desynchronisation of the rhythmic activity within the oscillating loops.



An explanation for the excellent improvement of rest tremor after ventralis intermedius (Vim) lesions or stimulation is more difficult, as this lesion is not within the anatomical target of the basal ganglia loop in the thalamus but within the cerebello-thalamo-cortical loop. A simple view could be that either the anatomical projection of pallidothalamic fibers partially project to the Vim or that the pallidothalamic pathway is passing through the Vim. Alternatively, interrupting the cerebellothalamic circuitry may block parkinsonian tremor, suggesting a critical role for complex basal ganglia-cerebellum relationships (at the level of the thalamus or cortex).

These observations leave us with the paradox that parkinsonian symptoms are generated within the basal ganglia loop but they can be successfully treated, not only by blockade of the cortico-basal ganglia-cortical loop but also by blockade of the cerebello-thalamo-cortical loop. The beneficial effect of the Vim-lesion/stimulation must then be due to an interaction between the basal ganglia-thalamo-cortical and the cerebello-thalamo-cortical projection. As this interaction is unlikely to occur at thalamic level because the two projections are believed to be separated up to the cortex,<sup>154,169,170</sup> we must assume that such interaction takes place at cortical level. Indeed, our preliminary studies of the simultaneous activity of neurons in the primary motor cortex of MPTP monkeys showed abnormal bursting synchronization at this structure.<sup>140</sup> If so, it must be further hypothesized that cortical stimulation at the cortical targets of the basal ganglia and cerebello-thalamo-cortical loops would also ameliorate the tremor and other parkinsonian signs. This has not yet been investigated in patients but it was shown that stimulation of the motor cortex can induce tremor.<sup>171,172</sup> Further studies will answer the question for such a cortical suppression of tremor and other parkinsonian symptoms.

In conclusion, the topographically segregated basal ganglia loops seem to be the most likely candidates for the multiple generators of parkinsonian symptoms. Taken all the evidence together, this happens in the basal ganglia network level, and it is influenced by cerebellar and brainstem (PPN) mechanisms as well. Neurosurgical procedures, such as lesions or high-frequency stimulation, may be effective not only by changing the tonic level of the neuronal activity,<sup>173</sup> but also by desynchronization of the abnormal coupled neuronal circuits and oscillators.

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