Evolving metabolic changes during the first postoperative year after subthalamotomy

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Object. Short-term benefit from unilateral subthalamotomy for advanced Parkinson disease (PD) is associated with metabolic alterations in key targets of subthalamic nucleus (STN) and globus pallidus (GP) output. In this study positron emission tomography (PET) scanning was used to assess these changes and their relation to long-term benefits of subthalamotomy.

Methods. To determine whether the early postoperative changes persisted at longer-term follow up, the authors assessed six patients with advanced PD by using [18F]fluorodeoxyglucose–PET at 3 and 12 months postsurgery. The authors compared each of the postoperative images with baseline studies, and assessed interval changes between the short- and long-term follow-up scans.

Clinical improvement at 3 and 12 months was associated with sustained metabolic decreases in the midbrain GP internus (GPi), thalamus, and pons of the lesioned side (p < 0.01). The activity of a PD-related multiregional brain network, which correlated with bradykinesia and rigidity, was reduced at both postoperative time points (p < 0.05). Comparisons of 3- and 12-month images revealed a relative metabolic increase in the GP externus (GPe) (p < 0.001), which was associated with worsening gait, postural stability, and tremor at long-term follow up.

Conclusions. These findings indicate that subthalamotomy may have differential effects on each of the functional pathways that mediate parkinsonian symptomatology. Sustained relief of akinesia and rigidity is associated with suppression of a pathological network involving the GPi and its output. In contrast, the recurrence of tremor may relate to changes in the function of an STN–GPe oscillatory network.

KEY WORDS • Parkinson disease • subthalamotomy • positron emission tomography • subthalamic nucleus • globus pallidus

H YPERACTIVITY of the STN plays an important role in the origin of parkinsonian signs and symptoms.23 The development of stereotactic surgical techniques to alter STN activity represents a major advance in the treatment of patients with PD.29 Although deep brain stimulation of the STN has become commonplace,30,33,37 stereotactically guided lesioning of this structure has also been implemented as an effective therapeutic alternative.2,36 In a recent clinical study, we demonstrated a sustained benefit for akinesia and rigidity for at least 18 months after unilateral subthalamotomy;36 diminished efficiency in gait, postural stability, and tremor recurrence were noted, however, at the 12-month follow up.

In an ancillary imaging study, we used FDG-PET to assess the metabolic basis of the early clinical benefit of unilateral subthalamotomy.35 In six patients with advanced PD in whom PET scans were obtained at baseline and at 3 months postsurgery, a clinical benefit was associated with metabolic reductions in the STN and globus pallidus output nuclei. We also found that subthalamotomy suppressed the activity of a PD-related functional brain network that comprised key elements of the motor corticostriatal-pallido-thalamocortical loop.5,35,39

In this investigation, we obtained repeated scans in these patients at 12 months after subthalamotomy to determine whether the early metabolic changes detected at 3 months persisted at extended follow up. Because of the late reemergence of tremor, we also determined whether there were specific changes in local glucose utilization that developed during the interval between the two postoperative scans.

Clinical Material and Methods

Patient Population

We studied six patients with advanced PD (ages 56 ± 9 years, Hoehn and Yahr7 Stage 4.5 ± 0.5 [means ± SE])
Effect of subthalamotomy on glucose metabolism in PD

### TABLE 1
Characteristics of six patients with advanced PD*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>UPDRS Part III Score†</th>
<th>UPDRS Motor Score‡</th>
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<tr>
<td></td>
<td></td>
<td>Gait</td>
<td>Postural Stability</td>
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<tr>
<td>1</td>
<td>42, F</td>
<td>3/2/2</td>
<td>3/2/2</td>
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<tr>
<td>2</td>
<td>58, M</td>
<td>2/1/2</td>
<td>3/0/2</td>
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<tr>
<td>3</td>
<td>63, F</td>
<td>3/1/2</td>
<td>3/2/2</td>
</tr>
<tr>
<td>4</td>
<td>64, M</td>
<td>3/2/3</td>
<td>4/2/2</td>
</tr>
<tr>
<td>5</td>
<td>48, F</td>
<td>3/3/3</td>
<td>2/2/3</td>
</tr>
<tr>
<td>6</td>
<td>62, M</td>
<td>4/3/3</td>
<td>4/3/3</td>
</tr>
<tr>
<td>mean</td>
<td>56.2</td>
<td>3/2/2</td>
<td>3.2/1.8§/2.3</td>
</tr>
</tbody>
</table>

* Scores are presented in the following format: preoperative baseline/3 months postoperatively/12 months postoperatively. All ratings were assigned with the patient in the off state after a 12-hour medication washout.
† Items 29 (gait) and 30 (postural stability).
‡ Motor ratings for limbs contralateral to subthalamotomy.
§ p < 0.05 (comparison of postoperative and baseline values; paired Student t-test, two-tailed).

who were treated with stereotactically guided unilateral STN ablation for their symptoms. The clinical characteristics of these patients and their outcome data are summarized in Table 1. A diagnosis of PD was made if the patient had “pure” parkinsonism (no history of causative factors such as encephalitis or neuroleptic treatment) and did not have dementia, gaze abnormalities, or ataxia. All patients had responded well to levodopa early in their treatment but later experienced typical complications of this therapy. The patients were candidates for unilateral subthalamotomy if they had the following: 1) severe disabling rigidity or akinesia refractory to medical management; or 2) severe response fluctuations, disabling “on”-state dyskinesias, or both.

All patients underwent microelectrode-guided unilateral subthalamotomy; the side contralateral to the more affected limbs was selected for surgery. Coronal T2-weighted spin echo MR images (TR 3000 msec, TE 45 and 90 msec) were obtained preoperatively and repeated 5 to 7 days after surgery to confirm the location of the STN lesion. Written consent was obtained from each patient following a detailed explanation of the procedures.

### Positron Emission Tomography

While in a fasting state, each patient underwent scanning with FDG-PET on the GE Advance Tomograph (General Electric Medical Systems, Milwaukee, WI) at National Taiwan University Hospital in Taipei, Taiwan. Imaging was performed in three-dimensional mode after a 12-hour medication washout. The PET scans were obtained at baseline before subthalamotomy and repeated at 3 and 12 months postsurgery. At each time point, patients were rated according to the UPDRS. The details of the PET findings and the results of the 3-month imaging data have been reported by us previously.

### Data Analysis

Data processing was performed using SPM (version 99; Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Mathworks, Sherborn, MA). The scans from each patient were aligned, stereotactically normalized, smoothed, and proportionally scaled to reduce interindividual variability in gyral anatomy and in global metabolism. Images obtained in two patients in whom lesions were placed in the left hemisphere were reversed prior to statistical analysis so that the lesion appeared on the right side. Data analysis was performed at North Shore University Hospital by investigators blinded to clinical outcome.

Metabolic measurements made 3 and 12 months postoperatively were compared with baseline values by using the general linear model in SPM as described previously. This approach was also used to detect changes in regional glucose metabolism occurring between 3 and 12 months postsurgery. Comparisons between time points were performed in a hypothesis-testing mask obtained in an independent cohort of 30 patients with PD and 20 age-matched healthy volunteers. The mask included the putamen, GPi, GPe, thalamus, pons, cerebellum, and motor cortex. Within this space, metabolic changes were considered significant at probability values less than 0.01, uncorrected for multiple statistical comparisons.

In addition, we adopted an MR image-guided VOI approach to quantify postoperative metabolic changes in specific anatomical regions associated with the STN and its projection zones. In each patient, baseline MR imaging was used to place VOIs (volume 4 × 4 × 4 mm) corresponding to the GPi and GPe as well as to the ventral thalamus and the caudal pons in the area of the pedunculopontine nucleus. These regions were placed on the aligned coplanar PET scans obtained at each of the three time points; VOI coordinates in each patient were fixed over time. To account for interindividual variability in global metabolic rate, each patient’s regional metabolic values were ratio normalized by their own global counts; VOI measurements in lesioned and nonlesioned hemispheres were quantified separately. In each hemisphere postoperative regional glucose metabolism was compared with the baseline values by using paired Student t-tests (two-tailed); regional changes during the postoperative period were assessed by comparing 3- and 12-month values. Comparisons between time points were made separately for each hemisphere; changes were considered significant at probability values less than 0.05. Additionally, postoperative changes in regional metabolism at each VOI in the lesioned and nonlesioned hemispheres were correlated with concurrent changes in UPDRS motor scores by computing the Pearson product–moment correlation coefficients. Correla-
Postoperative changes in local metabolism were identified using SPM or VOI analysis, but these methods do not take into account functional interactions between regional components of spatially distributed neural networks. Using a multivariate network modeling approach based on principal components analysis, we have found that PD is marked by a specific pattern of regional covariation characterized by pallidothalamic and pontine hypermetabolism that is associated with relative metabolic decreases in cortical motor regions (Fig. 1). The expression of this PDRP has been found to be abnormal in multiple independent cohorts of patients with PD, and is reduced by levodopa infusion as well as by pallidal ablation and deep brain stimulation. We have recently shown that a marked reduction in PDRP expression (that is, patient scores) occurs at 3 months after unilateral subthalamotomy. To determine whether metabolic network suppression was sustained at long-term follow up, we quantified PDRP scores obtained at each PET time point on an individual case/hemisphere basis.

This was achieved using an automated computational procedure (available at http://www.neuroscience-nslj.org) that was blinded to time of observation (baseline, 3 months, and 12 months), side of surgery (lesioned or nonlesioned), and clinical outcome (UPDRS ratings). We compared PDRP patient scores for each of the two postoperative time points with baseline values. Additionally, we assessed changes in pattern expression occurring between 3 and 12 months postoperatively. Separate analyses were used to quantify the differences in the lesioned and nonlesioned hemispheres. Comparisons between time points, as well as correlations between postoperative changes in PDRP scores and clinical outcome measures, were considered significant at probability values less than 0.05. The SPM and network computations were conducted on personal computers running Windows NT. Post hoc statistical comparisons were made using JMP software (SAS Institute, Inc., Cary, NC) for personal computers.

**Results**

**Clinical Outcome**

Individual scores for bradykinesia, rigidity, and tremor in
the limbs contralateral to the lesioned side are presented for each time point (Table 1). At 12 months, “off”-state ratings for bradykinesia and rigidity were significantly reduced compared with preoperative baseline values (50 and 73%, p < 0.05). Tremor ratings were still improved at 12 months (57%, p < 0.08) compared with preoperative levels, but less significantly relative to the 3-month measure (86%, p < 0.03). At 3 months, gait and postural stability improved (33 and 42%, p < 0.03) but the improvement was not sustained at 12 months (16 and 26% with respect to baseline, p > 0.09). The levodopa dosage was 840 ± 416 mg preoperatively, 642 ± 341 mg at 3 months, and 608 ± 320 mg at 12 months. Changes in UPDRS ratings in the limbs ipsilateral to the side of surgery were not significant at either of the two postoperative time points (p > 0.3).

**Positron Emission Tomography**

Effect of Subthalamotomy on Regional Glucose Metabolism. The SPM analysis revealed that the postoperative changes in regional metabolism at 12 months resembled those reported previously at 3 months.29 A significant metabolic decline (p < 0.01) was present in the ipsilateral midbrain, which involved the SNr and extended rostrally to include the STN lesion site. As they were at 3 months, postoperative metabolic reductions were identified at 12 months in the caudal pons, GPi, and ventral thalamus. Significant increases in metabolic activity were noted in lobules III–VI of the cerebellum.32 Comparison of 12-month and 3-month postoperative images revealed a significant metabolic increase over time within the GP (Fig. 2), which was most pronounced in the GPe (Zmax = 3.25; x = 24, y = −10, z = 4; p < 0.001; uncorrected). Regional metabolism in the nonlesioned hemisphere did not change after surgery.

The VOI analysis revealed significant metabolic reductions (p < 0.05) at 3 months in both GP segments, as well as in the thalamus and pons of the lesioned hemisphere (Table 2 and Fig. 3). At 12 months, reductions persisted in the GPi, ventral thalamus, and pons (p < 0.05) without significant change between the two postoperative time points (p > 0.3). In contrast, GPe metabolism increased between 3 and 12 months postsurgery (p < 0.04; Fig. 3 upper left), rising to nearly preoperative values. No significant changes

<table>
<thead>
<tr>
<th>VOL, Side</th>
<th>Baseline</th>
<th>3 Mos Postop</th>
<th>12 Mos Postop</th>
<th>% Change Bwn 3 &amp; 12 Mos Postop</th>
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<tr>
<td>GPe</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>lesioned</td>
<td>1.39 ± 0.06</td>
<td>1.21 ± 0.06↑</td>
<td>1.33 ± 0.10‡</td>
<td>9.5§</td>
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<td>nonlesioned</td>
<td>1.35 ± 0.03</td>
<td>1.39 ± 0.02</td>
<td>1.42 ± 0.05</td>
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<tr>
<td>GPI</td>
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<td></td>
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<td></td>
</tr>
<tr>
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<td>1.20 ± 0.04</td>
<td>1.07 ± 0.07↑</td>
<td>1.11 ± 0.07‡</td>
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<tr>
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<td>1.21 ± 0.10</td>
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<tr>
<td>lesioned</td>
<td>1.00 ± 0.07</td>
<td>0.89 ± 0.09↑</td>
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<tr>
<td>lesioned</td>
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<td>1.41 ± 0.07↑</td>
<td>1.43 ± 0.09‡</td>
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<tr>
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<td>1.63 ± 0.13</td>
<td>1.55 ± 0.09</td>
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<td>1.1</td>
</tr>
</tbody>
</table>

* Values reflect globally normalized regional glucose metabolism in selected volumes within the lesioned and nonlesioned hemispheres. The first two rows reflect subthalamic output projections to the GPe and GPi. The last two rows reflect pallidal output projections to the ventral thalamus and caudal pons (see text). Values are expressed as the mean ± SE.  
† p < 0.001 (comparison of postoperative and baseline values; paired Student t-test, two-tailed).  
‡ p < 0.05 (comparison of postoperative and baseline values; paired Student t-test, two-tailed).  
§ p < 0.05 (comparison of 12- and 3-month postoperative values; paired Student t-test, two-tailed).
Discussion

Our results indicate that the majority of regional metabolic changes detected at 3 months after unilateral subthalamotomy persist during an extended 12-month follow-up period. Specifically, we found that, at both postoperative time points, the regional metabolism was reduced at the STN lesion site as well as in subthalamic projections to the GPi and SNr, and also in the thalamus and pons, which are major targets of inhibitory pallidofugal output.\textsuperscript{24,26} Additionally, an independent multiregional network analysis revealed suppression of pathological PDRP activity at both postoperative time points, which correlated with clinical improvement in motor ratings. Thus, our imaging studies indicate that sustained changes in the function of the motor cortico-striato-pallido-thalamocortical loop occur after subthalamotomy, in keeping with the long-term relief of bradykinesia and rigidity that has been observed in patients treated with this procedure.\textsuperscript{36}

Despite the overall stability of the clinical and metabolic improvement that occurred during the 1st year postsurgery, discrete metabolic changes were detected during the 9 months between the two time points for postoperative scanning. Voxel comparisons of the 3- and 12-month images revealed a relative increase in pallidal glucose utilization during this time interval. Secondary VOI analysis performed in conjunction with coplanar MR imaging to quantify metabolic changes in each GP segment confirmed that this reversal was most pronounced in the GPi.

The STN is the major source of excitatory input to the GPi/SNr and to the GPe.\textsuperscript{6,25–27} Subthalamotomy is therefore expected to reduce GPi activity and inhibitory pallidofugal output, thereby alleviating the akinetoric-rigid symptoms of Parkinsonism.\textsuperscript{38} Pathways from GPe to thalamus may also be selectively damaged as a result of lesioning of the lentiform fasciculus, which adjoints the dorsal border of the motor subthalamus.\textsuperscript{30,25} In contrast to the sustained reductions in GPi activity that occur after STN lesioning, GPe metabolism increased after the 3-month time point, returning to nearly preoperative values at 12 months. Thus, the functional disruption of STN output to the GPi that was present at 3 months may represent a transient effect, especially given the comparatively larger number of potentially undamaged fibers involved in this projection pathway.\textsuperscript{34}

Recent studies have shown that microcircuits of STN and GPe form a recurrent excitatory–inhibitory interaction and that under the influence of external input from motor cortex, the two nuclei can be switched between states of high and low activity.\textsuperscript{4,15} This STN–GPe microcircuit is a central pacemaker of the basal ganglia and contributes to parkinsonian pathophysiology.\textsuperscript{4,15,17} The STN plays a prominent role in tremor production.\textsuperscript{34} Tremor-synchronous burst activity has been recorded in the STN and GP,\textsuperscript{18,23} supporting the notion of a microcircuit composed of these structures in the mediation of this symptom.\textsuperscript{38} In patients with PD without tremor, the STN can generate oscillations consisting of bursts of 15- to 30-Hz activity repeated at a low rate.\textsuperscript{4,12,15,19} Treatment with amorphine and levodopa suppresses the oscillations during a time course that correlates with improvement in the off symptoms of PD.\textsuperscript{9} The 15- to 30-Hz synchronous activities in STN are also present in the GPe, and this network interaction may promote tremor-related synchronization in the basal ganglia.\textsuperscript{4,19,21} Reduction in
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the metabolic activities in the STN–GPe during the early postoperative period might account for the dramatic clinical improvements. Nevertheless, partial restoration of the depressed GPe activities and consequent increases in 15- to 30-Hz synchronization in the STN–GPe microcircuit may underlie the reemergence of tremor and lost benefits in gait and postural stability during the late postoperative time period.

The regional metabolic findings on the lesioned side contrast with those identified contralaterally in the nonlesioned hemisphere. Regional metabolism on the nonlesioned side did not differ from baseline at either 3 or 12 months, nor were significant changes detected in this hemisphere when the two postoperative time points were compared with each other. Nevertheless, during the interval between the postoperative PET scans, small (1–2%) metabolic increases were detected in both segments of the GP and in the pons of the nonlesioned side, perhaps reflecting disease progression. By contrast, a relatively larger increase (7%) was present in the thalamus of the nonlesioned hemisphere. This may be attributed to connections between the GPe and the reticular thalamic nucleus, allowing for bilateral pallidothalamic functional interactions. Thus, the interim rise in GPe metabolism ipsilateral to the lesion may be associated with parallel changes in the thalamus of the opposite hemisphere. Alternatively, the relative increase in thalamic metabolism on the nonlesioned side may reflect subtle worsening of PD-related tremor in limbs ipsilateral to the lesion during the follow-up period. We also observed that the direction of metabolic change after subthalamotomy was similar on both sides of the pons, although the postoperative decrease did not reach significance on the side contralateral to the lesion. This finding may be attributed to signal spillover across the two pontine VOIs, although the possibility of altered GPi output to the contralateral pedunculopontine nucleus cannot be excluded.

Although postoperative changes in local glucose metabolism may differ across regions, a consistent pattern of network modulation is seen in our data. In the more affected, lesioned hemisphere, PDRP expression was relatively elevated at baseline and declined at both postoperative time points. These observations are consistent with the sustained postoperative improvement in bradykinesia and rigidity, the clinical features of parkinsonism that are best correlated with PDRP activity. Indeed, our data demonstrate that across patients, this reduction in abnormal network expression is highly correlated with improvement in these manifestations of parkinsonism. By contrast, baseline PDRP scores were lower for the less affected hemisphere, and network expression did not change after STN ablation on the opposite side. This indicates that network abnormalities remain after unilateral surgery, despite improvement on the more severely affected, lesioned side. It is therefore likely that bilateral interventions are required for additional clinical benefit. The degree to which further network modulation can be achieved with STN lesioning of the other hemisphere is a topic under investigation.

Acknowledgment

We thank Ms. Christine Edwards for valuable editorial assistance.

References

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