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Common and unique responses to dopamine agonist therapy and deep brain stimulation in Parkinson's disease: an H₂¹⁵O PET study

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Abstract

Background—Dopamine agonist therapy and deep brain stimulation (DBS) of the subthalamic nucleus (STN) are antiparkinsonian treatments that act on a different part of the basal ganglia-thalamocortical motor circuitry, yet produce similar symptomatic improvements.

Objective/Hypothesis—The purpose of this study was to identify common and unique brain network features of these standard treatments.

Methods—We analyzed images produced by H₂¹⁵O positron emission tomography (PET) of patients with Parkinson's disease (PD) at rest. Nine patients were scanned before and after injection of apomorphine, and eleven patients were scanned while bilateral stimulators were off and while they were on.

Results—Both treatments produced common deactivations of the neocortical sensorimotor areas, including the supplementary motor area, precentral gyrus, and postcentral gyrus, and in subcortical structures, including the putamen and cerebellum. We observed concomitant activations of the superior parietal lobule and the midbrain in the region of the substantia nigra/STN. We also detected unique, treatment-specific changes with possible motor-related consequences in the basal ganglia, thalamus, neocortical sensorimotor cortex, and posterolateral cerebellum. Unique changes in non-motor regions may reflect treatment-specific effects on verbal fluency and limbic functions.

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Conclusions—Many of the common effects of these treatments are consistent with the standard pathophysiological model of PD. However, the common effects in the cerebellum are not readily explained by the model. Consistent deactivation of the cerebellum is interesting in light of recent reports of synaptic pathways directly connecting the cerebellum and basal ganglia, and may warrant further consideration for incorporation into the model.

Keywords

Parkinson's disease; deep brain stimulation; apomorphine; positron emission tomography

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, affecting approximately 0.3 percent of the general population and 3 percent of people over the age of 65 worldwide (1). In an attempt to explain the pathophysiology of PD as well as the effects of treatment, researchers have modeled the interactions among the basal ganglia (BG), thalamus, and cortex (Fig. 1a) (2). According to the standard model, in the untreated condition, a decrease in striatal dopamine (DA) modulates the network from a healthy state to a parkinsonian state by destabilizing the normal functional interactions within and between subcortical and cortical structures. This destabilization results in abnormal activity in the motor cortices, accounting for tremor, rigidity, bradykinesia, and several other motor-related symptoms observed with PD (Fig. 1b). According to the model, treatment can bring about a reversal of this parkinsonian state by directly acting at a variety of sites within the network, leading indirectly to normalization in activity of the motor cortices.

Two antiparkinsonian therapeutic interventions – dopaminergic pharmacotherapy and deep brain stimulation (DBS) – have successfully provided symptomatic improvement (3). In the late 1960s, levodopa therapy emerged as a treatment for PD, and the subsequent introduction of direct-acting DA agonist medications that stimulate DA receptors in the DA-depleted striatum came into use. DBS for advanced PD, introduced in the 1980s, is a reversible surgical intervention whose success had been suggested by the same model. Modern DBS intervention most commonly involves stimulating the subthalamic nucleus (STN) through implanted electrodes. Thus, the two different forms of treatment act at different sites within the basal ganglia-thalamocortical circuitry that comprises the standard model of PD, but both show significant improvements in PD symptoms (Fig. 1b).

Empirical evidence for a common set of physiological effects, common to both of these treatments, should provide a better understanding of the pathophysiological mechanisms at the root of PD and offer a pragmatic means of assessing the standard model. It should be noted that researchers continue to propose important additions to this model, such as direct projections from the motor cortex to the STN (4), globus pallidus externa (GPe) to the striatum (5), and GPe to the globus pallidus interna (GPi) (6), but we will adhere to the common practice of referencing the essential elements of the standard model for clarity of explanation.

Functional neuroimaging has proved to be an invaluable research tool for investigating PD. Most notably, researchers have employed positron emission tomography (PET) or blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) to measure hemodynamic changes coupled to neural activity in the central nervous system. Functional neuroimaging studies have evaluated the effect of an intervention while patients were at rest (7–15) or during the performance of cognitive or motor tasks (16–20). The results from these imaging studies, most of which have assessed the response to a single treatment, are largely consistent with the standard model of PD. The present study aimed to identify both

the common and unique effects of DA agonist therapy and STN DBS at rest in a single comprehensive analysis.

We analyzed H₂¹⁵O PET images acquired from PD patients at a resting baseline state (withdrawn from PD medications and off STN DBS) and following the (re)institution of each treatment. We employed a combination of contrast and conjunction methods to identify both the common and unique effects of these treatments. In order to examine the neural regions most commonly reported to be affected by PD, we constrained the analysis of the common effects (conjunctions) to sensorimotor regions likely to affect motor control in PD. We expanded the regions of interest for the analysis of the unique effects to assess non-motor consequences of treatment.

Methods and Materials

Patient groups

Two groups of patients with the diagnosis of idiopathic PD were studied. Nine patients (7 males, 2 females; age 60 ± 11 years (Mean $\pm$ SD), age range 43 – 77 years, duration of disease 16 ± 6 years) without implanted stimulators, but on a waiting list for surgery, were scanned before and after the injection of apomorphine, a mixed D1/D2 agonist. Eleven patients (7 males, 4 females; age 60 ± 12 years, age range 41 – 77 years, duration of disease 15 ± 5 years) were studied 2 ± 1 years following placement and activation of bilateral STN implants. This group was scanned in a single session after DBS stimulators were deactivated and again following activation of stimulators at their optimal settings. Disease severity ranged from stages III through V on the Hoehn and Yahr scale (21). To rule out group differences in severity, as reflected in standard clinical measures, three two-sample, two-tailed, *t*-tests ($p < 0.05$) were performed between baseline scores using the Unified Parkinson's Disease Rating Scale (UPDRS) part III: for tremor, rigidity, and bradykinesia. To further rule out group differences, two-tailed *t*-tests ($p < 0.05$) were performed for age and disease duration. Table 1 summarizes the clinical features of the patients. All subjects gave written informed consent prior to participation in the study which was approved by the NINDS/NIDCD Institutional Review Board.

Dose finding

Prior to the scanning sessions, dose finding was conducted in patients that were to receive apomorphine by administering increasingly higher doses of apomorphine HCl (dissolved in sterile water and injected intravenously) and measuring the motor response to each dose. Motor effects were evaluated using items from the UPDRS part III. Tremor, rigidity, and bradykinesia were selected for the abbreviated scale because they could also be scored while patients were in the PET scanner. A rater, blinded to dose, evaluated motor performance just prior to the injection of apomorphine and every ten minutes thereafter until the patient's motor state returned to baseline. The dose that produced the optimal antiparkinsonian effect with the least dyskinesia was chosen for administration during the PET scan. No blood pressure changes, nausea, or vomiting were observed during evaluations at the dose selected. The mean dose of apomorphine selected at dose finding and administered during the scan was $0.04 \text{ mg/kg} \pm 0.02 \text{ mg/kg}$. Although some patients experienced dyskinesia in response to the selected doses of apomorphine during the dose-finding phase, review of videotapes showed that no patient experienced overt dyskinesia during PET scanning.

Optimal settings for left and right DBS stimulators (Activa, Medtronic) were determined by each patient's treating neurologist prior to their visit to the Clinical Center at the National Institutes of Health. For the left and right stimulators respectively, the average settings were

3.0 ± 0.7 and 3.1 ± 1.0 V for amplitude, 79 ± 15 and 82 ± 19 μ s for pulse width, and 164 ± 16 and 158 ± 21 Hz for rate.

Scanning

PET scans were performed on a General Electric Advance scanner (GE Medical Systems, Waukesha, WI) operating in 2D-acquisition mode, which acquires 35 slices simultaneously with a spatial resolution of 6.5 mm full width at half-maximum (FWHM) in x, y, and z axes. A transmission scan, using a rotating pin source, was performed for attenuation correction. For each scan, 10 mCi of H_2^{15}O was injected intravenously in a bolus preparation over ten seconds. Scans commenced automatically when the count rate in the brain reached a threshold value (approximately 20 seconds after injection). The scan duration was one minute with an interscan interval of five minutes. During all scans, subjects' eyes were closed and light was occluded by eye patches. A thermoplastic mask immobilized the head. All scans were performed with subjects at rest. Antiparkinsonian medications were discontinued in all patients 12 hours prior to the scan procedure and held until scanning was completed.

Patients in the apomorphine group received 20 mg of oral domperidone four times a day beginning the day before testing and continuing for the duration of the study. Scans 1 – 5 were acquired prior to the injection of apomorphine and served as baseline scans. Prior to scan 6, patients were injected with the dose of apomorphine that had been selected in the dose-finding phase. Scans were then acquired every five minutes while patients continued to exhibit the antiparkinsonian effects of apomorphine, which resulted in an average of 5 scans of apomorphine effects. Parkinsonian signs (tremor, rigidity, and bradykinesia) were evaluated between each scan, both before and after the injection of apomorphine, by the investigator that had performed the clinical ratings during the dose-finding phase. The “on” state lasted a variable number of scans for each patient; each patient’s “on” scans were used in the statistical analysis. Each scanning session was videotaped, and the tape was reviewed to record the presence or absence of dyskinesia or other adventitious movements.

In the STN DBS group, antiparkinsonian medications were discontinued 12 hours prior to the scan procedure as outlined above, but DBS was continued at each patient’s optimal settings throughout the night. On the morning of the scanning session, stimulators were turned off 20 minutes prior to the first scan. Following acquisition of the 3 “off” scans, stimulators were reactivated and 3 “on” scans were acquired after 20 minutes, when the clinical response was determined to be optimal. The “off” and “on” conditions were not randomized due to the protracted effects of STN DBS. Parkinsonian signs were evaluated between each scan. These sessions were videotaped, and the tape was reviewed to record the presence or absence of dyskinesia or other adventitious movements.

Data analysis

PET scans were coregistered, resliced, and normalized to an MNI (Montreal Neurological Institute) PET template image, smoothed with an isotropic Gaussian kernel of 10 mm FWHM, and statistically analyzed using Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London, UK). Results were obtained from three statistical analyses ($p < 0.05$): First, individual treatment effects were determined by contrasting rCBF during treatment and rCBF during the baseline rest condition. Next, common treatment effects were determined by a conjunction performed between individual treatment effects. Finally, unique effects of individual treatments were determined by exclusively masking each individual treatment contrast with the other individual treatment contrast. Each of the three analyses was performed separately for increases and decreases from baseline due to treatment, and the images of increases and decreases were rendered

onto a single-subject, T1-weighted brain image template using MRICro version 1.40 (22). For the conjunction analysis, the sample space was confined to sensorimotor-related areas of the brain since these areas included the components of the standard model of PD pathophysiology as well as the most likely candidates for inclusion into the model. The areas included were the BG, thalamus, supplementary motor area (SMA), precentral gyrus (PrG), postcentral gyrus (PoG), superior parietal lobule (SPL), and cerebellum. For the analysis of unique effects of each treatment, the sample space was unconstrained to include regions outside of these areas that may be related to non-motor side effects. For tabulating results, voxel coordinates were converted from MNI space to Talairach space (23).

Results

Analysis of baseline differences

The three two-sample, two-tailed, *t*-tests between UPDRS measures of tremor, rigidity, and bradykinesia obtained at baseline (off-treatment) in the apomorphine and DBS groups concluded that there were no statistically significant ($p > 0.05$) differences in disease severity as reflected by these clinical measures. In addition, the *t*-tests for age and disease duration indicated no statistically significant ($p > 0.1$) group differences.

Common effects of treatments

The conjunction analysis showed that bilateral STN DBS and apomorphine injection each deactivated rCBF in sensorimotor areas of the neocortex, BG, and cerebellum. The deactivated neocortical areas were the SMA, PrG, and PoG, and the deactivated BG structure was the putamen. Each antiparkinsonian treatment also increased rCBF in the SPL and midbrain. Given the small size of the midbrain, it is possible that the activation could have been in the periaqueductal midbrain, but we attribute this midbrain activation to the more likely region of the substantia nigra (SN)/STN. These results are displayed in Table 2 and Fig. 2.

Unique effects of treatments

While apomorphine and STN DBS both decreased rCBF in the SMA, PrG, and PoG, DBS exhibited more widespread decreases, while apomorphine, in contrast, activated portions of these neocortical sensorimotor regions. In subcortical areas, the GP was activated by DBS but unaffected by apomorphine, and apomorphine deactivated relatively wider areas of the putamen and cerebellum. In addition, apomorphine and DBS had several reciprocal effects. In the posterolateral cerebellum (Crus II), rCBF was increased by DBS but decreased by apomorphine. Activity of the ventrolateral thalamus followed the same trend where it was increased by DBS but decreased by apomorphine. Outside of the sensorimotor regions, DBS exclusively activated the amygdala, and both treatments activated the hippocampus with DBS acting on more ventral portions. The inferior frontal gyrus was activated by DBS but deactivated by apomorphine. The superior temporal gyrus was uniquely activated by apomorphine whereas DBS had no effect. DBS activated anterior portions of the middle temporal gyrus while deactivating posterior portions. These results are displayed in Tables 3 and 4 and Fig. 3.

Discussion

The standard model of PD pathophysiology attempts to explain the disease as well as the effects of antiparkinsonian treatment in terms of interactions within circumscribed cortico-basal ganglia-thalamocortical circuits (Fig. 1) (2). DA agonist therapy and STN DBS are present prototypical treatments, each acting at different sites within the network described by this model, resulting in improvement of parkinsonian symptoms.

As with all centrally acting drug and surgical treatments, both of these treatments produced a wide range of responses as revealed by neuroimaging; some of these represent therapeutic effects while others represent side effects that are otherwise nonspecific.

The common effects identified by the conjunctions of the two treatments should, at least in part, reveal the common pathway by which they work. That is, these overlaps should constitute the essential features of effective antiparkinsonian therapy but, of course, may also reflect motor complications that happen to be common to these treatments. The latter possibility appears unlikely, however. The most common motor side effects of antiparkinsonian treatment are dyskinesia, such as choreiform, dystonic, or other involuntary movements commonly seen with DA agonist medications but infrequently seen with DBS. Moreover, while antiparkinsonian effects were clearly demonstrated in our patients, no dyskinesia or dystonia were present during the scans included in the analysis. Therefore, rCBF responses related to abnormal involuntary movements are less likely to appear in a conjunction of treatment effects.

Responses that are unique to each treatment, i.e., those that do not overlap should, on the other hand, reflect differences in efficacy or production of motor complications, or idiosyncratic effects unrelated to primary antiparkinsonian activity, perhaps related to unique side effects of these treatments. In this context, it is important to note that the two groups of PD patients did not significantly differ in age, disease duration, or disease severity.

Common effects of treatments

Most of the significant conjunctions we report involve regions included in the standard pathophysiological model of PD. Apomorphine injection and DBS each produced decreases of rCBF in the putamen, SMA, PrG, and PoG and increases in the SPL and midbrain in the region of the SN/STN. These changes in rCBF have been reported in other functional neuroimaging studies of PD patients at rest undergoing STN DBS (8,10,12–15) or receiving DA agonist medication (7,9,11,12). Studies have shown that regions of the SMA/primary sensorimotor cortex and SPL are hyperactive and hypoactive respectively at rest in untreated PD patients relative to healthy controls (11,13,24); therefore, treatment may normalize activity in these regions of interest. These findings are consistent with our observed deactivation of the SMA, PrG, and PoG and activation of the SPL due to treatment. It is possible that decreased activity in the putamen could be due to a reduction in afferent input from the deactivated SMA and primary sensorimotor cortex (25).

While the mechanism by which stimulation brings about therapeutic benefit is controversial, one view focuses on a decrease in afferent input to the target region (26) while another view focuses on increased activity in target outputs of the structure in which the stimulating leads are implanted (27). We believe our findings support the latter view. Since the SN receives excitatory input from the STN, this might provide a mechanism whereby STN stimulation activates the midbrain in the region of the SN/STN, consistent with the standard model (8).

In contrast, the significant change in activity in the cerebellum that is common to both treatments is not readily explained by synaptic connections within the standard model. The modulation of cerebellar activity we observed could represent antiparkinsonian treatment effects, but might also reflect adventitious motor side effects common to both treatments although, as noted above, the latter appears less likely. Instead the significant deactivation of the cerebellum may represent essential features of antiparkinsonian therapy that are not accounted for by the standard model. It is well established that the cerebellum, like the BG, plays a central role in motor control, facilitating tasks such as self-paced movement preparation and motor adaptation and learning: functions shown to be impaired in PD

(15,28,29). Evidence for its involvement in the pathophysiology and treatment of PD has been demonstrated by functional neuroimaging and anatomical studies. In the functional neuroimaging literature, hyperactivity of the cerebellum in untreated PD has been reported (11,24,30,31) as has normalization of this hyperactivity due to antiparkinsonian treatments (7,9,11,12,15,32,33). One explanation for these findings is that the cerebellum could play a compensatory role in the organization of movement in the face of BG dysfunction (24,34).

It is also possible that the cerebellum plays a more integral role in the pathophysiology and treatment of PD. The neocerebellum has a pattern of connections that are roughly parallel to those outlined in the standard model: like the BG, the cerebellum receives massive projections from the cerebral cortex and projects back to the cortex via the ventral thalamic nuclei. Previously, it had been assumed that the BG and cerebellum communicated principally via convergent projections to the motor cortex (35). However, a relatively recent study has demonstrated more direct synaptic connections between cerebellar and BG circuitry (36). Neurons of the deep cerebellar output nuclei project to the ventrolateral and intralaminar thalamic nuclei, both of which project in turn to the putamen. In the putamen, the target of these cerebello-thalamic projections appears to be the population of medium spiny stellate neurons that project to the GPe. The cerebellum is thus in a position to regulate activity within the “indirect” BG-thalamocortical pathway, which mediates the effects of DBS and, in part, DA agonist therapy. The establishment of direct pathways connecting cerebellar output to the input stage of BG processing raises the intriguing possibility that the significant impact of each of the two successful therapeutic interventions on cerebellar activity might represent an essential antiparkinsonian feature of these treatments.

Unique effects of treatments

In addition to conjunctions, each treatment had unique effects on rCBF in frontal, parietal, temporal, occipital, striatal, thalamic, limbic, and cerebellar regions. Tables 3 and 4 and Fig. 3 summarize these findings. However, for clarity of presentation, we focus here on the regions we believe to be most pertinent to our investigation.

These unique effects on rCBF may, in part, reflect differences in efficacies for treatment of rigidity, tremor, bradykinesia, and disturbed gait. Varma et al. (37) demonstrated that STN DBS may be more effective in remediating these symptoms than apomorphine therapy alone, thus, the fact that DBS deactivated the SMA, PrG, and PoG in a more widespread fashion than apomorphine might reflect its greater efficacy in reducing cardinal parkinsonian symptoms. In fact apomorphine additionally increased activity in anterior portions of the SMA and anterolateral portions of the PrG and PoG. Several studies that investigated the neural correlates of symptoms found that activity in SMA and PrG negatively covaried with improvement in rigidity (14,24). Since rigidity is more improved with DBS than with DA agonist therapy alone (37), these unique effects of apomorphine in central motor regions might reflect the limited improvement in rigidity by DA agonists. While both treatments caused decreased activity in some regions of the cerebellum, DBS uniquely activated the left posterolateral cerebellar in Crus II. Interestingly this cerebellar region has been associated with gait imagery (38), which could represent a mechanism by which DBS improves gait disturbances in PD patients (39).

Probably the most intriguing treatment difference that may relate to possible motor consequences is that STN DBS increases but DA agonist medication decreases activity in the ventrolateral thalamus, a finding that has been reported previously (12). It is possible that this differential effect of treatment on thalamic activity is related to unique effects of treatment on tremor and on bradykinesia. Sturman et al. (40) and Blahak et al. (41) reported that STN DBS improved tremor more than DA agonist therapy, possibly suggesting an improved therapeutic benefit associated with the unique way in which tremor-related cells in

the thalamus (42) are altered by DBS. Karimi et al. (14) found that increased thalamic activity due to STN DBS was correlated with improvement in bradykinesia. This putative connection between thalamic activity and bradykinesia and our report of reciprocal activation could further explain the observation of Timmermann et al. (43) that DA agonist therapy and STN DBS exhibit complementary effects on bradykinesia.

Despite the uncertainty of their motor consequences, several additional treatment differences deserve attention. First, we found that DBS exclusively activated the GP. This finding is supported by Hilker et al. (8) and Hershey et al. (12) (but see Asanuma et al. (44)). Again assuming that DBS activates target regions, it follows that STN stimulation may directly increase synaptic input to GP. Second, apomorphine deactivated relatively wider areas of the putamen and cerebellum. Synaptic connections linking the putamen and cerebellum (36) might account for the fact that these effects are coupled, however the significance remains unclear.

Other unique treatment effects we observed may reflect non-motor consequences of antiparkinsonian therapy. In the limbic system, the treatments differentially activated the hippocampus and amygdala, which play a central role in emotional and mnemonic processing. Both treatments strongly activated the hippocampus, but apomorphine activated a more ventral section. DBS exclusively activated the amygdala. Other unique changes possibly related to differences in emotional processing were observed in the middle frontal and orbital gyri and the anterior and posterior cingulate cortices.

While there are a variety of reports that have examined neuropsychological changes due to these therapies, the most consistent finding is that verbal fluency is negatively affected by STN DBS (45). We found that in the inferior frontal gyrus was differentially affected by the treatments, DBS causing increased, and apomorphine causing decreased activity. Broca's area plays a central role in verbal fluency (46), and Schroeder et al. (47) found that activity in this canonical anterior perisylvian language area correlated with declines in verbal fluency, consistent with our observation. We also observed differing responses to treatment in posterior perisylvian language areas – middle and superior temporal gyri – that might also reflect treatment-unique effects on verbal fluency (48,49).

Conclusions

We have identified both common and unique effects of two antiparkinsonian therapies, each of which acts at a different node within a network connecting the BG, thalamus, and cortex. Each treatment produced common changes in SMA, PrG, PoG, SPL, BG, and cerebellum. A number of these effects are consistent with the standard model of the pathophysiology of idiopathic PD; others suggest that the model might be modified to integrate regions that are significantly affected by both treatments. Particularly with respect to changes in the cerebellum, it will be important to further examine its functional connectivity with elements of the cortico-basal ganglia-thalamocortical circuitry and evaluate these interactions using computational models to determine the consequences of incorporating this region into the standard pathophysiological model of PD. Differential effects of apomorphine and DBS observed in other portions of the SMA, PrG, BG, thalamus, limbic system, and inferior frontal gyrus may offer preliminary explanations for differing motor consequences or potential explanations of non-motor consequences of the two treatments. It should again be noted that in this study, we chose to image the effects of treatment in PD patients at rest in order to provide a baseline for future evaluations of the clinical impact of these antiparkinsonian treatments on the cognitive or motor functions that they ultimately affect.

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References

1. Lang AE, Lozano AM. Parkinson's disease – First of two parts. *N Engl J Med*. 1998; 339:1044–1053. [PubMed: 9761807]
2. Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. *Curr Opin Neurobiol*. 1996; 6:751–758. [PubMed: 9000030]
3. Poewe W. Treatments for Parkinson disease--past achievements and current clinical needs. *Neurology*. 2009; 72:S65–73. [PubMed: 19221317]
4. Nambu A. A new dynamic model of the cortico-basal ganglia loop. *Prog Brain Res*. 2004; 143:461–466. [PubMed: 14653188]
5. Bolam JP, Hanley JJ, Booth PA, et al. Synaptic organisation of the basal ganglia. *J Anat*. 2000; 196:527–542. [PubMed: 10923985]
6. Hazrati LN, Parent A, Mitchell S, et al. Evidence for interconnections between the two segments of the globus pallidus in primates: a PHA-L anterograde tracing study. *Brain Res*. 1990; 533:171–175. [PubMed: 2085730]
7. Feigin A, Fukuda M, Dhawan V, et al. Metabolic correlates of levodopa response in Parkinson's disease. *Neurology*. 2001; 57:2083–2088. [PubMed: 11739830]
8. Hershey T, Revilla FJ, Wernle AR, et al. Cortical and subcortical blood flow effects of subthalamic nucleus stimulation in PD. *Neurology*. 2003; 61:816–821. [PubMed: 14504327]
9. Hershey T, Black KJ, Carl JL, et al. Long term treatment and disease severity change brain responses to levodopa in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2003; 74:844–851. [PubMed: 12810765]
10. Haslinger B, Kalteis K, Boecker H, et al. Frequency-correlated decreases of motor cortex activity associated with subthalamic nucleus stimulation in Parkinson's disease. *NeuroImage*. 2005; 28:598–606. [PubMed: 16081302]
11. Hosey LA, Thompson JL, Metman LV, et al. Temporal dynamics of cortical and subcortical responses to apomorphine in Parkinson disease: an H₂¹⁵O PET study. *Clin Neuropharmacol*. 2005; 28:18–27. [PubMed: 15711435]
12. Asanuma K, Tang C, Ma Y, et al. Network modulation in the treatment of Parkinson's disease. *Brain*. 2006; 129:2667–2678. [PubMed: 16844713]
13. Trošt M, Su S, Su P, et al. Network modulation by the subthalamic nucleus in the treatment of Parkinson's disease. *NeuroImage*. 2006; 31:301–307. [PubMed: 16466936]
14. Karimi M, Golchin N, Tabbal SD, et al. Subthalamic nucleus stimulation-induced regional blood flow responses correlate with improvement of motor signs in Parkinson disease. *Brain*. 2008; 131:2710–2719. [PubMed: 18697909]
15. Geday J, Østergaard K, Johnsen E, et al. STN-stimulation in Parkinson's disease restores striatal inhibition of thalamocortical projection. *Hum Brain Mapp*. 2009; 30:112–121. [PubMed: 18041743]
16. Carbon M, Eidelberg D. Functional imaging of sequence learning in Parkinson's disease. *J Neurol Sci*. 2006; 248:72–77. [PubMed: 16753182]
17. Goerendt IK, Lawrence AD, Mehta MA, et al. Distributed neural actions of anti-parkinsonian therapies as revealed by PET. *J Neural Transm*. 2006; 113:75–86. [PubMed: 16049638]
18. Grafton ST, Turner RS, Desmurget M, et al. Normalizing motor-related brain activity: subthalamic nucleus stimulation in Parkinson disease. *Neurology*. 2006; 66:1192–1199. [PubMed: 16636237]
19. Macrì MA, Garreffa G, Giove F, et al. A cluster-based quantitative procedure in an fMRI study of Parkinson's disease. *Magn Reson Imaging*. 2006; 24:419–424. [PubMed: 16677948]

20. Valálik I, Emri M, Lengyel Z, et al. Pallidal deep brain stimulation and L-dopa effect on PET motor activation in advanced Parkinson's disease. *J Neuroimaging*. 2008; 19:253–258. [PubMed: 19021848]
21. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology*. 1967; 17:427–442. [PubMed: 6067254]
22. Rorden C, Brett M. Stereotaxic display of brain lesions. *Behav Neurol*. 2000; 12:191–200. [PubMed: 11568431]
23. Talairach, J.; Tournoux, P. Co-planar stereotaxic atlas of the human brain. New York: Thieme Medical Publishers; 1988.
24. Yu H, Sternad D, Corcos DM, et al. Role of hyperactive cerebellum and motor cortex in Parkinson's disease. *NeuroImage*. 2007; 35:222–233. [PubMed: 17223579]
25. Lehericy S, Ducros M, Krainik A, et al. 3-D diffusion tensor axonal tracking shows distinct SMA and pre-SMA projections to the human striatum. *Cereb Cortex*. 2004; 14:1302–1309. [PubMed: 15166103]
26. Gradinaru V, Mogri M, Thompson KR, et al. Optical deconstruction of parkinsonian neural circuitry. *Science*. 2009; 324:354–359. [PubMed: 19299587]
27. Liu Y, Postupna N, Falkenberg J, et al. High frequency deep brain stimulation: what are the therapeutic mechanisms? *Neurosci Biobehav Rev*. 2008; 32:343–351. [PubMed: 17187859]
28. Contreras-Vidal JL, Buch ER. Effects of Parkinson's disease on visuomotor adaptation. *Exp Brain Res*. 2003; 150:25–32. [PubMed: 12698213]
29. Purzner J, Paradiso GO, Cunic D, et al. Involvement of the basal ganglia and cerebellar motor pathways in the preparation of self-initiated and externally triggered movements in humans. *J Neurosci*. 2007; 27:6029–6036. [PubMed: 17537974]
30. Rascol O, Sabatini U, Fabre N, et al. The ipsilateral cerebellar hemisphere is overactive during hand movements in akinetic parkinsonian patients. *Brain*. 1997; 120:103–110. [PubMed: 9055801]
31. Wu T, Long X, Zang Y, et al. Regional homogeneity changes in patients with Parkinson's disease. *Hum Brain Mapp*. 2009; 31:1502–1510. [PubMed: 18649351]
32. Hilker R, Voges J, Thiel A, et al. Deep brain stimulation of the subthalamic nucleus versus levodopa challenge in Parkinson's disease: measuring the on- and off-conditions with FDG-PET. *J Neural Transm*. 2002; 109:1257–1264. [PubMed: 12373559]
33. Hilker R, Voges J, Weisenbach S, et al. Subthalamic nucleus stimulation restores glucose metabolism in associative and limbic cortices and in cerebellum: evidence from a FDG-PET study in advanced Parkinson's disease. *J Cereb Blood Flow Metab*. 2004; 24:7–16. [PubMed: 14688612]
34. Akkal D, Dum RP, Strick PL. Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. *J Neurosci*. 2007; 27:10659–10673. [PubMed: 17913900]
35. Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res Brain Res Rev*. 2000; 31:236–250. [PubMed: 10719151]
36. Hoshi E, Tremblay L, Féger J, et al. The cerebellum communicates with the basal ganglia. *Nat Neurosci*. 2005; 8:1491–1493. [PubMed: 16205719]
37. Varma TR, Fox SH, Eldridge PR, et al. Deep brain stimulation of the subthalamic nucleus: effectiveness in advanced Parkinson's disease patients previously reliant on apomorphine. *J Neurol Neurosurg Psychiatry*. 2003; 74:170–174. [PubMed: 12531942]
38. Jahn K, Deutschländer A, Stephan T, et al. Imaging human supraspinal locomotor centers in brainstem and cerebellum. *NeuroImage*. 2008; 39:786–792. [PubMed: 18029199]
39. Xie J, Krack P, Benabid AL, et al. Effect of bilateral subthalamic nucleus stimulation on parkinsonian gait. *J Neurol*. 2001; 248:1068–1072. [PubMed: 12013584]
40. Sturman MM, Vaillancourt DE, Metman LV, et al. Effects of subthalamic nucleus stimulation and medication on resting and postural tremor in Parkinson's disease. *Brain*. 2004; 127:2131–2143. [PubMed: 15240437]
41. Blahak C, Wöhrle JC, Capelle HH, et al. Tremor reduction by subthalamic nucleus stimulation and medication in advanced Parkinson's disease. *J Neurol*. 2007; 254:169–178. [PubMed: 17334951]
42. Brodkey JA, Tasker RR, Hamani C, et al. Tremor cells in the human thalamus: differences among neurological disorders. *J Neurosurg*. 2004; 101:43–47. [PubMed: 15255250]

43. Timmermann L, Braun M, Groiss S, et al. Differential effects of levodopa and subthalamic nucleus deep brain stimulation on bradykinesia in Parkinson's disease. *Mov Disord.* 2008; 23:218–227. [PubMed: 18044706]
44. Hilker R, Voges J, Weber T, et al. STN-DBS activates the target area in Parkinson disease: an FDG-PET study. *Neurology.* 2008; 71:708–713. [PubMed: 18650492]
45. Benabid AL, Chabardes S, Mitrofanis J, et al. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol.* 2009; 8:67–81. [PubMed: 19081516]
46. Heim S, Eickhoff SB, Amunts K. Specialisation in Broca's region for semantic, phonological, and syntactic fluency? *NeuroImage.* 2008; 40:1362–1368. [PubMed: 18296070]
47. Schroeder U, Kuehler A, Lange KW, et al. Subthalamic nucleus stimulation affects a frontotemporal network: a PET study. *Ann Neurol.* 2003; 54:445–450. [PubMed: 14520655]
48. Schlösser R, Hutchinson M, Joseffer S, et al. Functional magnetic resonance imaging of human brain activity in a verbal fluency task. *J Neurol Neurosurg Psychiatry.* 1998; 64:492–498. [PubMed: 9576541]
49. Pihlajamäki M, Tanila H, Hänninen T, et al. Verbal fluency activates the left medial temporal lobe: a functional magnetic resonance imaging study. *Ann Neurol.* 2000; 47:470–476. [PubMed: 10762158]

Figure 1.

Standard model of connections between basal ganglia, thalamus, and cortex. Excitatory connections are orange, and inhibitory connections are blue with the width of the connections representing their strengths (SNc = substantia nigra pars compacta, GPi = globus pallidus interna, GPe = globus pallidus externa, STN = subthalamic nucleus). **a** Normal state of circuitry. **b** State of circuitry during Parkinson's disease. The target sites of dopamine agonists and STN DBS are shown to be the striatum and STN respectively.

Figure 2.

Common effects of STN DBS and apomorphine injection. Axial slices in neurological convention are overlaid with images of z-scores that represent activations (red = 1 to white = 4) and deactivations (blue = -1 to green = -4). Both DBS and apomorphine deactivated the SMA, PrG, PoG, putamen, and cerebellum and activated the SPL and the region of the SN/STN.

Figure 3.

Unique effects of STN DBS and apomorphine injection. Axial slices in neurological convention are overlaid with images of z-scores that represent activations (red = 1 to white = 4) and deactivations (blue = -1 to green = -4). **a** DBS uniquely activated the posterolateral cerebellum (Crus II), inferior frontal gyrus, GP, amygdala, hippocampus, and ventrolateral thalamus and deactivated the posterolateral cerebellum (Lobule VI), cerebellar vermis, PrG, SMA, PoG, and putamen. **b** Apomorphine uniquely activated the PrG, pre-SMA, PoG, and hippocampus and deactivated the posterolateral cerebellum (Crus II), inferior frontal gyrus, putamen, and ventrolateral thalamus.

Table 1

Clinical features of the two groups of PD patients

Patient	Age (years)	Sex	Duration (years)	Medications [*]	Tremor	Rigidity	Bradykinesia
<i>Apomorphine</i>							
1	52	M	17	1	0.9	2.6	2.6
2	43	F	25	1	0.8	2.3	3.6
3	48	M	12	1,2	0.4	0.8	1.3
4	57	M	6	1	0.5	1.3	1.9
5	57	M	15	1	0.4	2.4	2.4
6	75	M	8	1,3,4	0	1.7	2.0
7	62	M	17	1,3	0	1.3	2.3
8	77	M	20	1,3	1.0	0.6	1.3
9	66	F	21	1	0.3	1.4	1.4
Mean ± SD	60 ± 11	-	16 ± 6	-	0.5 ± 0.3	1.6 ± 0.7	2.1 ± 0.7
<i>STN DBS</i>							
10	48	F	17	1,5	NA	NA	NA
11	46	M	16	1,6	0.3	0.6	1.7
12	77	M	25	1	1.8	1.7	1.7
13	42	M	10	1,2,4,5	0	1.0	1.4
14	54	F	20	1,7,5	0.8	0.4	2.0
15	41	M	14	1,3,5	NA	NA	NA
16	58	F	13	1	1.7	1.8	2.2
17	42	M	10	1,3	0.4	1.8	1.2
18	53	M	20	1,3	0.2	0.5	1.9
19	48	F	7	1,2,5	0.2	1.2	1.6
20	68	M	11	1,4	0.1	0.6	1.5
Mean ± SD	52 ± 11	-	15 ± 5	-	0.6 ± 0.6	1.1 ± 0.5	1.7 ± 0.3
<i>Overall</i>							
Mean ± SD	56 ± 11	-	15 ± 5	-	0.5 ± 0.5	1.3 ± 0.7	1.9 ± 0.6

* Current medications: 1, carbidopa/levodopa; 2, pramipexole; 3, pergolide; 4, amantadine; 5, entacapone; 6, selegiline; 7, ropinirole NA: Not Available

Table 2

Common effects of treatments in sensorimotor-related regions

Region	z score	x	y	z
Increases				
<i>Neocortical</i>				
<u>Parietal</u>				
SPL	*2.41	-38	-44	57
<i>Subcortical</i>				
<u>Basal Ganglia</u>				
SN/STN	*2.52	-18	-18	-9
Decreases				
<i>Cerebellum</i>				
lateral	*-3.25	18	-53	-16
vermis	*-2.60	-2	-51	-13
<i>Neocortical</i>				
<u>Medial Premotor</u>				
SMA proper	*-3.50	8	-16	62
<u>Rolandic</u>				
dorsal PrG	-2.84	-36	-15	49
dorsal PoG	*-2.33	-24	-26	58
<i>Subcortical</i>				
<u>Basal Ganglia</u>				
putamen	*-2.88	30	-10	-1

Maximum z-scores are listed with their associated Talairach coordinates.

* = significant change in region of other hemisphere also
 $p < 0.05 = z > 1.65$ (increases) or $z < -1.65$ (decreases)
 $p < 0.01 = z > 2.36$ (increases) or $z < -2.36$ (decreases)

SPL = superior parietal lobule, SN = substantia nigra, STN = subthalamic nucleus, SMA = supplementary motor area, PrG = precentral gyrus, PoG = postcentral gyrus

Table 3

Unique increases in activity for treatments

Region	DBS			Aponorphine		
	z score	x	y	z score	x	y
<i>Cerebellum</i>						
posterolateral (Crus II)	3.13	-16	-84	-16		
<i>Neocortical</i>						
<u>Frontal</u>						
<i>Motor</i>						
precentral gyrus, dorsal				*2.90	-30	-8
<i>Premotor</i>						65
IFG (BA 44/45)	3.04	-55	9	22		
pre-SMA				*2.84	2	11
SFG, ventromedial				*4.28	-20	54
SFG, anterodorsal	3.11	-16	46	29		-1
SFG, posterodorsal	3.07	27	37	33	3.53	-22
					33	30
<i>Prefrontal</i>						
MFG, medial	2.02	32	14	47		
orbital gyrus	*4.56	8	64	-10	*5.55	30
					42	-7
<u>Occipital</u>						
occipital gyrus	*3.50	-4	-89	10	*2.69	-38
					-78	1
<u>Parietal</u>						
postcentral gyrus, dorsal				3.16	-36	-40
						63
precuneus	*3.81	-2	-52	54		
SII	3.56	-50	-18	21		
<u>Temporal</u>						
fusiform	*2.84	-40	-55	-7		
temporal gyrus, inferior				*4.19	-36	2
						-30
temporal gyrus, middle	4.01	-50	-12	-13		
temporal gyrus, superior (BA 22)				3.95	59	-10
					4	

Region	DBS			Apomorphine		
	z score	x	y	z score	x	y
<i>Proisocortical</i>						
cingulate cortex, anterior				2.08	-14	28
insula	*2.29	-42	16	12		15
<i>Subcortical</i>						
<u>Basal Ganglia</u>						
globus pallidus	*4.63	-22	-6	-5		
putamen	2.69	-20	10	-2		
<u>Limbic-Paralimbic</u>						
amygdala	*3.86	-34	1	-19		
hippocampus	*4.70	22	-29	-5	*4.09	16
<u>Thalamus</u>						
ventrolateral	*3.16	-10	-19	14		-36
						9

Maximum z-scores are listed with their associated Talairach coordinates.

* = increase in region is significant in other hemisphere also
 $p < 0.05 = z > 1.65$; $p < 0.01 = z > 2.36$

IFG = inferior frontal gyrus, BA = Brodmann Area, SMA = supplementary motor area, SFG = superior frontal gyrus, MFG = middle frontal gyrus, SII = secondary somatosensory cortex

Table 4

Unique decreases in activity for treatments

Region	DBS				Apomorphine			
	z score	x	y	z	z score	x	y	z
<i>Cerebellum</i>								
posterolateral (Crus II)					*-4.75	16	-81	-18
posterolateral (Lobule VI)	*-3.59	-22	-73	-13				
vermis	*-4.59	2	-53	-18				
<i>Neocortical</i>								
<u>Frontal</u>								
<i>Motor</i>								
precentral gyrus, dorsal	*-6.25	34	-21	53				
<i>Premotor</i>								
IFG (BA 44/45)					-2.24	-50	7	22
pre-SMA	*-4.01	0	14	44				
SFG, dorsolateral	-4.09	-24	43	42				
SMA proper	*-4.83	-4	-3	48				
<i>Prefrontal</i>								
MFG, lateral	*-4.52	44	36	28	-2.47	-48	27	30
orbital gyrus	-2.06	-22	32	-13				
<u>Occipital</u>								
occipital gyrus	-3.46	22	-83	10	*-5.45	6	-97	-4
<u>Parietal</u>								
inferior parietal lobule					*-4.66	-46	-54	43
postcentral gyrus, dorsal	*-6.69	34	-21	47				
precuneus					*-4.56	-10	-66	40
supramarginal gyrus	*-4.47	57	-37	37				
<u>Temporal</u>								
fusiform	-2.77	-36	-28	-22				

Region	DBS			Apomorphine		
	z score	x	y	z score	x	y
temporal gyrus, inferior	-2.47	-50	-26	-21	58	-60
temporal gyrus, middle	-2.84	-51	-45	-4		
temporal pole, superior				*-4.61	24	20
<i>Proisocortical</i>						
cingulate cortex, anterior	-3.81	-8	40	18		
cingulate cortex, posterior				-4.28	0	-30
<i>Subcortical</i>						
<u>Basal Ganglia</u>						
putamen	*-3.44	30	-4	0	*-6.91	15
<u>Thalamus</u>						
ventrolateral				*-3.66	8	-9
						8

Maximum z-scores are listed with their associated Talairach coordinates.

* = decrease in region is significant in other hemisphere also
 $p < 0.05 = z < -1.65$ (decreases); $p < 0.01 = z < -2.36$ (decreases)

IFG = inferior frontal gyrus, BA = Brodmann Area, SMA = supplementary motor area, SFG = superior frontal gyrus, MFG = middle frontal gyrus