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# Contributions of functional imaging to understanding parkinsonian symptoms

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Brain imaging experiments identify plausible circuits involved in the genesis of the cardinal symptoms of Parkinson's disease. Akinesia is linked to hypoactivation of the supplementary motor area secondary to insufficient thalamocortical facilitation. Overactivation in other areas such as the lateral premotor and parietal cortex probably represents a compensatory mechanism. Bradykinesia is associated with abnormal functioning within intrinsic basal ganglia circuitry for scaling movements to appropriate magnitude. Parkinson's disease tremor is localized to pontine- and mesencephalic-cerebellar-thalamic circuits, with abnormalities of both dopamine and serotonin neurotransmission. There is a need to understand the anatomic intersections where information is shared across these circuits.

## Addresses

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**Current Opinion in Neurobiology** 2004, **14**:715–719

This review comes from a themed issue on  
Motor systems  
Edited by Marjorie E Anderson and Ole Kiehn

Available online 2nd November 2004

0959-4388/\$ – see front matter

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DOI 10.1016/j.conb.2004.10.010

## Abbreviations

<b>BG</b>	basal ganglia
<b>fMRI</b>	functional magnetic resonance imaging
<b>GP</b>	globus pallidus
<b>PD</b>	Parkinson's disease
<b>PET</b>	positron emission tomography
<b>SMA</b>	supplementary motor area

## Introduction

Despite rapid advancements in the characterization of molecular and genetic events leading to the loss of nigrostriatal dopaminergic neurons in Parkinson's disease (PD), there remains a large gap in linking this change at the neural level to the emergence of cardinal signs of the disease. Understanding the pathophysiological basis for clinical signs in PD requires a systems level of analysis, motivated by an understanding of the normal function of the basal ganglia (BG). This systems level of analysis is also crucial for the development of rational targets of

therapy, such as deep-brain stimulation and neural transplantation. This review examines recent functional brain imaging studies of PD patients that focus on akinesia, bradykinesia and tremor. Clinically, these signs commonly appear and progress independently of each other. Functional imaging suggests that there are dissociable circuits for these signs as well, supporting functional anatomic models with a differential specialization role for motor initiation, scaling and online control.

## Akinesia

The ability to initiate movements, particularly those that are internally generated or sequentially structured, is a function of the premotor areas in the medial wall of the frontal lobe including the supplementary motor area (SMA) [1]. The SMA is influenced by the limbic and prefrontal cortex and has strong projections to the motor cortex [2]. It is central to motor selection and preparation of unimanual, bimanual and sequentially structured action. In PD patients, functional imaging with tasks requiring motor selection and initiation identified defective activation of the SMA [3]. This observation supports a circuit model of akinesia characterized by insufficient thalamocortical facilitation in PD [4]. This, in turn, is linked to excessive inhibitory activity of the internal segment of the globus pallidus (GP), resulting from unbalanced control by the direct and indirect striatofugal pathways because of dopamine deficiency within the striatum. Clinical scores of akinesia correlate significantly with the severity of striatal dopamine terminal integrity *in vivo*, with maximal involvement in the posterior putamen [5]. Because 'downstream' SMA activation can be normalized with dopamine therapy, ventral posterolateral pallidotomy or subthalamic nucleus deep-brain stimulation [6–11], it is argued that the crucial information-processing abnormality in this circuit is excessive pallidal inhibition of the ventrolateral thalamus.

Most functional imaging studies of akinesia in PD patients have used positron emission tomography (PET), which requires cross-sectional designs and small sample sizes because of the limitations of radiation exposure. An exciting new development is pharmacological functional magnetic resonance imaging (fMRI), in which the same patients can be studied across a range of tasks, both off and on medication. One recent study identified both SMA and contralateral motor cortex hypoactivation in drug naive early PD patients performing a simple finger movement task [12]. This hypoactivation normalized with L-dopa therapy. Motor performance was constant across conditions, suggesting that any change could be

ascribed to pharmacological modulation within basal ganglia–thalamocortical loops [13]. The PD akinesia model of reduced thalamocortical facilitation to the mesial frontal cortex is currently being tested in other disorders of motor initiation. For example, there is hypoactivation in the SMA and sensorimotor cortex in schizophrenic patients with severe akinesia during fMRI [14•].

Appealing as the akinesia model is, many imaging studies reveal a more complex pattern of cortical control in PD [15]. With the hypoactivation of the SMA there can be concomitant overactivation of the bilateral lateral premotor cortex and motor cortex. These changes might represent compensation because the lateral premotor association cortex is recruited to maintain task performance. This is supported by studies demonstrating increasing activity in mesial and lateral premotor areas with task complexity and effort [16]. A recent study using fMRI strongly supports the compensatory model by showing that maintenance of movement is accompanied by a shift of activation to lateral premotor areas [17]. In the same subjects, dopaminergic therapy normalized these activation patterns in the setting of constant motor performance. This interpretation assumes that in PD, the thalamocortical projection to the lateral premotor cortex is recruited normally and pallidothalamic inhibition affects only the projection to the mesial premotor areas. Alternatively, the overall selection pattern could be abnormal owing to a general disruption of thalamocortical circuitry. In the normal case, the BG–thalamocortical circuit is modeled like a center-surround filter for choosing among competing motor programs [18]. In PD, there might be cross-talk between competing programs, leading to appropriate facilitation of the lateral, rather than the medial, premotor areas. Imaging alone does not yet differentiate these opposing interpretations.

### Bradykinesia

Bradykinesia is the slowing of movement in PD secondary to reduced amplitude scaling and limb velocity [19]. It is one of the most common signs of disease and a major source of disability. Rating scores of bradykinesia correlate significantly with PET imaging of striatal fluoro-dopa uptake, as well as the density of dopamine transporter receptors, which is a complementary measure of presynaptic dopamine terminal integrity [5,20]. Numerous PET imaging studies identify metabolic signatures of PD using glucose metabolism [21,22]. Glucose metabolism is a marker of local synaptic activity and thus is a marker of both local neuronal and synaptic integrity, as well as damage to remote sources of afferent input to a site. In PD patients studied off or on medication and at rest, there is usually increased metabolism in the striatum and globus pallidus. Recent studies of patients on medications show a significant correlation between the severity of bradykinesia and bilateral putamen and globus

pallidus metabolism [23]. This is consistent with the expected increase in excitatory striatopallidal synaptic terminal activity as a result of nigrostriatal dopamine denervation. Broadly speaking, these results support a role for the BG in influencing motor amplitude or velocity for particular contexts of action.

Recent brain activation paradigms provide stronger evidence that the BG are involved in movement scaling. In normal subjects, there is greater activity in the contralateral GP with increasing movement velocity [24] and greater activity in the GP and putamen with increasing movement amplitude [25]. In PD patients performing visually guided tracking movements, there is a general underactivation of the sensorimotor cortex contralateral to the moving arm, bilateral dorsal premotor cortices and ipsilateral cerebellum [26••]. Unlike findings in the akinesia activation experiments, there is a greater than normal activation of the presupplementary motor cortex. Increasing movement velocity led to increased regional cerebral blood flow in many premotor and parietal cortical areas, as well as the BG, in PD patients, as opposed to the few cerebral locations that are velocity related in normal subjects. These findings suggest that the functional correlates of PD bradykinesia are: first, impaired recruitment of cortical and subcortical systems that normally regulate kinematic parameters of movement such as velocity; and second, increased recruitment of multiple premotor areas, including regions specialized for visuomotor control (ventral premotor and parietal cortices) and some that are not (presupplementary motor cortex). As with the akinesia experiments, overactivation of cortical regions might be a functional correlate of compensatory mechanisms or impaired selection as a facet of the primary pathophysiology of PD.

It remains unclear how basal ganglia circuits might be specifically involved in influencing movement parameters such as velocity or amplitude. There are some important clues. Behaviorally, there is extensive evidence that direction and amplitude are coded independently [27]. Pointing errors in PD patients consist of both under- and over-reaching. Directional errors are no different than in normal subjects [28]. This inaccuracy might partly result from a loss of kinesthetic sense. Unlike patients with cerebellar ataxia and normal individuals, PD patients demonstrate an impairment in the ability to detect elbow displacements in a passive movement task [29•]. Studies in Huntington's disease patients suggest that the BG might be involved in some sort of error feedback control during movement [30]. Pointing tasks in PD help to characterize this. PD patients demonstrate no impairment in automatic online adjustments while pointing to a target that is shifted without their awareness [31••]. By contrast, when patients are aware of a shift, there is a dramatic loss in their ability to generate corrective submovements.

Recording studies in monkeys demonstrate strong context sensitivity by GP neurons [32]. Although putamen and GP neurons are classically associated with motor execution, a recent study affirms that approximately 25% of neurons demonstrate preparatory responses [33]. Recent human behavioral data on reaching movements suggest that the transformation to encode limb position and velocity in intrinsic coordinates is made via a gain field; the representation is directionally dependent and modulated monotonically with limb position [34\*\*]. Combining these observations, one can propose a model in which this gain field is organized within the BG. Motor output, goal and sensory feedback are merged before movement onset and are used to adjust ongoing motor commands in reference to a desired gain field. Online corrections appear in the form of submovements amended to an ongoing movement. Disruption of this adjustment in PD would not abort movement but would limit the ability of the motor plant to scale rapidly to a desired context. Testing this hypothesis further will require a compilation of imaging, neurophysiology and behavioral studies.

### Tremor

It is widely recognized that multiple mechanisms are involved in genesis of tremor, and there are probably multiple anatomic correlates for different types of tremor. Resting 3–5 Hz and postural 4–8 Hz tremors might develop independently of the other signs of PD, suggesting that tremor could represent a special phenotype [35]. Attempts to show that tremor phenotype is linked to specific changes within cortical–BG–thalamic loops have been unsuccessful. To date, there is no definitive evidence for a specific pattern of striatal dopamine deficiency or postsynaptic dopamine receptor density reduction corresponding to this phenotype. One early imaging study showed a relationship between isolated rest tremor and presynaptic putamen dopamine loss [36]. However, most studies correlate dopamine loss to akinesia or rigidity, and do not reliably distinguish tremor patients [37–39]. A recent study using a sensitive measure of tremor amplitude improved on these findings by noting that rigidity and tremor were inversely related in their study patients. After accounting for variance associated with rigidity, there was no relationship between tremor and magnitude of dopamine loss [40]. Within the cerebellum, there is a correlation between resting metabolism and disease severity; however, this is not linked specifically to tremor [23,39]. Thus, the spatial distribution of striatal dopamine loss, or the change in glucose metabolism, is weak at identifying a specific tremor phenotype.

A more fruitful approach for understanding rest or postural tremor might be to examine alterations in neurotransmitter systems or neural circuits that could develop in parallel with dopamine deficiency of PD. Most animal models of tremor have focused on localization within

cerebellar or brainstem circuits rather than the cortical–BG–thalamic loops. Lesioning midbrain tegmentum is a reliable method of inducing a rest tremor by interrupting nigrostriatal projections, cerebellar connections to the red nucleus and rubrospinal projections [41,42]. With this lesion, there is a reduction in serotonergic and noradrenergic projections from the brainstem [43]. In concert with these animal studies, a recent PET imaging study identified a 27% reduction in midbrain raphe 5-HT<sub>1A</sub> receptors in PD patients compared with normal subjects [44\*]. Tremor scores, but not rigidity or bradykinesia, correlated with this reduction. This area is also probably interconnected with pontothalamic circuits. Using regional brain metabolism as the dependent measure, a PET study identified a network of correlated activity within pontothalamocortical areas in PD patients with tremor [45].

A second important approach has been to examine the effects of deep-brain stimulation to the ventral intermediate thalamic nucleus in PD patients with severe tremor. Tremor suppression is typically associated with a reduction in regional cerebral blood flow of the contralateral cerebellum [46]. A recent PET study found that regional cerebral blood flow correlated with tremor acceleration in the sensorimotor cortex and SMA, and tremor frequency correlated negatively with changes in the contralateral dentate nucleus and pons [47\*].

### Conclusions

Studies to date support the concept that the cardinal signs of PD are a result of differential involvement of motor circuits spanning the cortex, BG, cerebellum and brainstem. Anatomically, the BG and thalamus are in a privileged position for integrating information across these circuits [48,49]. In the future, it will be crucial to identify information sharing between BG and the cerebellar circuit, which are typically considered to be parallel and independent [50].

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