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The Cognitive Neuropsychology of Parkinson's Disease: A Functional Neuroimaging Perspective

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In Parkinson's disease (PD), the characteristic triad of motor deficits, bradykinesia, and rigidity and tremor is accompanied by a progressive pattern of neuropsychologic impairment, which in its earliest stages resembles that seen after frontal lobe excisions in patients (1–6). For example, patients with frontal lobe damage (7) and patients with mild (5) or moderate PD (3) are impaired on various aspects of performance on the Tower of London test, a series of visuospatial problems that require high-level cognitive planning. Similarly, frontal-like working memory deficits have been reported in PD (3,6,8) early in the course of the disease and in patients with severe clinical symptoms.

These deficits in patients with PD may reflect damage to one or more corticostriatal circuits that parallel the motor loop described by Alexander et al. (9) but that subserve cognitive rather than motor functions. According to this model, the widespread topographically organized cortical projections that converge on the striatum project back through pallidal, nigral, and thalamic structures to discrete frontal regions (Fig. 7-1). Different sectors of the caudate nucleus project to specific premotor regions, such as the supplementary motor area or to discrete regions within the dorsolateral and orbitofrontal cortex that are implicated in higher cognitive functions. Moreover, damage to different regions of the caudate nucleus produces cognitive deficits that resemble the effects of damage to their corresponding targets of projection within the prefrontal cortex (10). The fact that PD is associated with profound dopamine depletion in the striatum and less so in the prefrontal cortex (11–13) suggests that the frontal-like deficits observed result from either or both of these forms of pathology (14).

We used positron emission tomography (PET) combined with magnetic resonance imaging (MRI) to examine how blood flow in the frontal cortex and in the basal ganglia may be affected in PD during a number of cognitive tasks that involve frontostriatal circuitry (15,16). Six patients with PD and six age-matched (i.e., elderly) controls were scanned while performing a series of problems from the Tower of London planning test. During each scan, the subjects were presented with two sets of three colored balls (i.e., circles), one in the top half of the screen and the other in the bottom half (Fig. 7-2). The three balls were distributed in three pockets (i.e., socks) that could hold one, two, or three balls. On each trial, a red ball, a blue ball, and a green ball were placed in predetermined positions in the upper and the lower pockets of each of the two displays. The subjects were told that the balls in the top half of the screen could not be rearranged but that any ball in the bottom half of the screen could be moved between pockets by touching it with the index finger of the right hand and then by touching one of the empty positions in one of the other pockets. Once touched, a ball would be circled by a yellow ring, indicating that it was ready to be moved. When an empty pocket was touched, that location was also circled in yellow momentarily, before the selected ball moved automatically from its original position to the new one.

During the planning scan, the starting position of the balls in the bottom half of the screen was varied for each problem such that a solution could be reached in four or five moves. The subjects were told to examine the position of the balls in each problem and to attempt to find the correct solution. They were told not to make a first move until they were confi-

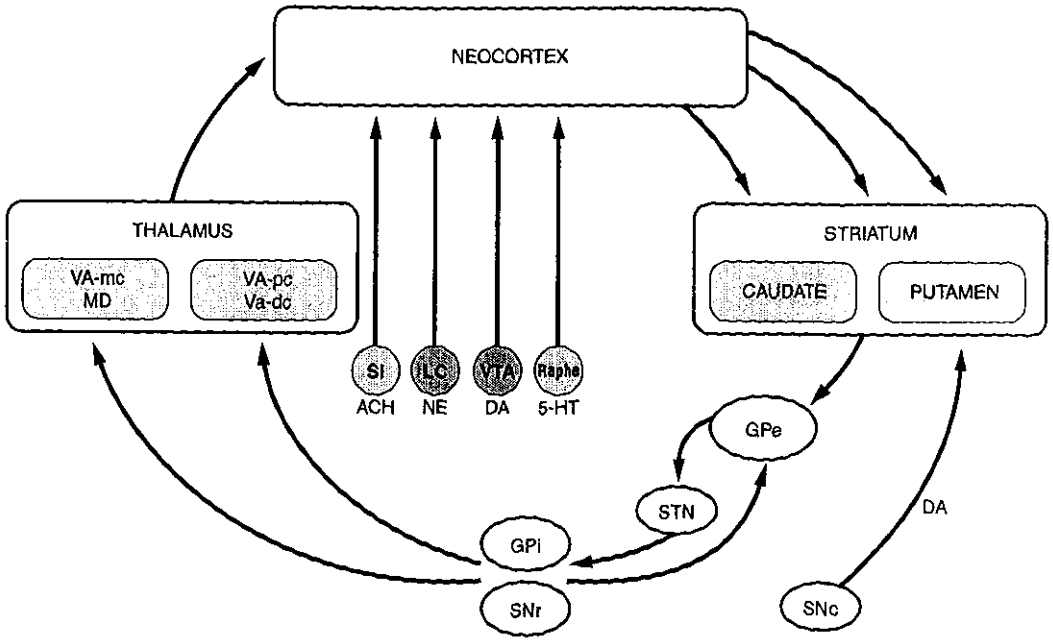

FIG. 7-1. An intimate anatomic association exists between the frontal cortex and the basal ganglia. Widespread topographically organized cortical projections converge on the striatum, which is connected to the other basal ganglia structures through direct and indirect projection systems. The inhibitory direct pathway projects monosynaptically onto the internal segment of the globus pallidus (Gpi) and the substantia nigra pars reticulata (SNr), which are the main output nuclei of the basal ganglia. The indirect pathway projects through the external segment of the globus pallidus (Gpe) and the subthalamic nucleus (STN) to the Gpi-SNr complex. The basal ganglia project back to discrete frontal lobe regions through various thalamic nuclei, closing the so-called frontostriatal loops. The activity of the basal ganglia thalamocortical circuitry is modulated by dopaminergic projections arising in the substantia nigra pars compacta (SNpc). In patients with Parkinson's disease (PD), the most significant structural damage is in the dopamine-producing cells of the SNpc, leading to degeneration of the nigrostriatal dopamine system and loss of dopamine in the striatum. PD is also characterized by degeneration of several other subcorticocortical projection systems, most notably the cholinergic (ACH), noradrenergic (NE), dopaminergic (DA), and serotonergic (5-HT) cortical projections from the substantia innominata (SI), the locus ceruleus (LC), the ventral tegmental area (VTA), and the raphe nucleus. MD, dorsomedial; VA-dc, ventral anterior, densocellular region; VA-mc, ventral anterior, magnocellular region; VA-pc, ventral anterior, parvocellular region. (Adapted from ref. 9, with permission.)

dent that they could execute the entire sequence needed to solve the problem. The computer presented the next problem automatically when a solution was completed or when a maximum of nine moves was made for four-move problems and 12 moves for five-move problems.

During a separate scan, a control task was employed to provide a baseline against which to examine the extent of activation in the planning condition. This task involved identical visual stimuli and motor responses to the difficult planning task. To prevent inadvertent planning, the initial configuration of the balls in the top half of the screen matched the initial configuration of the balls in the bottom half of the screen. The subjects were instructed to touch a series of locations in the bottom half of the screen that were highlighted with yellow rings. For each subject, the sequence of moves required in this control task corresponded exactly to the moves produced by that individual when performing the problems in the planning condition. In addition, the computer used the stored selection and movement latencies from that subject in the previous condition to pace the subject's responses in the control condition. As the subjects made each

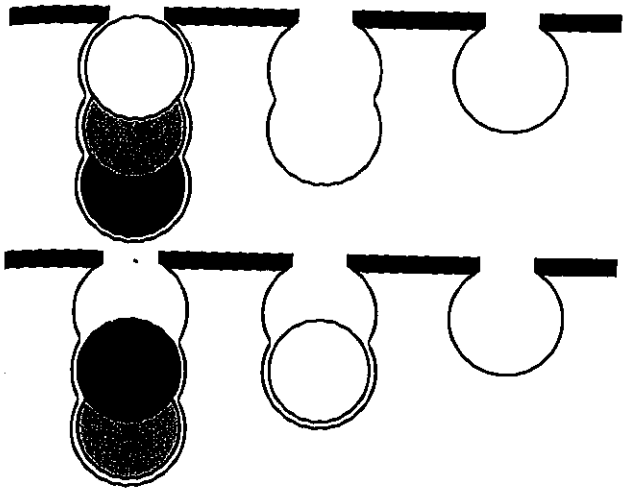

FIG. 7-2. Computerized Tower of London planning task. Subjects are required to move the balls around in the bottom half of the screen to match the goal arrangement in the top half of the screen. In each set, the left pocket can hold three balls, the middle pocket can hold two balls, and the right pocket can hold just one ball. The example shown is a five-move problem.

selection, the balls moved from pocket to pocket as before, and in this way, the subjects experienced the same visual stimuli and made the same series of arm movements (at exactly the same pace) as in the difficult planning condition. The subjects, who were unaware of this procedure, were only required to touch a series of externally defined positions on the computer screen.

For the six age-matched control subjects, significant increases in regional cerebral blood flow (rCBF) were observed in the dorsolateral, ventrolateral, and premotor areas of the left frontal lobe; in the ventral frontal, premotor, posterior parietal, and prestriate cortices of the right hemisphere; and in the striate cortex at the midline when the planning condition was compared with the visuomotor control task (15,16). In PD patients, similarly significant changes in rCBF were observed in dorsolateral, ventrolateral, and premotor regions of the right frontal lobe, and at a slightly but not significantly lower level of significance in the left mid-dorsolateral frontal region. Significant changes were also seen in the right posterior parietal cortex and in two regions of the left prestriate cortex in these patients (15).

When the patient and the control groups were compared directly, no significant difference in activation pattern was observed in the prefrontal cortex. Because previous studies in normal control subjects (17,18) had specifically implicated the mid-dorsolateral frontal region in planning, an exploratory qualitative analysis was conducted of this area. Mean normalized blood flow values (mL/100 g/min) were extracted for left and right hemispheres using 5-mm-diameter regions of interest around the highest peak of activation identified for each subject group within each subtraction (Fig. 7-3). Similar rCBF changes were observed in the mid-dorsolateral region of the frontal cortex in the control subjects and in the patients with PD.

The groups differed in one subcortical area centered on the right internal segment of the globus pallidus (GPi) (Fig. 7-4). When compared directly, there was a significant difference between the PD patients and the control subjects in the rCBF change observed in this region during the planning task.

The GPi constitutes the main basal ganglia outflow nucleus by which descending corticostriatal inputs project back to discrete frontal regions, including the mid-dorsolateral frontal cortex (19,20), through the thalamus, closing the so-called corticostriatal loops. Extraction of mean normalized rCBF values for this region revealed that, relative to the visuomotor control task, the planning task was associated with an increase in controls but a decrease in PD patients (Fig. 7-5). The same rCBF pattern (i.e., increase in controls and reduction in PD) was not observed in any other cortical or subcortical area examined, including the mid-dorsolateral frontal cortex, which is involved in these cognitive tasks.

This result is strengthened by the results of a parallel study in which the same six patients and age-matched controls were compared on a test of spatial working memory known to activate dorsal and ventral frontal lobe regions (17). When the patients and the controls were compared directly, no significant differences were observed in the prefrontal cortex during this task (15,16). The within-group analysis revealed similar changes in mid-dorsolateral frontal

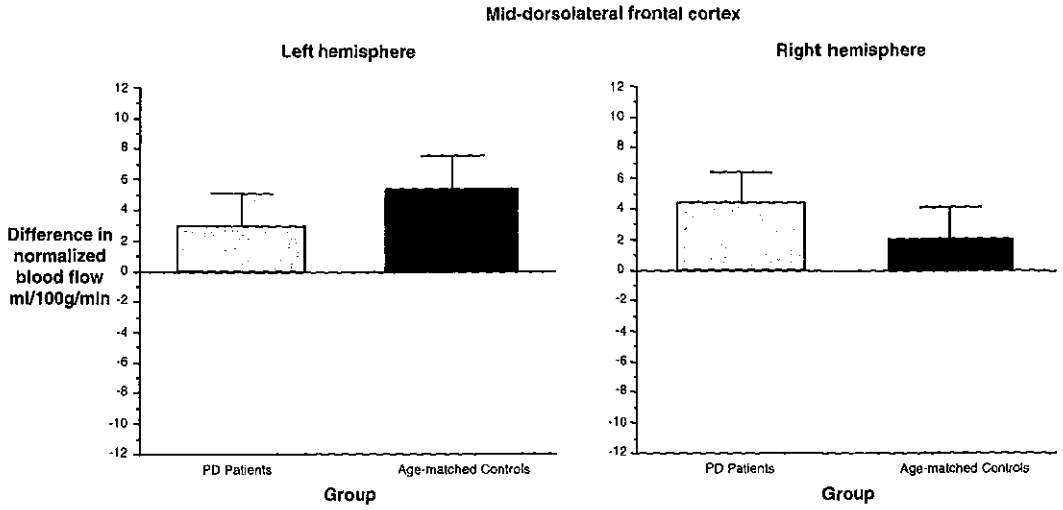

FIG. 7-3. Difference in mean blood flow (mL/100 g/min) for parkinsonian patients and for control subjects in the mid-dorsolateral frontal cortex. Mean normalized blood flow values (mL/100 g/min) were extracted for each scanning condition from the six patients and separately from the six control subjects for left and right hemispheres using 5-mm-diameter regions of interest centered on the stereotactic coordinates of the highest peak of activation identified for each group within each subtraction.

areas 9 and 46 in PD and in controls. Changes were also observed in both groups in the ventrolateral frontal region and in the dorsal and ventral frontopolar cortex. These results demonstrate that, like planning, working memory is associated with similar blood flow changes in the prefrontal cortex in patients with PD and age-matched control subjects.

The two groups differed in one subcortical area that was close to the right GPi, although in a slightly more medial position than that observed during the

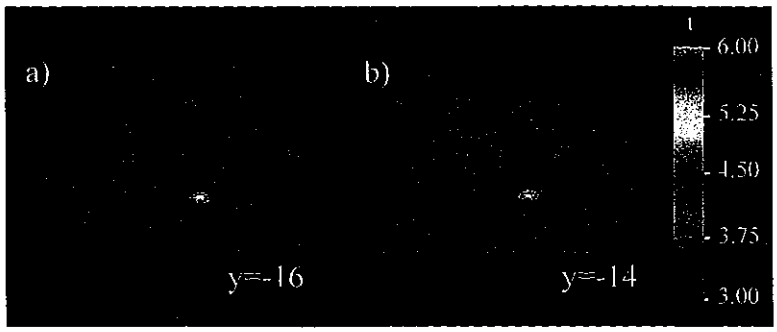

FIG. 7-4. The averaged positron emission tomography (PET) subtraction images are superimposed on the corresponding averaged magnetic resonance image (MRI) of all 12 subjects participating in the study. Direct comparisons between the six patients and the six control subjects yielded the focal differences in blood flow, shown as a *t* statistic image whose range is coded by the color scale placed to the right of the figure. In the coronal section, the y coordinate represents the position relative to the anterior commissure (positive = anterior) and has been chosen to illustrate the statistically significant difference in the region of the right globus pallidus, internal segment (GPi), between the control subjects and the parkinsonian patients when the difficult planning condition was compared with the visuomotor control condition. The same peak is shown in the horizontal plane ($z = -3$). The schematic diagram *(bottom right)* illustrates the approximate position of the two MRI slices shown. Identical slices *(left)* are shown from a high-resolution MRI of a single subject (i.e., normal control) to assist with anatomic localization of the significant blood flow change to the GPi.

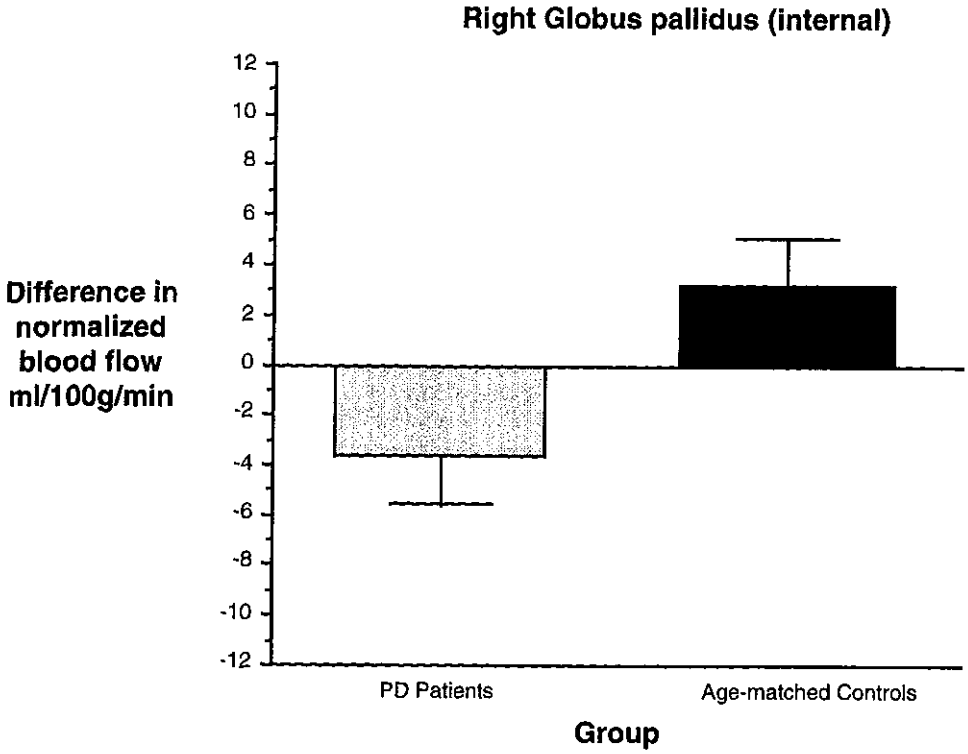

FIG. 7-5. Difference in mean blood flow (mL/100 g/min) for patients with Parkinson's disease and for control subjects at the peak coordinate in the region of the internal segment of the globus pallidus. Mean normalized blood flow values (mL/100 g/min) were extracted for each scanning condition from the six patients and separately from the six control subjects using a 5-mm-diameter region of interest centered on the stereotactic coordinates of the peak difference between the two groups.

planning conditions at the border of the GPi and the subthalamic nucleus (see Fig. 7-4). Extraction of normalized blood flow values revealed that the pattern of rCBF change observed in the region of the right GPi in the control subjects was opposite to and approximately equal to that observed in the patients with PD. Blood flow increases centered on the right GPi were observed in the age-matched control subjects, but blood flow decreases were observed in the patients with PD.

The difference between PD patients and controls in the region of the right GPi is unlikely to reflect the movement requirements of the tasks and the motor deficits that characterize PD for several reasons. In the direct comparison of PD patients and their age-matched controls, differences in the frequency and type of movements made during the difficult planning task was taken into account by subtracting the pattern of rCBF during the visuomotor control task, which required the same movements at the same relative moments in time. Moreover, the difference in the region of the GPi was only observed in the right hemisphere, ipsilateral to the side of movement, and was therefore unlikely to be related to motor factors in any direct way.

It seems probable that the group difference in the right GPi is related to cognitive rather than motor aspects of performance on the test of planning and on the test of working memory and, presumably, to the deficits that are observed in PD patients, although the relatively small number of subjects precludes measuring direct correlations between performance and rCBF. The most likely interpretation of these results is that striatal dopamine depletion disrupts the normal pattern of basal ganglia outflow in PD and consequently affects the expression of frontal lobe functions by interrupting normal transmission of information through frontostriatal circuitry.

On the basis of these results, the frontal cognitive deficits in planning and spatial working memory seen in early PD appear to result from abnormal processing of the prefrontal input through malfunctioning

basal ganglia circuitry, not from intrinsic prefrontal dysfunction per se. This surprising finding contrasts with the results of other PET or single photon emission computed tomography (SPECT) studies, which have demonstrated that motor slowing (i.e., bradykinesia) in PD is accompanied by reduced rCBF in the supplementary motor area and that this effect can be at least partially reversed by dopaminergic medication (21–24). However, these findings are entirely consistent with the fact that dopamine deficiency in early PD preferentially affects the striatum and not the prefrontal cortex, as demonstrated pathologically and in a PET study using ^{18}F-DOPA (25).

We tested the generality of these findings by comparing patterns of rCBF change in patients with PD and age-matched controls during a test of visuomotor skill learning (26–27). Skill learning (i.e., procedural memory) refers to the capacity to acquire an ability through practice. Skill learning deficits have been reported in patients with PD (27–30) and in patients with circumscribed cerebellar lesions (27), suggesting that performance on such tasks is mediated by distributed circuitry that includes the striatum and the cerebellum. Unlike planning and spatial working memory, skill learning appears not to depend critically on the integrity of the prefrontal cortex (27).

Six patients with PD and six normal control subjects were scanned using PET during a modified version of the Repeated Sequence Test (31). In this task, subjects were required to monitor four blue boxes aligned in a horizontal row on a computer screen. During each trial, a red circle appeared above one of the response boxes, and the subject's task was to touch the center of that box as quickly as possible while making minimal errors. As soon as the subject had touched the appropriate box correctly, the red circle disappeared, and the circle appeared over another of the four boxes. Unknown to the subject, the stimuli were presented in a fixed 10-item repeated sequence. Previous studies showed that, after extensive training, reaction times are significantly decreased in this task, demonstrating that the embedded sequence was implicitly learned, even though subjects exhibit no declarative or explicit knowledge of its existence (27).

The subjects were also scanned during a control task that was identical to the embedded sequence condition in every way, except that the order of stimulus presentation was entirely random. In normal control subjects, significant changes are observed in the right ventral striatum and in the dentate nucleus of the cerebellum when rCBF measured during the advanced stages of learning is compared with that measured during the random condition (26). Moreover, a direct comparison between six PD patients and an age-matched group of normal controls confirmed there was a significant difference between the groups in the rCBF change observed in a region of the globus pallidus during this task (J. Doyon et al., unpublished results). This difference is in a location similar to the peak change observed previously when PD patients and control subjects were compared during tests of planning and spatial working tasks (15,16). As in that study, these findings suggest that striatal dopamine depletion in PD disrupts the normal pattern of basal ganglia outflow through the globus pallidus and consequently affects cognitive functions that depend on components of this circuitry.

For the motor system, studies using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–treated monkeys show increased tonic discharge within the GPi (32,33). It is not possible to relate this phenomenon directly to the results described here, because a true resting condition was not included in any of these functional imaging studies. However, rCBF values in the region of the right GPi in PD tended to be higher than for controls in the visuomotor control condition described by Owen et al. (15,16).

In controls, the relative increase in rCBF in the right GPi during the studies of planning and working memory (15,16) is similar to the bilateral increases found in this region in a PET study of increasingly complex sequential finger movements (34). Because the influence of the GPi on cortex is inhibitory, a task-related increase in neuronal activity in the GPi most likely reflects increasing inhibition of cortical areas not needed for the task in question, and a decrease probably reflects facilitation, the so-called focusing function of the basal ganglia (35). Parent and Hazrati (36) showed that excitatory subthalamic input to the internal pallidum (i.e., the indirect pathway) could excite a large number of pallidal neurons, whereas the inhibitory striatal input (i.e., the direct pathway) exerted a more narrowly focused inhibitory influence on these same neurons, providing an anatomic substrate for this focusing mechanism. In this way, the selection of cortical areas required for a particular task is associated with a large excitatory input and a smaller, more focused inhibitory input onto the GPi. In the normal brain, this would produce an overall increase in synaptic activity in the GPi, and because rCBF is thought to reflect average local synaptic activity (37), an increase in rCBF in this region.

How does a lack of dopamine in PD disrupt this normal pattern of neuronal processing within the basal ganglia? The action of dopamine in the striatum is not fully understood, but it does not appear to have a uni-

form effect on all striatal neurons (38). Dopamine is released during conditioned learning tasks with a reward component, and on this basis, it has been suggested that dopamine acts as an error signal to facilitate the selection of the necessary corticostriatal loops for the particular task being performed (40). Depending on the activation state or the membrane potential of the target striatal neuron, dopamine may exert excitatory or inhibitory effects (38,41–43), which may drive the focusing mechanism described previously. Absence of dopamine in PD may therefore alter the efficacy of the normal corticostriatal volley arising from the prefrontal cortex during performance of planning or spatial working memory tasks (38,41–43). An inability to modulate the cortical excitatory input to striatal neurons may result in abnormal influence on the GPi through the direct or the indirect pathway, or both, and consequently abnormal processing of neuronal activity within the basal ganglia.

The fact that this abnormality produces a reduction in right GPi activity during performance of the complex planning and working memory tasks and during a visuomotor skill learning task is difficult to explain on the basis of known models of basal ganglia physiology. Such a reduction could reflect a decrease in excitation from the subthalamic nucleus or perhaps an increase in inhibition from the striatum.

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