HIGH LIGHT

Normalizing motor-related brain activity

Subthalamic nucleus stimulation in Parkinson disease

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Abstract—*Objective:* To test whether therapeutic unilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) in patients with Parkinson disease (PD) leads to normalization in the pattern of brain activation during movement execution and control of movement extent. *Methods:* Six patients with PD were imaged off medication by PET during performance of a visually guided tracking task with the DBS voltage programmed for therapeutic (effective) or subtherapeutic (ineffective) stimulation. Data from patients with PD during ineffective stimulation were compared with a group of 13 age-matched control subjects to identify sites with abnormal patterns of activation. Conjunction analysis was used to identify those areas in patients with PD where activity normalized when they were treated with effective stimulation. *Results:* For movement execution, effective DBS caused an increase of activation in the supplementary motor area (SMA), superior parietal cortex, and cerebellum toward a more normal pattern. At rest, effective stimulation reduced overactivity of SMA. Therapeutic stimulation also induced reductions of movement related "overactivity" compared with healthy subjects in prefrontal, temporal lobe, and basal ganglia circuits, consistent with the notion that many areas are recruited to compensate for ineffective motor initiation. Normalization of activity related to the control of movement extent was associated with reductions of activity in primary motor cortex, SMA, and basal ganglia. *Conclusions:* Effective subthalamic nucleus stimulation leads to task-specific modifications with appropriate recruitment of motor areas as well as widespread, nonspecific reductions of compensatory or competing cortical activity.

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Electrical modulation of the subthalamic nucleus (STN) by deep brain stimulation (DBS) is effective for treating Parkinson disease (PD).[1] However, the mechanism of action is not well understood. Current models hypothesize at least four nonexclusive physiologic mechanisms of DBS: depolarization blockade, synaptic inhibition, synaptic depression, and stimulation-induced modulation of pathologic network activity.[2] Imaging studies of the effects of therapy on brain activity in patients with PD are most commonly interpreted as demonstrating a reduction of excessive inhibitory activity originating in the pallidum, leading to enhanced thalamocortical facilitation.[3-12]

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An alternative mechanism of action for DBS could be increased STN output firing with a reduction of pathologic network activity in basal ganglia (BG) projection areas.[13-16] One imaging study of effective bilateral STN stimulation obtained at rest demonstrated increased cerebral blood flow (CBF) in STN and downstream subcortical nuclei (globus pallidus, thalamus) and reductions of relative CBF in cortical projection areas.[17] Imaging studies of Patients with PD during performance of motor tasks demonstrate more complex patterns of both overactivation and underactivation across many cortical areas that cannot be attributed solely to excessive thalamic inhibition.[8,18-23] If increased STN output from DBS blocked pathologic network activity, then imaging studies should demonstrate appropriate selection of cortical areas and normalization of activation patterns that are task specific. To test this, we directly

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Table 1 *Subject demographics*

Subject	Age, y	Preop Hoen and Yahr	Handedness	Sex	Side of Surgery	Months after surgery
1	37	On = 1, off = 3	R	F	L	5
2	45	On = 3, off = 3	R	F	L	5
3	69	On = 2, off = 3	R	M	L	5
4	61	On = 3.5, off = 3.5	R	M	L	5
5	48	On = 2, off = 3	R	M	L	4
6	64	On = 2, off = 3	R	M	R	5

compared functional data between healthy subjects and patients with PD to identify areas normalized by DBS. We tested two aspects of motor control, initiation and movement extent.

Methods. *Subjects.* Thirteen healthy adults {53 ± 8 [SD] years; range 40 to 68 years; seven women, six men) and six patients with advanced PD (54 ± 12 [SD] years; range 37 to 69; four men, two women) were recruited from ongoing prospective clinical studies on the efficacy of DBS for PD. Severity of disease was assessed with the Unified Parkinson's Disease Rating Scale (table 1). Exclusion criteria were history of stroke or other neurologic disease, depression, dementia, previous surgeries, or other major medical illnesses. The patients underwent unilateral microelectrode-guided stereotaxic placement of a Medtronic deep brain stimulator (3387) 4 to 5 months before the PET imaging session. Optimal stimulator settings were identified at least 3 months before imaging. Ineffective settings were achieved by reducing the voltage to one half of the effective voltage; all other stimulation parameters remained the same. The stimulator was in the left subthalamic nucleus in 5 subjects and the right nucleus in the others. Imaging data in the last subjects was flipped along the transverse axis to facilitate group analysis. Informed consent was provided in accordance with the Emory University Institutional Review Board. The apparatus, task and imaging methods, and results for the normal group were reported in detail previously.[24] The same methods were used for the patients with PD in the current study with the following modifications.

Apparatus and task. The patients controlled a freely moveable joystick in the medial and lateral direction with movement controlled mainly by proximal arm musculature. The arm and joystick were not visible to the subject. All subjects performed the task with the hand contralateral to the stimulator (five right hand, one left hand).

The joystick controlled the horizontal position of a hollow red 1.5-cm square displayed on the screen. During task performance, a "target" (solid white circle, 1.5 cm diameter) moved horizontally across the screen at a constant speed (10 cm/second) between two endpoints separated by 20 cm. On reaching the endpoints, the target reversed direction instantaneously (2 s/movement direction). Subjects were instructed to match the position of the target and cursor as closely as possible. On different scans, the gain of the relationship between the cursor and actual joystick movement was set to one of three levels corresponding to joystick displacements of 6, 12, and 18 cm to produce 20 cm cursor displacement. Note that only the healthy subjects performed the task with 24 cm displacements, so these were dropped from this analysis to match the PD population. During each scan acquisition, the subjects completed 25 cycles of leftward followed by rightward movement (100 s total task duration). An additional four PET scans with another task were also acquired on each day in all subjects. These were randomly intermixed with the tracking task but are not reported in this article. The scans (8 total in PD subjects, 10 total in healthy control subjects) were initiated at 10-minute intervals. Approximately 5 minutes before each scan, subjects were fully adapted to a new joystick-to-cursor gain relationship by practicing the upcoming gain for 100 s. The order of gain settings was randomized between subjects, so that subjects were not biased to adapt to any particular gain setting. Joystick position signals were digitized at 250 Hz. Arm movements were continuously monitored by the experimenters for dyskinesia and tremor.

Imaging. During each imaging session, four relevant scans were acquired, one for each of the three gain settings, and a fourth with the hand held motionless in midposition while subjects followed movements of the target with only the eyes. Task performance began 10 s before the onset of scanning and continued for 100 s. Patients with PD were scanned in the morning, off of their regular dose of anti-PD medications, which were withheld for approximately 10 hours before scanning. The first scan was always with the stimulator set to each subject's clinically optimal voltage based on empiric testing since the time of surgery. On the second day, the stimulator was programmed to a nonefficacious voltage (one half the therapeutic voltage). The two studies were separated by 24 hours. At the time of scanning, both patients and the study personnel were aware of the stimulator setting. Patients were given their normal anti-PD disease medications on the afternoon and evening between the two scans. Healthy subjects were scanned only once.

Images of relative cerebral blood flow (rCBF) were acquired as described previously.[24]

Kinematic analysis. The mean extent of movement for a scan was computed as the mean of the difference between movement extremes for each movement cycle. Joystick velocity was derived from the position signal by digital low-pass filtering (5 Hz cutoff) and differentiation.[25] The mean absolute velocity (i.e., speed) for a scan was computed from the velocity record after excluding periods during which absolute velocity decreased below a threshold of 1 cm/second. The mean temporal error was found by computing the mean difference between the times of reversals in the direction of arm movement and the times of reversals in target movement. The intermittency of tracking velocity was computed as the number of zero crossings in the acceleration record. In continuous visuomotor tasks, online corrections are reflected by changes in acceleration that can be detected as zero crossings.[26-28] A higher rate of zero crossings is considered evidence that continuous tracking is dominated by closed-loop as opposed to open-loop processes.

Effects of stimulation on a subject's task performance were assessed using analysis of covariance, using the target extent as the covariate of interest and stimulation condition as the grouping variable.

rCBF image analysis. Image coregistration, spatial normalization, global scaling, and image smoothing were performed as described previously.[24]

F omnibus effects were calculated on a voxel-by-voxel basis ($p < 0.05$) for two main effects: 1) movement vs rest—each of the three gain settings was compared to the rest condition of no arm movement pooled across both healthy subjects and patients; and 2) amplitude—a parametric scaling of contrast means in proportion to the three gain setting of the joystick–cursor setting pooled across both healthy subjects and patients. These two F tests were used as masks to reduce the search volume of the subsequent conjunction analyses and to reduce Type II error.

The following main effects were calculated for the subsequent conjunction analyses: 3) differences of movement-related activity between healthy subjects and patients with PD with nontherapeutic DBS—the contrast compared the three movement conditions vs the rest condition; 4) differences of movement related activity between therapeutic and nontherapeutic DBS in PD; 5) differences of movement extent–related activity between healthy subjects and patients with PD during ineffective stimulation—separate interactions were calculated for a pattern of increasing or decreasing brain activity with larger movement amplitudes and the opposite pattern in PD; and 6) differences of extent-related activity between effective and ineffective DBS—separate interactions were calculated for a pattern where increasing amplitude led to greater or lesser activity with ineffective stimulation and the opposite pattern for effective stimulation.

To determine areas where DBS led to a relative "normalization" of activation, two conjunction analyses were performed. 7) To identify brain areas where DBS led to a relative normalization in movement-related activity, a conjunction analysis of contrasts 3 and 4 described above was calculated. Two patterns were identified: areas where underactivity or overactivity in PD relative to healthy subjects was normalized with effective stimulation. 8) To

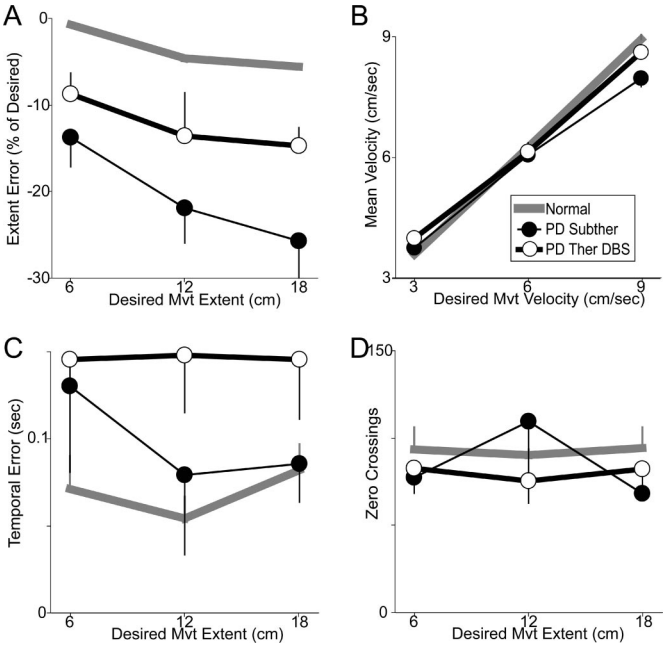

Figure 1. Deep brain stimulation (DBS) at therapeutic levels reduced bradykinetic symptoms but did not affect movement timing or smoothness. Mean (± SEM) task performance of parkinsonian subjects during subtherapeutic ("PD Off," solid circles) and therapeutic levels ("PD On," open circles) of subthalamic nucleus (STN) stimulation. The panels plot actual task performance for movement extent (A), velocity (B), temporal error (C), and number of zero crossings (D) vs the desired movement extent (Target Extent) or velocity. Mean performance values for 13 healthy subjects are shown for comparison (gray lines).

identify brain areas where DBS led to a relative normalization in amplitude related activity, a conjunction analysis of contrasts 5 and 6 described above was calculated. Two patterns were identified: areas where excessive or insufficient extent-related activity in PD relative to healthy subjects was normalized with effective stimulation.

The conjunctions resulted in two experiment-wise contrasts. Corresponding voxel-wise *t*-statistic maps, masked by the F omnibus results for movement or extent, were evaluated at a statistical threshold ($p < 0.05$, at least five contiguous voxels). Results were displayed on structural MRI scans derived from a healthy subject. BG nuclei were identified from cross-sectional atlases.[29,30] Post hoc data analysis of regional rCBF values was made by extracting the individual subjects' globally normalized rCBF values from the maximum *t*-statistic voxel for each significant activation corresponding to a spherical volume of interest of approximately 1 cm diameter.

Results. *Task performance.* The patients were also participating in a clinical study of DBS efficacy. Because of the blinding required for that study, independent clinical outcome measurements obtained during effective DBS were not available for the current experiment. Instead, the current study focused only on performance of the visuomotor tracking task acquired during imaging, which was obtained independent of the clinical trial. Therapeutic stimulation resulted in increases in the extent and velocity of movement with little change in other aspects of task performance (figure 1). Movement extent was increased by 10% on average [$p < 0.05$, $F(1,32) = 5.4$, analysis of covariance (ANCOVA) stimulation main effect], leading to a mean 48% reduction in the difference between PD and healthy subjects in movement extent (figure 1A). Mean movement velocity also increased during therapeutic stimulation [$p < 0.05$, $F(1,32) = 4.3$, ANCOVA stimulation main effect], resulting in a mean 60% reduction in the movement velocity deficits shown by PD subjects for the largest of the target extents (figure 1B). The mean velocities of PD subjects were slightly increased above normal during tracking of the smallest (6-cm) target extent, and therapeutic stimulation led to a further increase of velocities above normal during tracking of 6-cm target extents. The reason for this increase in velocity for small target extents remains unclear. Although the effects of therapeutic stimulation on both movement extent and velocity were greater for larger target extents, this interaction did not reach significance for either parameter ($p > 0.3$ for both extent and velocity, ANCOVA stimulation-by-gain interaction).

Therapeutic stimulation had no significant effect on the temporal error in tracking [$p > 0.1$, $F(1,32) = 2.6$, ANCOVA stimulation main effect; figure 1C]. In fact, PD subjects tended to lead movements of the target further during therapeutic stimulation, but this tendency was not significant. Neither did therapeutic stimulation influence the smoothness of smooth pursuit tracking, measured as the number of velocity zero crossing detected [$p > 0.5$, $F(1,32) = 0.1$, ANCOVA stimulation main effect; figure

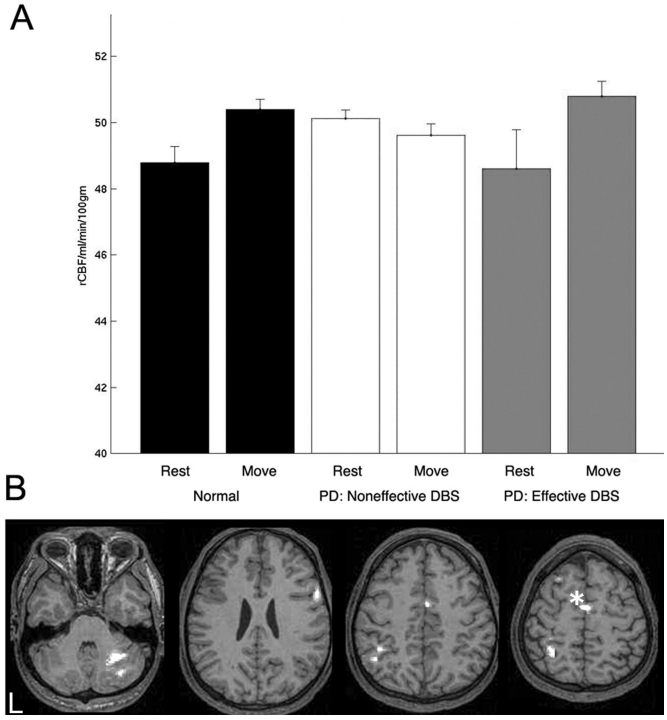

Figure 2. Effective deep brain stimulation (DBS) increased the movement-related activation of a subset of brain regions that were underactive during ineffective stimulation relative to healthy controls. (A) Plot of relative cerebral blood flow (CBF) in supplementary motor area for each group (labeled with asterisk in B). (B) Brain regions with differences in the conjunction analysis ($p < 0.01$) and a pattern of blood flow similar to that in panel A. Axial planes are located −28, 25, 39, and 50 mm with respect to the anterior–posterior commissure scaled to the Talairach atlas.[45]

Table 2 *DBS normalization of movement and gain-related activity in PD*

Anatomic location		Functional location	Talairach coordinates x	y	z	*p* Value	Conjunction pattern
R	Posterior cerebellar cortex		24	−52	−34	0.0001*	Figure 2
L	Medial superior frontal gyrus	BA 6 "SMA"	−2	−1	48	0.003*	Figure 2
R	Inferior frontal gyrus		59	15	25	0.004	Figure 2
L	Superior frontal gyrus	BA 11	−18	52	−18	0.005	Figure 2
R	Precentral sulcus	BA 6 "premotor"	42	−7	59	0.006	Figure 2
L	Superior parietal lobule	BA 7	−34	−46	58	0.009*	Figure 2
L	Anterior cerebellar cortex		−16	−47	−14	0.0001*	Figure 3
R	Anterior cerebellar cortex		12	−57	−6	0.003	Figure 3
R	Superior frontal sulcus	BA 6	30	2	35	0.01	Figure 3
R	Precentral sulcus	BA 6	18	−11	56	0.01	Figure 3
R	Cingulate gyrus	BA 26 "CMA"	2	2	37	0.0001*	Figure 4
L	Central sulcus	BA 4, 3, 1, 2 "sensorimotor"	−50	−12	41	0.0001*	Figure 4
R	Putamen/globus pallidus		26	0	−8	0.0001*	Figure 4
L	Postcentral parietal operculum	"SII"	−53	−24	21	0.008	Figure 4
R	Thalamus	Pulvinar	16	−26	14	0.008*	Figure 4

* *p* Values significant at 0.05, small volume correction.

Stimulator was in left subthalamic nucleus; task was performed with right hand.
Data for Subject 6 was flipped in x-axis to match others.

DBS = deep brain stimulation; PD = Parkinson disease; SMA = supplementary motor area; CMA = cingulate motor area; BA = Brodmann area.

1D]. Continuous observation of the patients during scanning revealed no tremor or dyskinesia. In summary, these results indicate that during smooth pursuit tracking of a predictably moving target, therapeutic stimulation had a selective effect on bradykinesia-related measures of task performance. The overall effects of stimulation on the timing of tracking movements were small, but a tendency was seen for therapeutic stimulation to increase the degree to which the subject's hand movements led movements of the target.

Movement task. The main effect of movement vs rest on rCBF was consistent with previously described paradigms[21,24,31] and is not reported here. More importantly, conjunction analysis identified common brain areas where patients with PD with ineffective DBS demonstrated different movement-related activity than healthy subjects and where effective DBS stimulation "normalized" the disease-related difference. In this type of conjunction analysis, there are four possible interactions. The most relevant of these interactions is shown in figure 2 and indicates inadequate movement-related activation in PD that is normalized by DBS. In this case, there is a pattern of underactivation or negative activation during movement and increased activity during rest with ineffective stimulation that both normalize with effective stimulation. As shown in figure 2 and table 2, areas with this pattern of normalization include the SMA, left intraparietal sulcus, right ventral premotor cortex, and right cerebellar cortex. All of these areas are commonly associated with movement-related activation across a broad range of motor tasks, and the SMA in particular is associated with inadequate activation in PD. The second most relevant pattern of change, potentially representing compensatory modulation of activity, was characterized as areas demonstrating overactivity during movement or underactivity at rest in patients with PD who normalized with effective DBS. As demonstrated in figure 3 and table 2, these sites included the left anterior cerebellar cortex and two regions within the right dorsal premotor cortex. All of these sites have been shown previously to be overactive in patients with PD during movement. The other two patterns, indicative of modulation related to the resting state, were defined as areas that are normally more active at rest and where effective DBS increases resting state activity. Of note, there was a large region within precuneate cortex and ventral mesial frontal cortex with this pattern (figures E-1 and E-2 and table E-1 on the *Neurology* Web site at www.neurology.org), consistent with the known preferential activation of these areas during resting states.[32,33] The results indicate that this rest-related activation is impaired in PD and restored by DBS (see figures 2 and 3).

In summary, the effect of effective DBS stimulation on movement-related activity in patients with PD relative to healthy subjects was consistent with enhanced recruitment of motor areas such as SMA that are typically underactive in PD and a concomitant reduction of movement-related overactivity in areas including premotor cortex and cerebellum. Areas where resting state activity is normally greater were also normalized, showing that the effects of DBS are widespread.

Amplitude control. To test whether DBS therapy was consistent across different behaviors, the effects of DBS on movement extent–related brain activity were examined. Of the four possible conjunction patterns, two were of partic-

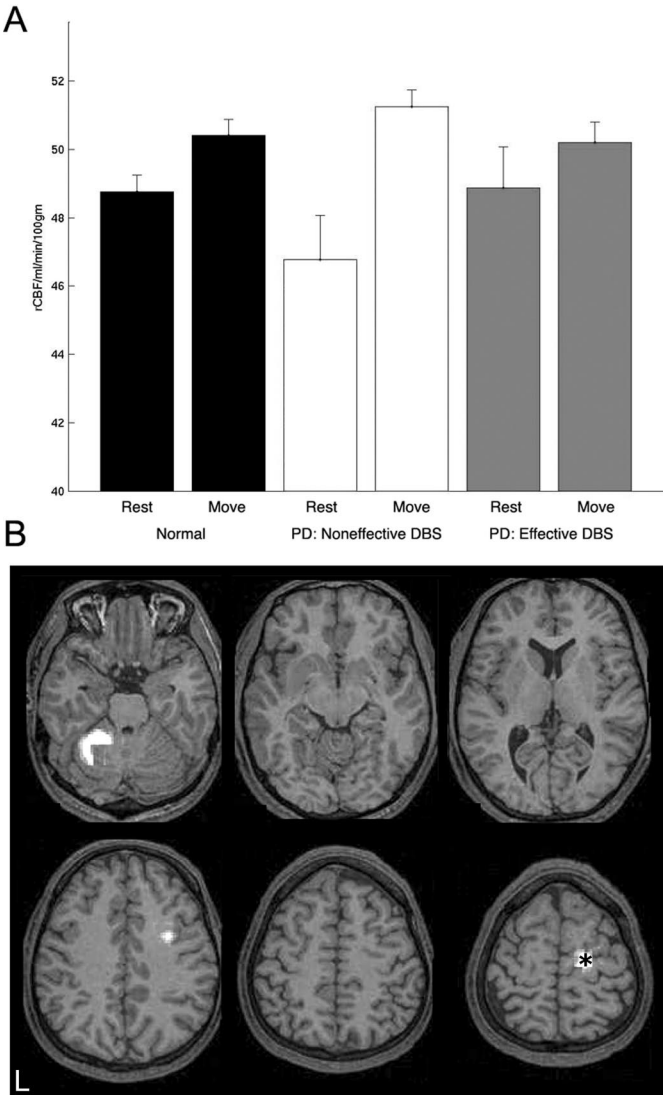

Figure 3. Effective deep brain stimulation (DBS) decreased the movement-related activation of some brain regions that were overactive during ineffective stimulation relative to healthy controls. (A) Plot of relative cerebral blood flow (CBF) in right premotor cortex (labeled with asterisk in B). (B) Brain regions with differences in the conjunction analysis ($p < 0.01$) and a pattern of blood flow magnitude similar to that in panel A. Axial planes are located −20, −11, 4, 36, 47, and 56 mm.

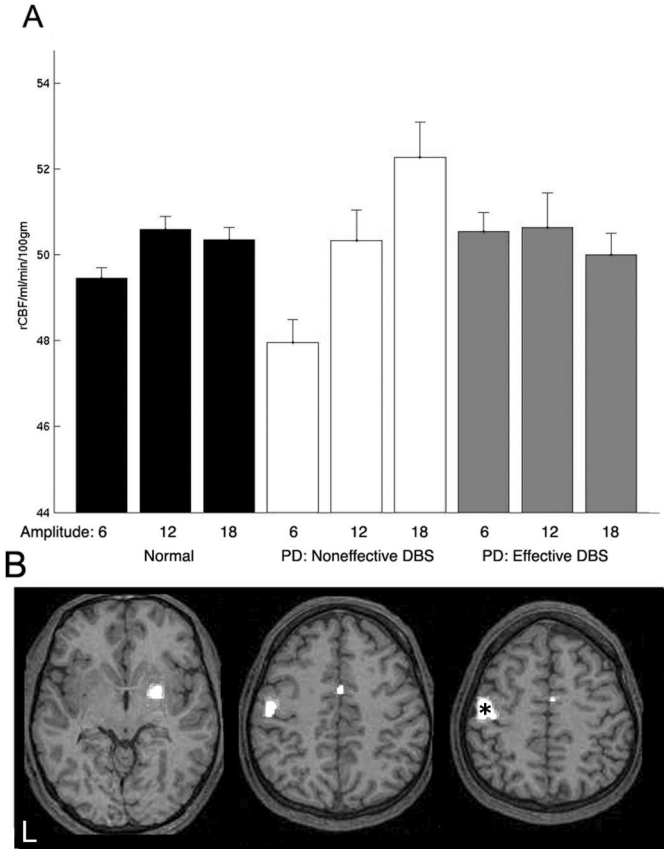

Figure 4. Effective deep brain stimulation (DBS) decreased the extent-related activation of brain regions with increased modulation during ineffective stimulation relative to healthy controls. (A) Plot of relative cerebral blood flow (CBF) in left motor area (labeled with asterisk in B). (B) Brain regions with differences in the conjunction analysis ($p < 0.01$) and a pattern of blood flow magnitude similar to that in panel A. Axial planes are located −2, 39, and 47 mm.

ular interest. The first pattern was characterized by regions where there was a greater modulation in neural activity in the patients as a function of movement amplitude relative to healthy subjects. These sites demonstrated a normalization of the increased modulation with effective stimulation. Sites that fit this pattern included the right putamen and globus pallidus, the cingulate motor area extending superiorly into the supplementary motor area, and the left sensorimotor cortex (figure 4 and table 2). This pattern matches many of the overactivations reported previously in a study of velocity and extent control in PD.[21] Interestingly, no brain area matched a second possible conjunction pattern in which reduced amplitude modulation in PD was normalized by therapeutic DBS. Another pattern, possibly representing aberrant compensation, was related to marked overactivity in bilateral rostral inferior frontal cortex at small amplitudes in patients with PD. This overactivity also normalized with effective stimulation (figure E-3 and table E-1). No areas fit the remaining possible patterns in which negative correlations between amplitude and blood flow were normalized by DBS.

Discussion. The mechanism by which DBS has a therapeutic effect is complex at cellular and systems levels of analysis.[2] Evidence to date suggests the clinical benefit is not based on a mechanism whereby DBS of STN increases BG dopamine.[34] Some evidence supports a mechanism where DBS suppresses activity from the stimulated structure. Previous research using functional brain imaging has usually been interpreted in this vein, with DBS reducing excessive inhibitory pallidothalamic activity and increasing activity in cortical motor areas. However, emerging physiologic evidence in animal models and also in humans demonstrates more complex downstream effects consistent with increased activation of output neurons within the stimulated structure and concordant changes in target areas.[13,15-17] The net re-

sult of this type of DBS effect would be a reduction of pathologic network activity in downstream areas, with both increases and decreases of activity depending on the circuit and task. Imaging studies of resting state activity are consistent with this latter interpretation. Bilateral STN stimulation reduces rest-state blood flow bilaterally in frontal, parietal, and temporal cortices,[17] and this reduction correlates with clinical response.[35,36] The current data of both rest- and movement-related activities with unilateral stimulation are consistent with this interpretation. Our data demonstrate that unilateral DBS causes task-specific alterations in brain activation (i.e., both increases and decreases) that differ depending on brain region and the task being performed. Effects of bilateral DBS have been proposed to generate both effects (i.e., changes to rest-state and task-related activity) by modifying BG output both within and beyond motor loops through the BG[37] rather than by a simple reduction of inhibitory activity from the pallidum. It is likely that DBS has additional effects on BG output and downstream projection areas beyond the patterns identified here in response to acute reductions of DBS voltage relative to chronic optimal treatment. It would be invaluable to also identify longer latency effects of DBS that emerge over the course of 2–3 weeks after the onset of therapy.

Deep brain stimulation effects identified by functional imaging could be a result of nonspecific blood flow responses, acute compensatory adjustments, or long-term adaptation. The current study identified acute compensatory adjustments by directly comparing PD and age-matched healthy subjects and by focusing only on the effects of DBS that can be characterized as task-related normalizations of brain activity. There are four potential limitations of the study. First, our patient group was small, and future studies with a larger cohort would be useful to extend these results. Second, the imaging results might be confounded by changes of motor performance irrespective of the effect of DBS. We believe this is not a problem for several reasons. Although the differences in movement extent between patients with PD with ineffective and effective DBS and healthy subjects were significant statistically, the maximal difference in movement magnitude was only 3 cm, and that in velocity was 1 cm/second. From our previous imaging studies using similar tasks, we would not expect to find significant correlations between blood flow responses and movement magnitude or velocity of such a small absolute magnitude.[24,38,39] From this, we would argue that differences of brain activity are unlikely to be due to differences in kinematics alone. By identifying the functional correlates of effective DBS relative to DBS at suboptimal (i.e., half therapeutic) voltages, our study controlled for many of the nonspecific effects DBS might have on the brain that are unrelated to clinical improvement. A third limitation was an order effect. Subjects were always scanned on optimal DBS therapy before suboptimal DBS. They might be less anxious or use different cognitive strategies on the second day. We believe these potential confounds are offset by the importance of having subjects scanned in their best "on-state" after months of careful stimulator optimization. The order we used avoids exposure to any residual effects from having the stimulator turned off the previous day. A fourth limitation is the statistical power of the image contrasts in a relatively small number of subjects. It should be noted, however, that an exceptionally restricted search volume was used in the conjunctions. Furthermore, the conjunction analysis required mutual significance in two independent contrasts. The effective significance in this case is greater than either contrast alone. Ultimately, only two conjunctions were obtained, minimizing the overall experiment-wise number of comparisons. By using a conjunction analysis, we focused on the identification of areas where DBS caused a normalization of brain activation that was abnormal in patients with PD when receiving ineffective therapy. Given this approach, our interpretation is limited to finding deviant activation patterns that are corrected by DBS.

The pattern of brain activation during movement relative to rest in the current study is consistent with many previous studies of PD. Effective stimulation led to a normalization of hypoactivation within areas normally associated with movement execution, including the SMA, premotor cortex, and ipsilateral cerebellum. This movement-related underactivation is normalized with dopaminergic therapy and unilateral pallidotomy.[3-8] Although therapy-related restoration of SMA activity in particular has been taken as evidence for the classic pathophysiologic model in which excessive pallidal outflow inhibits thalamocortical circuits,[11] this normalization could also result from a normalization of pathologic network activity. The current results point to this second, more nuanced interpretation if effects of DBS on the amplitude control contrast are also considered. The modulation of SMA activity with movement extent (small, medium, or large) was much greater in PD subjects than in healthy subjects, and this abnormal sensitivity to movement extent was normalized by STN DBS. Note that this modulation was not due to differential performance between the groups, but different levels of brain activation to achieve similar levels of performance. These findings are consistent with a pathophysiologic model of PD in which pallidothalamic input is not only excessively inhibitory, but also disruptive, culminating in a general underactivation of appropriate cortical motor areas as well as inappropriate modulation of brain activity to match the ongoing demands of the task.

The second major finding of this study is that patterns of overactivation provide evidence for both dynamic compensatory recruitment of cortical areas to meet task demands and impaired regulation of potentially competing brain activity. Previous imaging studies show that untreated patients with PD

activate a host of brain regions not normally involved in motor execution or the control of movement extent.[18,19,21] Some have ascribed this recruitment to compensatory mechanisms (e.g., increased reliance on visuomotor pathways). It has been unclear whether this compensation is a permanent adaptation in the face of disease or a dynamic adjustment. The current study demonstrates that a subset of these sites is overactive during motor execution, including the contralateral cerebellum and ipsilateral dorsal premotor cortex areas. These overactivations appear rapidly after the cessation of effective DBS. Other areas including globus pallidus and SMA were overactivated with increasing movement extent, and again, this overactivation appeared rapidly after the cessation of effective DBS. To the degree to which these overactivations are compensatory responses, the current findings suggest that they are dynamic task-specific changes, likely generated to maintain performance.

Alternatively, some overactivations may reflect a facet of the primary pathophysiology of PD, such as an inability to suppress contextually inappropriate activity.[10,21] This reduced control of regional cortical activity could arise from an impairment of normal BG function in PD,[40] or dysfunction of the thalamus or frontal lobes induced by abnormal BG outflow. Overactivations in PD may also be related to reduced intracortical inhibition, which is a known correlate of untreated parkinsonism[41,42] and is normalized by bilateral STN DBS.[43]

The current study does not disentangle the functional correlates of dynamic compensation and impaired suppression. Regardless of that ambiguity, the fact that cessation of optimal DBS within the BG leads rapidly to cortical overactivations implies that those overactivations are related directly to pathologic activity within the BG network. It is unlikely that they are due to pathology in other systems such as specific brainstem nuclei as described by Braak and Braak.[44] The current results confirm our previous observation that cortical overactivations are task specific, differing between the control of movement execution and extent.[21] The task-specific pattern of overactivity may ultimately provide information about the functional substrates of various parkinsonian symptoms (in this case, akinesia vs bradykinesia).

References

1. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925–1934.
2. McIntyre CC, Savasta M, Walter BL, Vitek JL. How does deep brain stimulation work? Present understanding and future questions. J Clin Neurophysiol 2004;21:40–50.
3. Grafton ST, Waters C, Sutton J, Lew MF, Couldwell W. Pallidotomy increases activity of motor association cortex in Parkinson's disease: a positron emission tomographic study. Ann Neurol 1995;37:776–783.
4. Grafton ST, Sutton J, Couldwell W, Lew M, Waters C. Network analysis of motor system connectivity in Parkinson's disease: modulation of thalamocortical interactions after pallidotomy. Human Brain Mapping 1994;2:45–55.
5. Ceballos-Baumann AO, Obeso JA, Vitek JL, et al. Restoration of thalamocortical activity after posteroventral pallidotomy in Parkinson's disease. Lancet 1994;344:814.
6. Jenkins IH, Fernandez W, Playford ED, et al. Impaired activation of the supplementary motor area in Parkinson's disease is reversed when akinesia is treated with apomorphine. Ann Neurol 1992;32:749–757.
7. Samuel M, Ceballos-Baumann AO, Turjanski N, et al. Pallidotomy in Parkinson's disease increases supplementary motor area and prefrontal activation during performance of volitional movements an H2(15)O PET study. Brain 1997;120:1301–1313.
8. Haslinger B, Erhard P, Kampfe N, et al. Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. Brain 2001;124:558–570.
9. Limousin P, Greene J, Pollak P, Rothwell J, Benabid AL, Frackowiak R. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. Ann Neurol 1997; 42:283–291.
10. Ceballos-Baumann AO, Boecker H, Bartenstein P, et al. A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson disease: enhanced movement-related activity of motor-association cortex and decreased motor cortex resting activity. Arch Neurol 1999;56:997–1003.
11. Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease (with comments). Brain 1994;117:877–897.
12. Strafella AP, Dagher A, Sadikot AF. Cerebral blood flow changes induced by subthalamic stimulation in Parkinson's disease. Neurology 2003;60:1039–1042.
13. Montgomery EB Jr, Baker LD. Mechanisms of deep brain stimulation and future technical developments. Neurol Res 2000;22:259–266.
14. Windels F, Bruet N, Poupard A. Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat. Eur J Neurosci 2000;12: 4141–4146.
15. Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosci 2003;23:1916–1923.
16. Anderson ME, Postupna N, Ruffo M. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J Neurophysiol 2003;89:1150–1160.
17. 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.
18. 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.
19. Samuel M, Ceballos-Baumann AO, Blin J, et al. Evidence for lateral premotor and parietal overactivity in Parkinson's disease during sequential and bimanual movements: a PET study. Brain 1997;120:963–976.
20. Jahanshahi M, Ardouin CM, Brown RG, et al. The impact of deep brain stimulation on executive function in Parkinson's disease. Brain 2000; 123:1142–1154.
21. Turner RS, Grafton ST, McIntosh AR, DeLong MR, Hoffman JM. The functional anatomy of parkinsonian bradykinesia. Neuroimage 2003;19: 163–179.
22. Grafton ST. Contributions of functional imaging to understanding parkinsonian symptoms. Curr Opin Neurobiol 2004;14:715–719.
23. Catalan MJ, Ishii K, Honda M, Samii A, Hallett M. A PET study of sequential finger movements of varying length in patients with Parkinson's disease. Brain 1999;122:483–495.
24. Turner RS, Desmurget M, Grethe J, Crutcher MD, Grafton ST. Motor subcircuits mediating the control of movement extent and speed. J Neurophysiol 2003;90:3958–3966.
25. Hamming RW. Digital filters. Englewood Cliffs, NJ: Prentice Hall, 1983.
26. Meyer DE, Abrams RA, Kornblum S, Wright CE, Smith JE. Optimality in human motor performance: ideal control of rapid aimed movements. Psychol Rev 1988;95:340–370.
27. Eichhorn TE, Gasser T, Mai N, et al. Computational analysis of open loop handwriting movements in Parkinson's disease: a rapid method to detect dopamimetic effects. Move Disord 1996;11:289–297.
28. Siebner HR, CL Peinemann A, Bartenstein P, Drzezga A, Conrad B. Brain correlates of fast and slow handwriting in humans: a PET-performance correlation analysis. Eur J Neurosci 2001;14:726–736.
29. Schaltenbraind G, Wahren W. Atlas for stereotaxy of the human brain. New York: Thieme, 1977.
30. Mai JK, Assheuer J, Paxinos G. Atlas of the human brain. San Diego: Academic Press, 1997.
31. Turner RS, Grafton ST, Votaw JR, Delong MR, Hoffman JM. Motor subcircuits mediating the control of movement velocity: a PET study. J Neurophysiol 1998;80:2162–2176.
32. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA 2001;98:676–682.
33. Gusnard DA, Raichle ME, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci 2001;2: 685–694.
34. Hilker R, Voges J, Ghaemi M, et al. Deep brain stimulation of the subthalamic nucleus does not increase the striatal dopamine concentration in parkinsonian humans. Mov Disord 2003;18:41–48.

35. Antonini A, Marotta G, Benti R, et al. Brain flow changes before and after deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neurol Sci 2003;24:151–152.
36. Payoux P, Remy P, Damier P, et al. Subthalamic nucleus stimulation reduces abnormal motor cortical overactivity in Parkinson disease. Arch Neurol 2004;61:1307–1313.
37. Schroeder U, Kuehler A, Lange KW, et al. Subthalamic nucleus stimulation affects a frontotemporal network: a PET study. Ann Neurol 2003; 54:445–450.
38. Turner RS, Hoffman JM, Grafton ST, DeLong MR. Functional neural activation in normal and Parkinsonian subjects related to movement frequency during predictive visuomotor tracking using PET. Soc Neurosci Abstracts 1996;22:2038.
39. Turner RS, Grafton ST, Votaw JR, Delong MR, Hoffman JM. Motor subcircuits mediating the control of movement velocity: a PET study. J Neurophysiol 1998;80:2162–2176.
40. Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 1996;50:381–425.
41. Ridding MC, Inzelberg R, Rothwell JC. Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. Ann Neurol 1995;37:181–188.
42. Priori A, Berardelli A, Inghilleri M, Accornero N, Manfredi M. Motor cortical inhibition and the dopaminergic system: pharmacological changes in the silent period after transcranial brain stimulation in normal subjects, patients with Parkinson's disease and drug-induced parkinsonism. Brain. 1994;117:317–323.
43. Pierantozzi M, Palmieri MG, Mazzone P, et al. Deep brain stimulation of both subthalamic nucleus and internal globus pallidus restores intracortical inhibition in Parkinson's disease paralleling apomorphine effects: a paired magnetic stimulation study. Clin Neurophysiol 2002;113: 108–113.
44. Braak H, Braak E. Pathoanatomy of Parkinson's disease. J Neurol 2000;247 (suppl 2):II3–II10.
45. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the brain: 3-Dimensional proportional system: An approach to cerebral imaging. New York: Thieme Medical Publishers, 1988.