Subthalamotomy in the treatment of Parkinson’s disease:
clinical aspects and mechanisms of action

A review

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Parkinson’s disease (PD) is a neurodegenerative condition that can be pharmacologically treated with levodopa. However, important motor and nonmotor symptoms appear with its long-term use. The subthalamic nucleus (STN) is known to be involved in the pathophysiology of PD and to contribute to levodopa-induced complications. Surgery is considered in patients who have advanced PD that is refractory to pharmacotherapy and who display disabling dyskinesia. Deep brain stimulation of the STN is currently the main surgical procedure for PD, but lesioning is still performed. This review covers the clinical aspects and complications of subthalamotomy as one of the lesion-based options for PD patients with levodopa-induced dyskinesias. Moreover, the authors discuss the possible effects of subthalamic lesioning.

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**Key Words** • subthalamotomy • Parkinson’s disease • hemiballismus • levodopa-induced dyskinesia • subthalamic nucleus • surgical therapy • lesion • functional neurosurgery

**Abbreviations used in this paper:** DBS = deep brain stimulation; GAD67 = glutamic acid decarboxylase; GPe = globus pallidus externus; GPi = GP internus; LEDD = levodopa equivalency daily dose; LID = levodopa-induced dyskinesia; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDA = N-methyl-d-aspartate; PD = Parkinson’s disease; PPN = pedunculopontine nucleus; RCT = randomized controlled trial; SNC = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; UPDRS = Unified Parkinson’s Disease Rating Scale; Zi = zona incerta; 6-OHDA = 6-hydroxydopamine.

**History of Subthalamotomy**

Historically, lesioning the STN has been avoided for fear of inducing hemiballismus. In fact, it has been known since the end of the 19th century that STN lesions provoked hemiballismus as observed in patients with PD who have suffered a stroke.34 It was demonstrated that lesions

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**Parkinson’s disease (PD)** is the second most common neurodegenerative disease, and its frequency is expected to increase as the population ages. Levodopa tremendously improves the cardinal symptoms of PD.52 However, its chronic administration leads to major motor complications, where patients may encounter motor fluctuations, wearing off, and dyskinesias.178 Dyskinesia describes aimless, involuntary movements for which no pharmacological treatments are currently approved.107 Around 40% of patients will develop levodopa-induced dyskinesias (LIDs) after 4–6 years of treatment, and this percentage increases to 90% after 9–15 years.3 This information led clinicians and surgeons to explore new ways to reduce these severe motor complications without affecting the beneficial effects of levodopa. The subthalamic nucleus (STN) is considered to play a pivotal role in the pathophysiology of PD and LID. Some patients with PD have seen their parkinsonian symptoms alleviated after a coincidental infarction in the STN.147,174,190 Subthalamic lesioning (subthalamotomy) performed in parkinsonian monkeys demonstrated promising results.17,18,23,64 Nowadays, the STN is one of the major targets of stereotactic lesioning and deep brain stimulation (DBS) for the treatment of movement disorders.53 Despite surgical interest in the STN, few reviews cover subthalamotomy as a treatment of PD.59,65,121 The present study reviews the clinical aspects and complications of subthalamotomy in the treatment of PD. Subthalamotomy is compared with other surgical treatments, and a discussion is provided on the possible mechanisms involved in the beneficial motor effects of subthalamic lesions.
confined to the STN in normal monkeys were at high risk for hemiballismus, and destruction of 20% of the STN's volume was enough to provoke this involuntary movement. The development of hemiballismus in normal monkeys was confirmed in nonparkinsonian patients following lesioning restricted to the STN. Nevertheless, several authors performed so-called subthalamotomies for PD, giving rise to a great wealth of publications in the 1960s and 1970s. During the lesioning era, the target for subthalamotomy was not the STN as it is today. In fact, authors performed their lesioning in the zona incerta (Zi), the subventrolateral thalamus, the posterior subthalamic area, and the Raprl (prelemniscal radiations) or H. Field of Forel (lenticular fasciculus), all under the term “subthalamotomy,” while others coined the term “camptotomy.” However, none of these authors targeted the STN itself. Instead, lesions were made in the subthalamic area, mainly in the fiber bundles. As pointed out by Spiegel et al., the advantage of targeting the pallidothalamic fibers is that a smaller lesion is needed to obtain clinical results than when targeting the globus pallidus internus (GPI). On the other hand, since precise imaging and electrophysiological data were scarce, if not completely lacking at that time, it is difficult to compare these publications with current subthalamotomy knowledge. In the 1960s and 1970s, lesioning in the subthalamic area was not restricted to PD treatment, but was also used for the treatment of tremor, cerebral palsy, hyperkinetic movements, including dystonia, intractable spasms, athetosis, hemiballismus, and dyskinesia.

Clinical Outcome of Subthalamotomy

Parkinsonian Symptoms

The last 2 decades have seen many studies addressing the motor and cognitive effects of subthalamotomy for PD (Table 1); there have also been several case reports. A recollection of studies indicates that subthalamotomies have beneficial effects on the motor symptoms in both off- and on-medication states with better results from bilateral lesions. The surgery significantly reduces contralateral cardinal symptoms (tremor, bradykinesia, and rigidity). The improvements obtained with unilateral lesions seemed to increase in the first 12 months and to decrease in the 2nd year after surgery (see the averages in Table 1). Small benefits were also observed ipsilateral to STN lesions but did not last for more than 1 year.

Effects on Levodopa Needs and LID

Dyskinesias, assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS) Part IV, are highly improved by both unilateral and bilateral STN lesions (Table 1). A striking feature is the consistency of improvement in LID over the first 2 years, where a steady 65% reduction is observed (see the averages in Table 1). Contralateral diphasic dyskinesias and off-medication dystonia seem to respond best to subthalamotomy, whereas peak-dose dyskinesias remain unchanged. Furthermore, ipsilateral LIDs are unresponsive to STN lesions. It is usually assumed that the reduction of LIDs is the result of reduced levodopa equivalency daily doses (LEDDs) after altering STN activity. One and 2 years after subthalamotomy, the LEDD was reduced by approximately 45% and 30%, respectively. The progression of the disease may, in part, explain the diminishing improvements in motor and levodopa needs. Nevertheless, the reduction in LEDD cannot be the sole explanation of the improvements in LIDs for 2 main reasons. First, the mean reduction in LIDs remained constant despite LEDD changes over a 2-year period. Second, ipsilateral LIDs continued to increase even if levodopa was greatly reduced. Another interesting feature of subthalamotomy is the potentiation of response to levodopa. It was reported that the on-time duration without significant dyskinesia increased 4-fold when the medication was halved. Daily off-time periods were reduced from 50% to near abolition in the 1st year. Lesions created by the insertion of microelectrode probes or DBS electrodes were found to have positive effects on parkinsonian symptoms peri- and postoperatively. This observation provided evidence to the knowledge that small and confined STN inactivation can be sufficient to produce an improvement of PD, as replicated in animal models. These so-called microlesions appear to have similar effects on the metabolic activity of the globus pallidus, the striatum, the thalamus, and the cortex as those measured after subthalamotomy, but to a lesser extent.

Cognitive Outcome

Surgical procedures in the basal ganglia can potentially induce neuropsychological impairments, as observed after bilateral pallidotomy or subthalamic DBS. Contrary to this, subthalamotomy has not been shown to cause major cognitive impairment. In fact, no studies using a cognitive test (mini–mental state examination) observed a decline after unilateral or bilateral lesions. A recent study demonstrated decreased attention, inhibition, and verbal learning in up to 30% of the patients, but these did not affect patients globally. Finally, executive functions and memory remained unaffected by STN lesions.

Subthalamotomy Versus Other Surgical Treatments

According to the recent review of evidence-based medicine for the treatment of the motor symptoms of PD by the Movement Disorders Society, unilateral pallidotomy and bilateral GPi or STN DBS were found effective for motor complications of PD. Unilateral posteroverentral pallidotomy is known to result in 20%–35% improvement in off-medication motor symptoms during the first 2 years after surgery. In a randomized controlled trial (RCT) comparing unilateral pallidotomy with medical therapy, contralateral dyskinesias were reduced by 75% and 78% at 6 and 24 months postpallidotomy, respectively, and re-
mained unchanged with medical therapy.\textsuperscript{177} In the same study by Vitek et al., ipsilateral dyskinesias were also improved significantly. However, levodopa needs remained the same after 6 months (0.4% decrease in pallidotomy and 7.1% increase with the medical therapy only).

Bilateral subthalamic DBS is assumed to be the most widely used surgical procedure for PD treatment.\textsuperscript{1,85,145} In a recent 6-month RCT, bilateral STN DBS was compared with the best medical therapy.\textsuperscript{182} It was demonstrated that off-medication motor symptoms were improved by 28.6% and remained unchanged with medical therapy. Similar results were obtained for motor complications (36.9% vs 5.4% for STN DBS and medical therapy, respectively). Levodopa equivalencies were reduced by 23.1% after 6 months of STN DBS, whereas they increased insignificantly (1.1%) with the best medical therapy.

Subthalamotomy is still regarded as an experimental procedure for PD.\textsuperscript{54,165} Paradoxically, a recent study demonstrated that neurosurgeons performed subthalamotomies as often as pallidotomies or thalamotomies in most or all of their cases.\textsuperscript{85,145} It was shown that lesioning was more often offered to patients in countries with lower economical development or when patients financed their own surgeries. Subthalamotomy was not included in the rec-

### TABLE 1: Review of published literature on motor and dyskinesia evaluations, and on levodopa equivalency daily doses after subthalamotomy

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Follow-Up in Mos (no. of patients)*</th>
<th>% UPDRS Part III Score Improvement</th>
<th>% UPDRS Part IV Score Improvement</th>
<th>% LEDD Off Medication</th>
<th>On Medication</th>
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<td>unilaterial lesions</td>
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<td>Alvarez et al., 2001</td>
<td>11</td>
<td>12 (n = 10)</td>
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<td>59 (n = 5, &gt;12 mos)</td>
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<td>Alvarez et al., 2009\textsuperscript{a}</td>
<td>89</td>
<td>12 (n = 68)</td>
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<td>Coban et al., 2009</td>
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<td>Hanağasi et al., 2011</td>
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<td>Parkin et al., 2001</td>
<td>11</td>
<td>5.4 (n = 8)</td>
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<td>Patel et al., 2003</td>
<td>26</td>
<td>6 (n = 16)</td>
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<td>Rodriguez et al., 1998\textsuperscript{142}</td>
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<td>12 (n = 7)</td>
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<td>Su &amp; Tseng, 2002; Su et al., 2002\textsuperscript{160}</td>
<td>13</td>
<td>6 (n = 12)</td>
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<td>Vilela Filho &amp; da Silva, 2002</td>
<td>23</td>
<td>13.5 (n = 21)</td>
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<td>Witjas et al., 2009</td>
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<td>12 (n = 2)</td>
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<td>6 mos</td>
<td>20.8 ± 3.4</td>
<td>20.4 ± 3.0</td>
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<td>44.7 ± 10.9</td>
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<td>12 mos</td>
<td>44.2 ± 9.1</td>
<td>46.4 ± 12.0</td>
<td>65.5 ± 9.4</td>
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<td>24 mos</td>
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<td>Alvarez et al., 2005</td>
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<td>Alvarez et al., 2009\textsuperscript{***}</td>
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<td>Merello et al., 2008</td>
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<td>Tseng et al., 2007</td>
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* The number of patients is given only if the number of patients differs from the number of patients who underwent surgery.
† Calculated based on the cardinal scores.
‡ UPDRS Part IV items 32–33.
§ UPDRS Part IV items 32–35.
¶ Dyskinesia rating scale.
** Some of the patients may have been presented in Alvarez et al., 2005.
†† UPDRS Part IV items 32–35.
ommended procedures for motor complications because of insufficient evidence. Two studies met Level I criteria, depicted by at least 1 high-quality RCT, but these studies were not included in the review because of their small sample sizes. In the first study, unilateral subthalamotomy was compared with unilateral pallidotomy and bilateral STN DBS. The authors concluded that both procedures offered major motor improvement and that these 2 surgeries were equally effective for the motor treatment of PD. Also, they observed that unilateral subthalamotomy had the advantage of reducing levodopa needs, whereas the needs remained unchanged with unilateral pallidotomy. In the second RCT comparing bilateral subthalamotomy and bilateral STN DBS, the 2 surgical procedures had similar benefits on motor symptoms in patients with PD and the results were comparable to previous literature. Although these 2 RCTs provided evidence on the positive effects of STN lesions, larger RCTs are warranted to fully assess the cost-effectiveness and the role of subthalamotomy in the treatment of PD.

The tremendous improvements and low complications profile observed in patients treated with DBS are obvious reasons for its vast use worldwide. However, STN lesioning may be an alternative when DBS is not a possible treatment for certain reasons, such as access to care and health status. Lesion therapies are much less expensive than DBS. In fact, the direct and indirect costs of a DBS system outweigh lesion-based costs. Moreover, patients have shorter hospital stays after lesioning than those who receive DBS implants. Subthalamotomy also presents advantages that are not seen with other lesioning treatments. Patients undergoing unilateral subthalamotomy seem to respond as well as those undergoing unilateral pallidotomy when considering motor and dyskinesia improvements. Bilateral subthalamotomy does not seem to induce severe cognitive decline as seen in bilateral pallidotomy. Subthalamic nucleus lesions allow for a reduction in levodopa, whereas levodopa remains practically unchanged after pallidotomy. This advantage is valuable when patients have levodopa-induced hallucinations. Although there are no studies on this matter, STN DBS was recently shown to reduce hallucinations after medication adjustments and could be achieved with STN lesions.

**Cellular and Biochemical Effects of Subthalamotomy**

**Neuroprotection**

There is evidence suggesting that dopaminergic cells are sensitive to excitatory glutamatergic input implicated in neurotoxicity in PD. Dopaminergic cells present both N-methyl-d-aspartate (NMDA) and non-NMDA glutamate receptors, and antagonizing the former receptor was shown to protect substantia nigra pars compacta (SNc) cells against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity. The STN is the main excitatory structure of the basal ganglia and has efferences in the SNc. It was originally hypothesized that STN overactivity in PD could contribute to progression of the disease and its inactivation may slow or prevent it.

In rats, most of the studies failed to demonstrate a neuroprotective effect of previous STN lesions before large exposure to the neurotoxin 6-hydroxydopamine (6-OHDA) on dopaminergic cells survival. It was, however, shown that the phenotype, measured by tyrosine hydroxylase immunohistochemistry, the rate-limiting enzyme in the production of dopamine synthesis, was preserved in the surviving cells in the first weeks after exposure to 6-OHDA. On the contrary, some authors observed neuroprotection in rats with small dopamine depletion, but its effectiveness decreased in a time-dependent manner and was no longer detected after 1 week.

In primates, a recent study showed the neuroprotective effects of dopaminergic cells, when subthalamotomy is performed 2 weeks before or 1 week after MPTP insult. More recently, we observed no changes in tyrosine hydroxylase–positive immunohistochemistry or in dopamine or its metabolite concentrations after unilateral subthalamotomy. This discrepancy might be explained by the same 3 main factors seen in rodents: the extent of dopamine depletion, the extent of the STN lesion, and the time between the 2 insults. The dopaminergic degeneration was much more profound in our monkeys than it was in the study by Wallace and colleagues. Monkeys in that study had 50% dopaminergic loss in the SNc, whereas monkeys in our study had a near complete loss. Neuroprotective effects of STN alteration are inversely proportional to the extent of the MPTP insult. A study in MPTP-injected monkeys failed to show neuroprotection with 85% of dopaminergic loss. The survival time between MPTP administration and subthalamotomy is also likely to explain the difference. In the study by Wallace et al., monkeys received a subthalamotomy only 6 days after MPTP and were killed roughly 14 days after lesioning, whereas the monkeys in our previous study were rendered parkinsonian many years before the STN lesion and were killed several weeks after surgery. Lastly, the STN is not the only glutamatergic source to the SNc. In fact, the latter receives excitatory input from the pedunculopontine nucleus (PPN) and the cortex and may also contribute to the glutamate-mediated excitotoxicity.

Clinically, PD cardinal symptoms appear after 80% of striatal dopaminergic loss, and patients with PD undergo surgery when their disease becomes pharmacologically refractive to levodopa or when LIDs are disabling. Thus, neuroprotective studies do not reflect surgical practices in a clinical perspective and clearly cannot be applied in a clinical context.

**Neurophysiology**

Subthalamic nucleus activity in PD is known to increase in frequency and to increase burst firing. In humans and primates, similar changes were observed in the STN output nuclei, that is, the GPi and substantia nigra pars reticulata (SNr). Globus pallidus internus neuronal activity increases from 60–70 Hz in the normal state to 70–85 Hz in PD and from 60 to 70 Hz in the SNr. The administration of levodopa not only reverses these increases but also tends to further reduce the basal activity of the GPi and SNr. Exerts comparable effects by restoring normal electrophysiological activity. Subthalamic
nucleus lesions decreased the GPi firing rate in normal monkeys\textsuperscript{46} and reversed the increased GPi neuronal activity induced by 6-OHDA in rats.\textsuperscript{11} Some authors observed only that the GPi firing pattern returned to normal, resulting mainly in reduced burst firing without any change in firing rate.\textsuperscript{44} However, the MPTP-induced GPi oscillations persisted in parkinsonian monkeys.\textsuperscript{83} Similarly, SNr electrical activity was also decreased after subthalamotomy in normal\textsuperscript{10,33,67,71} and 6-OHDA rats\textsuperscript{12,17,32} with reduced burst firing.\textsuperscript{114,117} Moreover, the 6-OHDA-induced increase in the PPN firing rate was prevented with STN lesions in rats, but no change was observed in normal rats after STN destruction.\textsuperscript{84} On the contrary, subthalamotomy in normal rats increased the number of PPN neurons that displayed bursting activity by more than 30%, whereas 6-OHDA lesions with or without STN lesions increased the number by only 8%–12%.\textsuperscript{84} These last 2 observations indicate that the changes in PPN activity following STN lesioning are not due to a direct subthalamo-pedunculopontine connection. Lastly, SNc neurons were also observed to reduce their firing rate and their burst activity after STN lesioning,\textsuperscript{26,148,149} but those findings were not replicated by others.\textsuperscript{190} Thus, it is generally agreed that subthalamotomy decreases neuronal activities in GPi, SNr, and SNc, which is consistent with the fact that STN exerts an excitatory input on these structures.

**Neurochemistry**

The consequences of these physiological changes in STN output translate into measurable biochemical modifications (Table 2). Reductions in cytochrome oxidase and succinate hydrogenase, both markers of cellular activities, were found in the GPi and SNr after STN lesioning in normal and 6-OHDA rats,\textsuperscript{27,28,132} corroborating the decrease in firing rates and patterns. Messenger RNA of enzyme glutamic acid decarboxylase (GAD\textsubscript{67})—which is needed for the conversion of glutamate to \(\gamma\)-aminobutyric acid present in the globus pallidus externus (GP\textsubscript{e}), GPi, and SNr—also decreases with subthalamotomy in MPTP monkeys and 6-OHDA rats.\textsuperscript{44,132} This indicates that these cells are less active and consume less energy after subthalamotomy.\textsuperscript{111} However, increases in GAD\textsubscript{67} levels were observed in the GPi and GP\textsubscript{e} of normal monkeys after STN lesions.\textsuperscript{10} As for the changes in the SNc electrophysiology, some studies reported increased striatal dopamine and tyrosine hydroxylase positivity,\textsuperscript{10,36} others reported a reduction.\textsuperscript{48}

**Subthalamotomy Complications**

**Hemiballismus**

Subthalamic nucleus lesions have been known to induce hemiballismus, which is the violent, irregular, and involuntary movement of one half of the body.\textsuperscript{114} Hemiballismus is usually observed contralateral to STN lesions in patients with PD (Table 3), but ipsilateral hemiballismus was also described secondary to STN infarct or hemorrhage in nonparkinsonian patients.\textsuperscript{2,9,2,3,13,17} Hemiballismus has many causes and may be caused by lesions in the STN, but also by lesions in other structures of the basal ganglia.\textsuperscript{46,56,61,139,174} In patients with PD who undergo subthalamotomy, transient hemiballismus (< 1 year) was observed in 13.2% (40 of 303 patients enrolled in studies or case reports) with spontaneous recovery or with successful pharmacological treatment, whereas it remained permanent in 9.9% (includes 2 patients receiving ipsilateral thalamotomy during the same surgical procedure since they presented with hemiballismus/hemichorea by the end of STN surgery\textsuperscript{25,177}). It has been suggested that smaller lesions would allow for compensatory mechanisms within the basal ganglia, tending to reestablish equilibrium and cease hemiballismus. Conversely, in larger STN lesions, a persistent decrease in GPi and SNr activities was observed.\textsuperscript{169} Recently, 2 cases were described in which transient hemiballismus was the result of a small hemorrhage or an infarct in the STN.\textsuperscript{113} Both patients recovered within 4 weeks after the symptoms appeared, without any pharmacological or surgical treatment, supporting this hypothesis. Other authors have suggested that lesions confined to the nucleus were more prone to induce hemiballismus and lesions extending its boundaries could prevent the development of hemiballismus by reducing pallidothalamic outflow.\textsuperscript{26,49} This hypothesis is supported by the fact that pallidotomies can completely abolish hemiballismus in patients with PD.\textsuperscript{162} Finally, hemiballismus is not strictly caused by STN lesions. It was also observed in patients with PD after thalamotomy\textsuperscript{48} and subthalamic DBS.\textsuperscript{90,123} Although these 2 hypotheses (size and location of the lesion) neither exclude nor invalidate one another,\textsuperscript{184} the underlying mechanisms of hemiballismus after subthalamotomy have yet to be clarified.

**Postural Disturbance**

Patients with PD may present with postural abnormailties such as neck flexion and camptocormia.\textsuperscript{83} Patients with postural asymmetry show lateral curvature of the spine with an inclination of the trunk toward the ipsilateral side that is more depleted in dopamine. This instability of posture responds poorly to levodopa.\textsuperscript{103} Similar postural asymmetry was observed after STN lesioning in nonparkinsonian\textsuperscript{104} and PD patients.\textsuperscript{102,159} These patients displayed a body tilt contralateral to the lesion accompanied by head rotation. Head rotations were seen in normal and parkinsonian monkeys in which the STN was lesioned.\textsuperscript{10,33,67} It was proposed that an imbalance of the dopaminergic influence between the lesioned and nonlesioned hemispheres\textsuperscript{159} and/or the glutamatergic imbalance between the STN and the SNr may occur.\textsuperscript{86} Finally, transient postural disturbance was also reported after unilateral and bilateral subthalamotomy.\textsuperscript{110,175}

**Other Complications**

In the series by Alvarez and colleagues\textsuperscript{8} consisting of 89 patients undergoing unilateral subthalamotomy, some patients presented with transient dysarthria, infection of the scalp, asymptomatic bleeding, and seizures. All of these complications were observed in less than 5% of patients. Speech and dysarthria complications were seen in 3 patients undergoing bilateral STN lesioning. Two of these patients also displayed trunk and gait ataxia.\textsuperscript{8} Ataxia was associated with larger lesions in those patients.\textsuperscript{7} Subthalamic nucleus lesions were also shown to induce blepha-
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Conclusions

The STN plays a pivotal role in the basal ganglia, since it is connected to many other structures within the basal ganglia and to nuclei outside of it. It is widely ac-

TABLE 2: Neurochemical changes after unilateral subthalamotomy in normal and parkinsonian animals*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Treatment</th>
<th>% DA Denervation</th>
<th>% STN Lesion</th>
<th>Effect of STN Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>studies in rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blandini et al., 1995</td>
<td>normal</td>
<td>none</td>
<td>near complete</td>
<td>↓ mitochondrial complex I activity in EN &amp; SNr; ↓ SNr NMDA receptor binding; no effect on AMPA receptor binding</td>
</tr>
<tr>
<td>Blandini &amp; Greenamyre, 1995</td>
<td>normal</td>
<td>none</td>
<td>near complete</td>
<td>↓ SDH &amp; CO mitochondrial activities in striatum, SNc, &amp; GP</td>
</tr>
<tr>
<td>Price et al., 1993</td>
<td>normal</td>
<td>none</td>
<td>complete</td>
<td>↓ AMPA &amp; kainate receptor binding in ipsilateral SNr; ↓ NMDA receptor binding in ipsilateral GP</td>
</tr>
<tr>
<td>Aristieta et al., 2012</td>
<td>6-OHDA</td>
<td>complete loss</td>
<td>≈60%</td>
<td>↑ striatal FosB/DFoB ipsilateral to STN lesion in 6-OHDA rats treated w/ levodopa; ↑ striatal pDARPP32/DARPP32; reverses the increased D2/D1 ratio in 6-OHDA rats treated w/ levodopa</td>
</tr>
<tr>
<td>Bacci et al., 2004</td>
<td>6-OHDA</td>
<td>complete loss</td>
<td>near complete</td>
<td>reverses the increased striatal enkephalin mRNA levels in 6-OHDA rats; reverses the increased GAD67 mRNA levels in 6-OHDA rats in the EN &amp; SNr; no effect on the decreased levels of substance P mRNA in 6-OHDA rats</td>
</tr>
<tr>
<td>Biandini et al., 1997</td>
<td>6-OHDA</td>
<td>complete loss</td>
<td>partial (20%–70%) complete</td>
<td>partial lesion: ↓ CO in EN &amp; SDH in GP, EN; complete lesion: ↓ CO &amp; SDH in EN, GP; both partial &amp; complete STN lesions prevented the increase in CO &amp; SDH in SNr</td>
</tr>
<tr>
<td>Centonze et al., 2005</td>
<td>6-OHDA</td>
<td>complete loss</td>
<td>near complete</td>
<td>reverses the 6-OHDA-induced overactive frequency &amp; amplitude of striatal glutamate-mediated spontaneous excitatory postsynaptic currents</td>
</tr>
<tr>
<td>Delfs et al., 1995</td>
<td>6-OHDA</td>
<td>&gt;90% loss of DA uptake</td>
<td>near complete</td>
<td>↓ the increase in GAD67 mRNA in the GP induced by 6-OHDA; no effect in ipsilateral EN; no effect on encephalin &amp; substance P</td>
</tr>
<tr>
<td>Hwang et al., 2006</td>
<td>6-OHDA</td>
<td>66% loss of striatal DA; 50% loss of GPe DA</td>
<td>NA</td>
<td>↑ striatal &amp; pallidal content of DA &amp; HVA in normal &amp; 6-OHDA rats</td>
</tr>
<tr>
<td>Levandis et al., 2008</td>
<td>6-OHDA</td>
<td>&gt;97% loss of striatal DA; &gt;93% loss of SNc DA</td>
<td>&gt;50% loss</td>
<td>↑ striatal FosB/DFoB ipsilateral to STN lesion in 6-OHDA rats treated w/ levodopa</td>
</tr>
<tr>
<td>Périer et al., 2003</td>
<td>6-OHDA</td>
<td>98% loss of DAT</td>
<td>near complete</td>
<td>↓ the increase in CO subunit I &amp; GAD67 mRNA in the striatum induced by 6-OHDA when combined w/ levodopa</td>
</tr>
<tr>
<td>Touchon et al., 2004</td>
<td>6-OHDA</td>
<td>80–85% loss of striatal TH</td>
<td>NA</td>
<td>↓ striatal glutamate in 6-OHDA, STN lesion, or the combination of both lesions associated w/ an increase in glutamate immunolabeling in nerve terminals</td>
</tr>
<tr>
<td>Walker et al., 2009180</td>
<td>6-OHDA</td>
<td>90% loss of SNc TH</td>
<td>&gt;50% loss</td>
<td>↑ striatal glutamate in normal rats; ↓ the striatal increase of glutamate in 6-OHDA rats</td>
</tr>
<tr>
<td>Walker et al., 2009179</td>
<td>6-OHDA</td>
<td>90% loss of SNc TH</td>
<td>&gt;50% loss</td>
<td>↓ striatal DA &amp; DA metabolites, ↑ in the HVA/DA ratio in normal rats; ↓ striatal DA, ↑ DA metabolites, DA metabolites/DA ratio unchanged in 6-OHDA rats</td>
</tr>
<tr>
<td>studies in primates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andrén et al., 1995</td>
<td>normal</td>
<td>none</td>
<td>NA</td>
<td>↑ GAD67 in bilateral caudate nucleus, GPi, GPe, VA/VL &amp; ipsilateral putamen; ↑ GABA in CM/Pf; ↑ DA in dorsal contralateral putamen; ↑ TH in bilateral GPi &amp; contralateral striatum</td>
</tr>
<tr>
<td>Guri et al., 1996</td>
<td>MPTP</td>
<td>near complete</td>
<td>80–90% loss</td>
<td>↓ GAD67 mRNA in GPi, GPe, SNr; ↑ GAD67 mRNA in reticular thalamic nucleus</td>
</tr>
<tr>
<td>Mitchell et al., 2000</td>
<td>bicuculline injection</td>
<td>none</td>
<td>&gt;50% loss</td>
<td>↓ 2-deoxyglucose activity in GPe &amp; GPi</td>
</tr>
<tr>
<td>Shimo &amp; Wichmann, 2009</td>
<td>normal</td>
<td>none</td>
<td>bicuculline injection</td>
<td>↓ striatal dopamine</td>
</tr>
</tbody>
</table>

* AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CM/Pf = centromedian and parafascicular thalamic nuclei; CO = cytochrome oxidase; DA = dopamine; DAT = dopamine transporter; EN = entopeduncular nucleus, rat homolog of the primate GPe; GABA = γ-aminobutyric acid; GP = rat globus pallidus, homolog of the primate GPi; HVA = homovanillic acid; NA: not available; SDH = succinate dehydrogenase; TH = tyrosine hydroxylase; VA/VL = ventroanterior and ventrolateral thalamic nuclei; ↑ = increases; ↓ = decreases.

*ospasm or ptosis in healthy individuals,126 as well as in PD43 or dystonic patients69 undergoing subthalamotomy to alleviate their symptoms. Finally, neuropsychiatric side effects were also associated with STN alterations, such as hyperphagia,31 hypersexuality,2 and impulse behavior.2,126
Accepted that its overactivity in patients with PD is one of the pathophysiological causes underlying the cardinal symptoms of PD and dyskinesias. Despite the fact that the STN is the main target for DBS in patients with PD, subthalamotomy remains an alternative surgical option for patients whose conditions are refractory to pharmacological treatment or those who are unable to receive DBS implants due to medical reasons or access limitations. Several studies demonstrated the effectiveness of subthalamotomy in the treatment of PD. It reduces daily levodopa needs and was associated with few, mainly transient, complications. Nevertheless, more clinical evidence is needed to warrant its use as a treatment option for PD.

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Author contributions to the study and manuscript preparation include the following. Analysis and interpretation of data: Jourdain. Drafting the article: Jourdain, Schechtmann. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Di Paolo.

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