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Unilateral subthalamotomy in the treatment of Parkinson's disease

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Summary

Hyperactivity in the subthalamic nucleus (STN) is seen in animal models of Parkinson's disease, and lesioning of the STN dramatically relieves the animal's parkinsonism. Deep brain stimulation (DBS) of the STN is an effective treatment for patients with advanced Parkinson's disease. We have studied the effects of a unilateral lesion placed in the STN in predominantly hemi-parkinsonian patients. Twenty-one patients with advanced idiopathic Parkinson's disease were studied. Seventeen had asymmetrical tremor-dominant Parkinson's disease and four had bilateral disease. All patients underwent radiofrequency lesioning of the dorsolateral part of the STN under stereotactic guidance. The four patients with bilateral disease had, in addition, an electrode implanted contralaterally in the STN. Twenty-one patients have been followed for a minimum of 12 months. Clinical evaluation included the use of the Unified Parkinson's Disease Rating Scale (UPDRS) before and after surgery. Post-operative high-resolution MRI was performed in each patient to confirm lesion location, and this was correlated with clinical outcome. There was improvement in contralateral tremor, rigidity and bradykinesia in all patients followed for 6, 12 and 24 months, with the effect on tremor being greatest. L-dopa equivalent daily intake was approximately halved, and this resulted in a significant reduction in dyskinesia. Psychometric test scores were mostly unchanged or improved. All lesions were successfully located in the dorsolateral STN. Nineteen of the 21 lesions extended beyond the STN to involve pallidofugal fibres (H2 field of Forel) and the zona incerta (ZI). Lesion-induced dyskinesias were not a management problem except in one patient, whose lesion was confined to the STN. This patient was successfully treated with deep brain stimulator placement in the region of H2/ZI. Unilateral STN lesions can be made safely and are an effective alternative to thalamotomy, pallidotomy and unilateral STN DBS for the treatment of asymmetrical tremor-dominant advanced Parkinson's disease. Combined lesioning of the dorsolateral STN and H2/ZI is particularly effective.

Keywords: Parkinson's disease; subthalamic nucleus; lesioning; pallidofugal fibres; zona incerta; cognition

Abbreviations: DBS = deep brain stimulation; GPi = globus pallidus interna; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale; ZI = zona incerta

Introduction

Lesions of the subthalamic nucleus (STN), usually strokes, have long been known to cause hemiballism. There are also reports of patients with Parkinson's disease who improved after spontaneous STN haemorrhage (Sellal *et al*., 1992; Vidakovic *et al*., 1994). Historically, the STN region has been the target for several types of surgery in Parkinson's disease. After the success of pallidotomy and thalamotomy in the 1950s, surgeons attempted to improve those results with smaller lesions targeted at pallidofugal fibres. These fibres pass through the H2 field of Forel, the zona incerta (ZI) and prerubral field that lie immediately dorsal to the STN. Lesions in this region may well have involved STN to a greater or lesser extent (Fager, 1968). Lesions of H2 field of Forel (campotomy) or the posterior subthalamus were reported to produce results similar to those of thalamotomy (Andy *et al*., 1963; Spiegel *et al*., 1963; Mundinger, 1969). The lesions provoked transient hemiballism in some cases but were reported to be otherwise safe (Andy *et al*., 1963).

With the greater theoretical understanding of the basal ganglia circuitry in the direct/indirect pathway model (Albin

et al., 1989) and the availability of an animal model of Parkinson's disease in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkey, the pivotal role of the STN in basal ganglia function became evident. MPTP-treated monkeys develop hyperactivity of the STN (Bergman *et al*., 1994). Lesioning or deep brain stimulation (DBS) of the STN in these monkeys produces symptomatic improvement (Bergman *et al*., 1990; Aziz *et al*., 1991, 1992; Benazzouz *et al*., 1993).

The suitability of the STN as a target for surgical treatment of Parkinson's disease is reflected in the results of chronic DBS of the STN by the Grenoble group (Benabid *et al*., 1994; Limousin *et al*., 1995, 1998). However, lesioning of the STN may be a suitable alternative, and avoids the device-related complications and maintenance costs of DBS. In 1997, we commenced a programme of lesioning of the dorsolateral STN in patients with Parkinson's disease that was poorly controlled on optimal medication.

Material and methods

Patients

Between 1997 and 2000, unilateral subthalamotomies were performed on 26 patients (17 men, nine women). Approval from the Frenchay Hospital Research Ethics Committee was received before this series was commenced. The selection criteria were that the patient should have idiopathic Parkinson's disease that was responsive to L-dopa but nonetheless severely disabling despite all drug therapies, and that was not associated with dementia as indicated by a significant drop in cognitive function on neuropsychological testing as compared with estimates of pre-morbid cognition. In addition, the patient should be able to function at a reasonable level of independence for at least some part of the average day. Twenty-two of the 26 patients had asymmetrical and tremor-predominant Parkinson's disease, and underwent lesioning of the STN contralateral to the worst affected side. Four (two men, two women) had significant bilateral Parkinson's disease and had unilateral lesioning with contralateral implantation of electrodes in the STN.

Clinical evaluation

Evaluations were performed pre-operatively and at 6, 12 and 24 months post-operatively. Clinical evaluations were based on the Core Assessment Program for Intracerebral Transplantations, a validated protocol for evaluating surgical treatments of idiopathic Parkinson's disease (Langston *et al*., 1992). All patients were assessed on the Unified Parkinson's Disease Rating Scale (UPDRS). Patients were assessed pre-operatively, both OFF and ON medication. Post-operatively, patients who had undergone unilateral STN lesioning were assessed both OFF and ON medication; those who, in addition, had had a contralateral electrode implanted were assessed both OFF and ON medication with stimulation OFF. Before they were assessed OFF medication, patients fasted and medications were withdrawn overnight. Those with contralateral DBS electrodes had their stimulation switched OFF overnight. The same assessments were then repeated after administration of 200 mg of L-dopa.

In addition, pre- and post-operative neuropsychological assessment of attention, memory, executive function, language and verbal intellect were undertaken with a battery of tests designed to minimize potential contamination of cognitive effects by motor symptoms (McCarter *et al*., 2000).

Surgery

All patients gave fully informed consent and were aware of the potential risks of stereotactic subthalamotomy, including those of hemiballism and haemorrhagic stroke. The STN was localized with high-resolution MRI T_2-weighted scan sequences (1.5 Tesla TR 2500, TE 150, TSE 11, NSA 12) and pre-operative macro-stimulation was used for adjustment. Under general anaesthesia, a modified Leksell stereotactic frame was affixed parallel to the orbito-meatal plane. The anterior (AC) and posterior (PC) commissures were identified in a mid-sagittal planning scan. Axial images (Fig. 1) 2-mm thick were acquired parallel to the AC–PC plane and coronal images (Fig. 2) orthogonal to these were then obtained. We found these sequences to give optimum delineation of the STN and related structures. We used magnified hard copies of the MRI scans and overlaid the T_2 scans with inverted T_2 images further to enhance the definition of STN boundaries, and these were cross-checked with the Schaltenbrand atlas (Schaltenbrand and Bailey, 1959). Stereotactic coordinates of the target, the dorsolateral STN, were recorded and a trajectory was planned, orientated along the axis of the nucleus in the coronal plane. The target in the dorsolateral STN was taken as the centre of the dorsal half of the posterior third of the nucleus.

At surgery patients were awake and in an 'OFF' state, anti-parkinsonian medications having been stopped 24 h previously. A 1.24 mm diameter electrode with a 2 mm exposed tip (Radionics Inc., Burlington, MA, USA) was guided to the dorsolateral STN. The target was stimulated at 100 Hz, 0.75–2 V, with 1 ms pulse width, during which changes in tremor, rigidity and bradykinesia were monitored. Probe position was adjusted to gain maximal clinical improvement without the development of side effects. We very often found that the optimal clinical benefit was obtained when stimulating ~2 mm dorsal to our planned target. A lesion was made at this location, typically at 80°C for 60 s. In a number of cases a second lesion was made ventral to the first, i.e. at the site of the planned target.

Within a few hours of surgery, the patient underwent high-resolution MRI to confirm lesion position. Axial and coronal T_2 images were obtained with the same slice configurations in relation to the AC–PC line, as before surgery, allowing for direct comparison of the images (Fig. 2). In post-operative

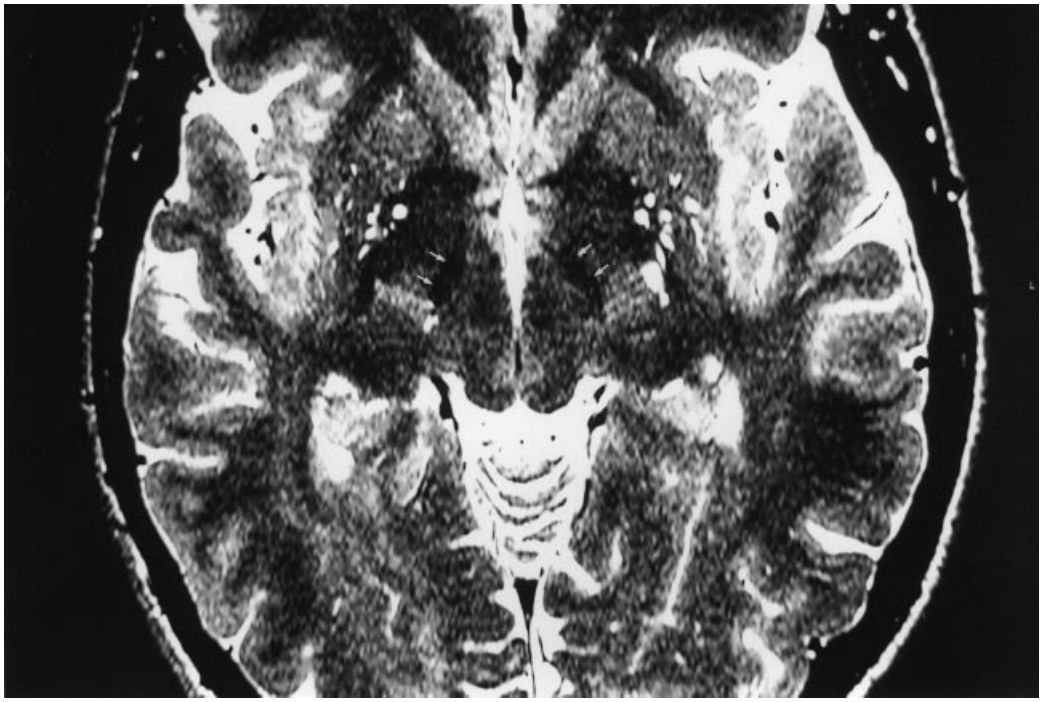

Fig. 1 High-resolution axial T_2-weighted MR images delineating the STN bilaterally (arrows).

images, the coagulum corresponded to the lesion and was usually surrounded by a ring of oedema.

Anti-parkinsonian medication was reintroduced as required and reviewed at follow-up.

Psychometric evaluations

Seventeen of the 21 patients (six with right subthalamotomy, seven with left subthalamotomy and four with subthalamotomy plus contralateral stimulator) underwent pre- and post-operative neuropsychological testing. The findings in 12 of these patients have been described previously, as has the test battery (McCarter *et al*., 2000).

Statistical evaluations

The outcome measures were the scores on UPDRS II (activities of daily living), UPDRS III (motor examination) and UPDRS IV (complications of therapy); the Hoehn and Yahr global stage; the dose of L-dopa; and neuropsychometric tests. In addition, the post-operative images were analysed to identify lesion location, and this was correlated with the outcome measures.

The non-parametric data were analysed using the paired Wilcoxon signed-rank and sign tests.

The psychometric data were analysed using a Reliable Change Index (Jacobson, 1991). This is increasingly used as a robust and often clinically more meaningful method of analysing change in neuropsychological performance than are traditional measures of statistical significance or group differences. The latter may mask significant individual change in groups of patients who may show heterogeneous outcomes, as described after surgery for Parkinson's disease (Troster, 1997; Trepanier, 1998).

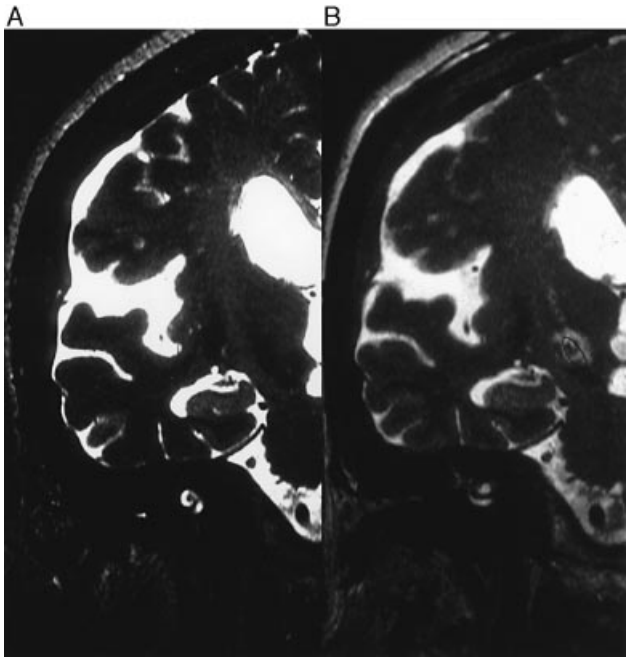

Fig. 2 (**A**) Pre- and (**B**) post-operative high-resolution coronal T_2-weighted image showing lesioning of the right dorsolateral STN.

Results

A marked improvement of their parkinsonian features, especially tremor, was observed in all patients immediately following surgery. Five of the 26 patients were lost to follow-up: two failed to attend clinics, two lived abroad and were unable to return, and one patient developed metastatic carcinoma soon after surgery. Of the remaining 21 patients, 16 cases were reviewed at 6 months, 15 cases at 12 months and 18 cases at 24 months. The 21 cases followed-up had a mean age of 60 years (range 36–73 years) and mean disease duration of 12 years (range 3–24 years). Unilateral subthalamic nucleotomy was performed on the right in 12 of these cases and on the left in nine. The four cases with bilateral Parkinson's disease all underwent right-sided subthalamic nucleotomy and had stimulators inserted on the left.

Contralateral to the subthalamic nucleotomy there was a significant reduction ($P < 0.01$) in the motor UPDRS scores OFF medication at 6, 12 and 24 months (Fig. 3A and Table 1). At 12 months, the contralateral motor UPDRS scores were also significantly reduced ($P < 0.05$) on medication (Table 1). Contralateral subscores for bradykinesia, rigidity and tremor declined both OFF and ON medication (Fig. 2A and B, and Table 1). The reduction in OFF state bradykinesia at 24 months was significant ($P < 0.05$). The effect on contralateral tremor was pronounced, with significant reductions at 6, 12, and 24 months both OFF and ON medication. Disease progression over the period of the study was evidenced by an increase in ipsilateral motor UPDRS subscores for bradykinesia both OFF and ON medication, with significant change at 12 ($P < 0.05$) and 24 ($P < 0.01$) months (Table 1).

The scores for UPDRS II (the activities of daily living) were reduced both OFF and ON medication, with significantly lower off scores at 6 months ($P < 0.05$) (Table 1).

Contralateral L-dopa-induced dyskinesias were significantly reduced at 6, 12 and 24 months ($P < 0.01$; UPDRS IV, items 32–35) (Fig. 4). The mean disability related to dyskinesias was significantly improved (UPDRS IV, item 33, range 0–4), and the mean duration of dyskinesias significantly shortened (UPDRS IV, item 32, range 0–4). Motor fluctuations were also significantly attenuated at 6, 12 and 24 months ($P < 0.01$; UPDRS IV, items 36–39). The score for the duration of the 'OFF' period fell from 1.8 ± 1.1 to 0.9 ± 0.6 at 6 months ($P < 0.05$, UPDRS IV, item 39; range 0–4) (Table 1). The duration of the 'ON' period increased correspondingly (Fig. 5).

The mean dose of L-dopa was decreased by 34–47%, with significant reductions at 6, 12 and 24 months (Table 1). One patient stopped treatment after surgery. Three patients remained off L-dopa both before and after surgery. In five patients, L-dopa was increased at follow-up after surgery, and in one patient therapy remained unchanged.

For all patients followed up, post-operative MRIs were examined to identify lesion location. All 21 lesions were successfully located in the dorsolateral STN. Nineteen lesions extended dorsally beyond the STN into the pallidofugal fibres (H2) and ZI. Two lesions were confined to the STN (Fig. 6). The mean position of the dorsolateral STN target centre of all 21 cases with respect to the AC–PC line midpoint was 12.6 mm lateral (SD 1.2), 3.7 mm posterior (SD 1.1) and 2.6 mm inferior (SD 1.2). In comparison, the mean position of the lesion centre of all 21 cases was 12.7 mm lateral (SD 1.3), 3.3 mm posterior (SD 1.4) and 2.1 mm inferior (SD 1.3). The mean lesion diameter as seen on MRI was 4.2 mm (SD 1.5).

It was observed at follow-up that the two patients with lesions confined to the STN had less clinical benefit than had the patients in whom H2/Z1 was also involved. Immediately after surgery, these two patients had shown clinical benefit but this gradually wore off, an occurrence that may have been related to the resolution in oedema. In one of the patients with a lesion confined to the STN (Fig. 6) the L-dopa-induced dyskinesia score was unchanged, and in the other dyskinesia contralateral to the lesion was less severe but remained disabling despite substituting a dopamine agonist for L-dopa.

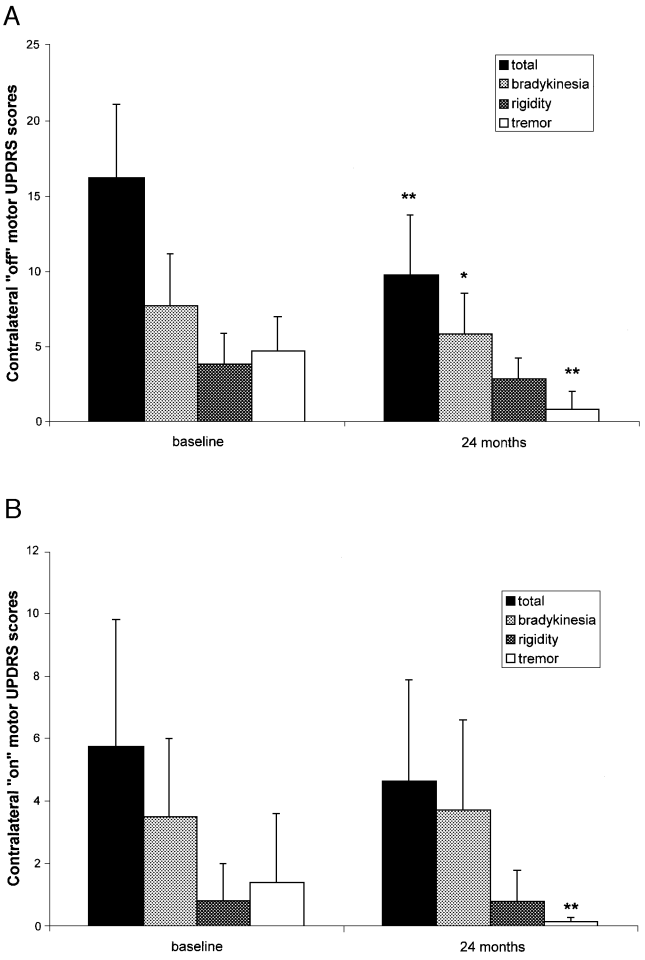

Fig. 3 Mean (± SD) contralateral (**A**) OFF medication and (**B**) ON medication scores, respectively, for motor examination before and 24 months after surgery. The subscores are for UPDRS III. $*P < 0.05$ and $**P < 0.01$, for the comparison with the same condition before surgery.

Table 1 *UPDRS scores and L-dopa medication requirements in patients following unilateral subthalamotomy*

	6 months (n = 16)				12 months (n = 15)				24 months (n = 18)			
	Pre-op		Post-lesion		Pre-op		Post-lesion		Pre-op		Post-lesion	
	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON
Total UPDRS	73.4 ± 27.2[†]	36.7 ± 15.0	56.7 ± 25.7**	27.7 ± 10.9**	69.6 ± 26.3	39.5 ± 16.7	58.1 ± 29.1*	31.9 ± 12.6	66.4 ± 25.5	35.5 ± 17.4	53.9 ± 24.2*	31.6 ± 18.6
UPDRS II	21.0 ± 9.4	10.4 ± 7.0	16.9 ± 7.9*	7.9 ± 4.0	19.7 ± 9.4	10.7 ± 8.4	17.1 ± 9.5	7.9 ± 4.2	18.6 ± 8.8	10.0 ± 8.4	16.9 ± 10.5	9.3 ± 7.6
UPDRS III	42.4 ± 15.5	15.8 ± 8.2	34.4 ± 15.8**	14.3 ± 7.7	38.5 ± 14.4	16.5 ± 8.6	33.4 ± 16.1	15.6 ± 6.6	37.5 ± 14.4	14.7 ± 8.4	31.7 ± 12.9*	15.7 ± 8.9
UPDRS IV-a	4.3 ± 3.2		1.8 ± 1.7**		4.4 ± 3.2		2.1 ± 2.6**		4.5 ± 3.2		1.6 ± 1.6**	
UPDRS IV-b	4.6 ± 2.1		2.8 ± 1.6**		5.0 ± 2.3		3.5 ± 2.5**		4.2 ± 2.2		2.6 ± 2.3**	
Contralateral UPDRS III	17.4 ± 5.3	5.9 ± 3.8	11.0 ± 5.1**	3.6 ± 2.9	15.7 ± 4.2	6.2 ± 3.9	9.9 ± 4.8**	3.9 ± 2.3*	16.2 ± 4.9	5.7 ± 4.1	9.8 ± 4.0**	4.6 ± 3.3
Contralateral Tremor	4.6 ± 2.3	1.2 ± 1.5	1.4 ± 1.4**	0.2 ± 0.4**	4.8 ± 2.5	1.8 ± 2.3	1.3 ± 1.1**	0.4 ± 0.8**	4.7 ± 2.3	1.4 ± 2.2	0.9 ± 1.2**	0.1 ± 0.2**
Contralateral Rigidity	4.1 ± 2.3	1.0 ± 1.4	3.1 ± 2.1	0.3 ± 0.5	3.8 ± 2.1	1.0 ± 1.5	3.0 ± 1.9	0.7 ± 1.0	3.8 ± 2.1	0.8 ± 1.2	2.9 ± 1.4	0.8 ± 1.0
Contralateral Bradykinesia	8.7 ± 3.7	3.7 ± 2.6	6.5 ± 3.2	3.1 ± 2.7	7.1 ± 2.7	3.4 ± 1.6	5.5 ± 3.3	2.8 ± 2.0*	7.7 ± 3.5	3.5 ± 2.5	5.9 ± 2.7*	3.7 ± 2.9
Ipsilateral UPDRS III	12.3 ± 6.6	3.3 ± 2.6	11.8 ± 6.8	3.9 ± 3.6	10.7 ± 6.5	3.1 ± 2.4	12.6 ± 6.8	4.9 ± 3.3*	10.1 ± 6.5	2.8 ± 2.3	11.1 ± 5.1	4.9 ± 2.7**
Ipsilateral Tremor	3.4 ± 3.5	0.7 ± 1.3	2.9 ± 2.8	0.7 ± 2.1	3.1 ± 3.1	1.0 ± 1.5	2.7 ± 2.9	0.9 ± 2.2	2.9 ± 3.0	0.8 ± 1.4	1.6 ± 2.1*	0.5 ± 1.1
Ipsilateral Rigidity	3.5 ± 2.3	0.6 ± 0.9	3.2 ± 1.7	0.3 ± 0.6	3.0 ± 2.3	0.5 ± 0.9	3.5 ± 2.0	0.9 ± 1.5	2.9 ± 2.4	0.4 ± 0.7	3.0 ± 1.9	1.2 ± 1.3*
Ipsilateral Bradykinesia	5.3 ± 3.4	1.9 ± 1.6	5.7 ± 4.1	2.8 ± 2.1	4.6 ± 3.6	1.6 ± 1.3	6.3 ± 3.7*	3.1 ± 2.1*	4.3 ± 3.2	1.6 ± 1.6	6.5 ± 3.3**	3.2 ± 2.0**
Off duration	1.8 ± 1.1		0.9 ± 0.6*		1.9 ± 1.3		1.1 ± 1.1		1.8 ± 1.3		1.1 ± 1.1	
Dyskinesia duration	1.8 ± 1.2		0.8 ± 0.7**		1.7 ± 1.2		1.1 ± 1.2		1.7 ± 1.2		0.6 ± 0.6**	
Dyskinesia disability	1.5 ± 1.4		0.6 ± 0.8**		1.3 ± 1.2		0.3 ± 0.7**		1.4 ± 1.3		0.7 ± 1.1**	
Gait disturbance	1.6 ± 1.3	0.6 ± 0.6	1.3 ± 1.1	0.3 ± 0.6	1.3 ± 1.1	0.6 ± 0.5	1.4 ± 1.3	0.6 ± 0.8	1.3 ± 1.2	0.5 ± 0.5	1.3 ± 1.3	0.7 ± 0.9
Postural instability	1.6 ± 1.1	1.1 ± 1.1	1.3 ± 1.1	0.3 ± 0.6	1.7 ± 1.0	1.0 ± 1.1	1.4 ± 1.2	0.9 ± 1.2	1.3 ± 1.1	1.0 ± 1.1	1.3 ± 1.0	1.1 ± 1.1
Speech	1.4 ± 0.9	0.8 ± 0.9	1.1 ± 0.8	1.1 ± 0.9	1.3 ± 0.9	0.8 ± 0.7	1.5 ± 0.9	1.2 ± 0.8*	1.2 ± 0.9	0.8 ± 0.8	1.5 ± 1.0	1.3 ± 1.0*
Global stage of disease ± Hoehn and Yahr	3.1 ± 1.2	2.5 ± 0.9	2.9 ± 0.7	2.5 ± 0.6	3.1 ± 1.3	2.5 ± 0.9	3.0 ± 1.1	2.5 ± 0.9	2.9 ± 1.3	2.4 ± 1.0	3.0 ± 1.1	2.6 ± 1.0
L-dopa ± mg	490.6 ± 319.0		260.9 ± 210.7**		520.0 ± 351.9		286.7 ± 241.6**		480.6 ± 343.9		319.4 ± 234.0*	

[†]Values are shown as mean ± SD. UPDRS = Unified Parkinson's Disease Rating Scale. For all scores, a reduction indicates an improvement in function. UPDRS II = scores for activities of daily living, items 5 – 17, maximal points = 52; UPDRS III = motor scores, items 18 – 31, maximal points = 108; UPDRS IV-a = scores for dyskinesia, items 32 – 35, maximal points = 13; UPDRS IV-b = scores for motor-fluctuations, items 36 – 39, maximal points = 10; Unilateral UPDRS III motor scores, maximal points = 36; Unilateral Tremor subscores, items 20 and 21, maximal points = 12; Unilateral Rigidity subscores, item 22, maximal points = 8; Unilateral Bradykinesia subscores, items 23 – 26, maximal points 16; *$P < 0.05$ for comparison with the condition before surgery; **$P < 0.01$ for comparison with the condition before surgery.

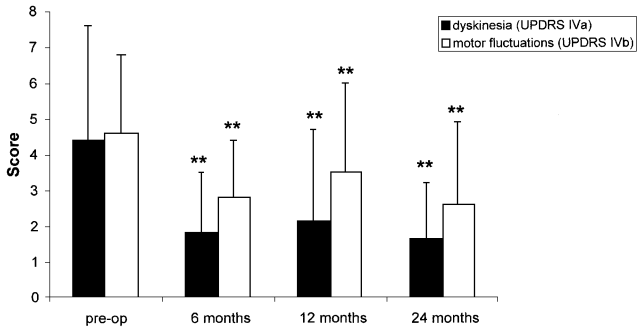

Fig. 4 Mean (± SD) scores for drug-induced dyskinesias and motor fluctuations before and 6, 12 and 24 months after surgery. The subscores are for UPDRS IV-a and IV-b, respectively. $^{**}P < 0.01$, for comparison with the same condition before surgery.

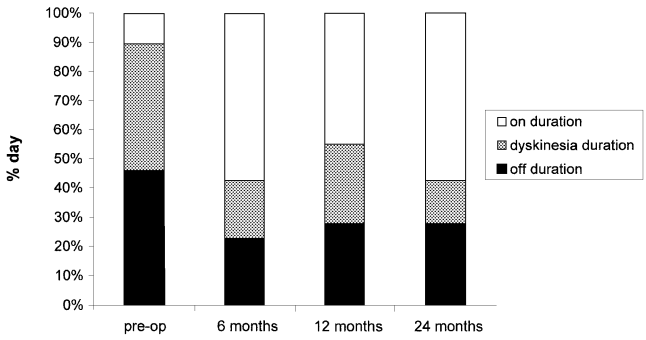

Fig. 5 Mean ON and OFF medication motor fluctuation durations before, and 6, 12 and 24 months after surgery. The dyskinesia and OFF-period durations correspond to items 32 and 39 of UPDRS IV, respectively.

This latter patient had also had a DBS electrode implanted on the left side and when the stimulator parameters were set to control right-sided symptoms optimally, hemiballism was provoked on the left. Her left-sided dyskinesia/hemiballism was ameliorated 2 years later by the insertion of a DBS into the Z1/H2 area on the lesioned side, and this also improved her contralateral bradykinesia.

One patient died from angiotropic B-cell lymphoma 18 months post-surgery. At 6 month follow-up he had shown marked improvement in contralateral UPDRS motor scores, with predominant effect on tremor (Table 2). Examination of the brain after fixation revealed a lesion involving the dorsolateral STN and extending dorsally to involve H2 and ZI (Fig. 7). The histologically defined location of the lesion correlated closely with that determined radiologically on post-operative MRI. Cryostat sections stained with oil red O and by the Marchi method revealed products of fibre degeneration extending from the lesion towards and into (not shown) the globus pallidus [predominantly interna (GPi)], the reticular nucleus of the thalamus, and caudally on the medial aspect of the subthalamus towards the brainstem. In cryostat sections through the midbrain, products of fibre degeneration were visible in the pars reticulata of the substantia nigra. Histology also confirmed the diagnosis of Parkinson's disease, with Lewy bodies in the substantia nigra and locus ceruleus.

Surgical side-effects

One patient experienced problematic dyskinesias until these were ameliorated by further intervention as described above.

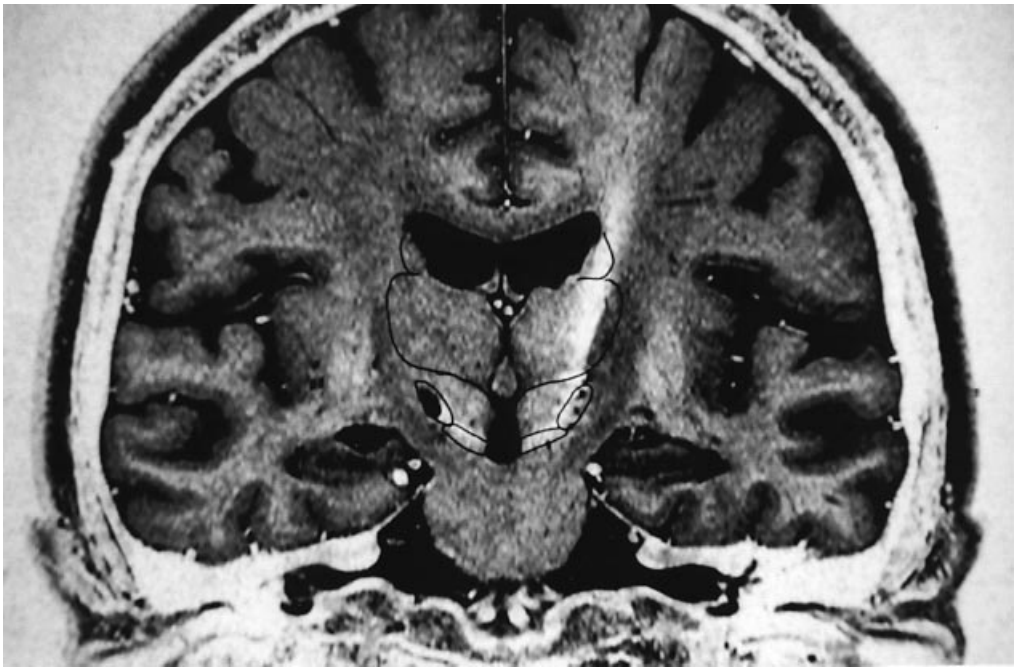

Fig. 6 Interval high-resolution coronal inverted T_2-weighted MRI of the patient with persistent problematic dyskinesia showing a right lesion confined to STN and contralateral STN DBS.

Another patient, with a previous history of seizures, sustained a post-operative grand mal seizure and subsequent Todd's paresis, but recovered fully over the next few days. No patients developed sensory or speech deficits. All 26 patients had high-resolution post-operative MRIs, none of which revealed intracerebral haematoma.

Cognitive assessment of 17 of the patients suggested few adverse cognitive effects of the surgery, although discrete neuropsychological changes in aspects of verbal learning, attention and planning were seen in some patients. Most of test scores (91% of a total of 204 scores) remained unchanged or improved, according to the Reliable Change Index. Only 9% of the test scores showed 'reliable' deterioration. Only two tests, the Stroop and the Rey Auditory Verbal Learning Test, showed >25% probability of reliable deterioration, and this was almost exclusively confined to left subthalamotomy patients and those with subthalamotomy plus contralateral (left) stimulator. Previous analysis of data for 12 patients (McCarter *et al*., 2000) showed no vulnerability of the Rivermead Story Memory Test. However, on analysis of 17 patients, 18% showed deterioration of the Rivermead Story Memory Test. Right subthalamotomy patients had less likelihood of deterioration in cognitive test scores, with only 5% of their scores being reliably lower post-operatively, compared with deterioration in 25% of scores for left subthalamotomy patients and 30% of scores for those with subthalamotomy plus contralateral stimulator.

Table 2 *Motor UPDRS subscores on the patient who died with post mortem confirming a dorsolateral STN/ZI lesion*

	Pre-operative		6 months post-operative	
	OFF	ON	OFF	ON
Contralateral UPDRS III	15	5	7	2
Contralateral tremor	6	1	1	1
Contralateral rigidity	4	3	3	0
Contralateral bradykinesia	5	1	3	1
Ipsilateral UPDRS III	11	3	8	2
Ipsilateral tremor	4	1	2	0
Ipsilateral rigidity	4	1	2	0
Ipsilateral bradykinesia	3	1	4	2

Discussion

Unilateral subthalamotomy resulted in a marked improvement in contralateral motor function in this group of disabled patients. The effects of lesioning were generally most

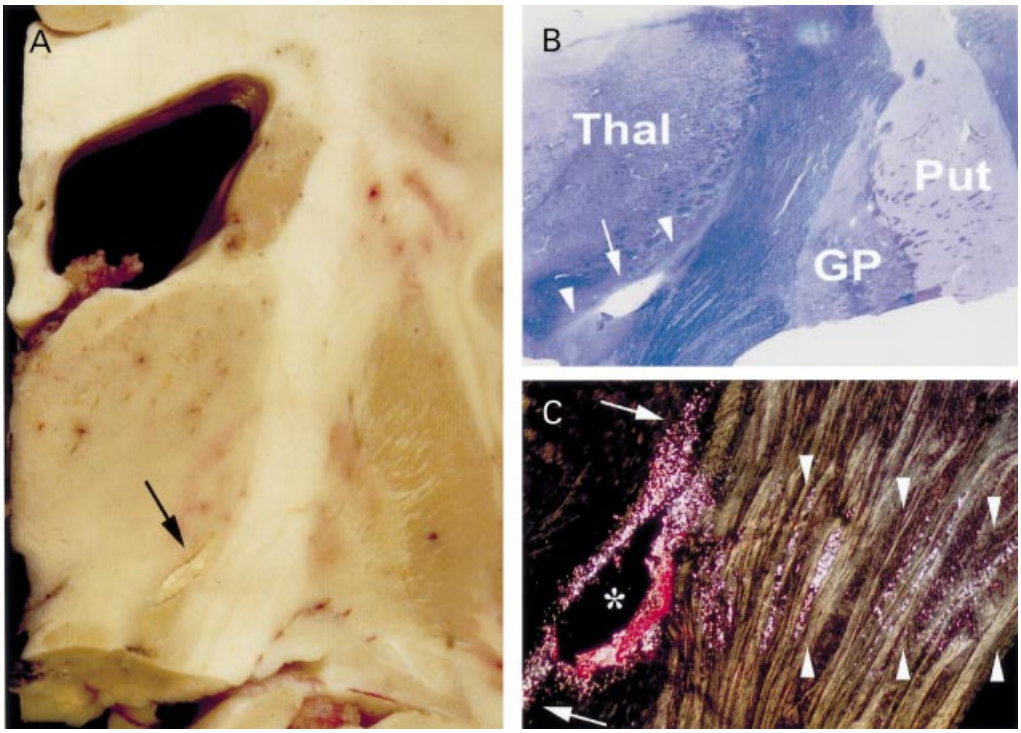

Fig. 7 Autopsy neuropathological findings in the patient who died from angiotropic lymphoma. (**A**) Coronal slice through the fixed brain at the level of the stereotactic lesion (arrow), which involves the upper part of the subthalamus and the H2 field of Forel and overlying ZI. (**B**) The location of the lesion (arrow) is more clearly defined in this crytostat section stained with Luxol Fast Blue and Cresyl Violet. Streak-like zones of slight myelin pallor (arrowheads) extend dorsolateral and ventromedial to the main lesion. Thal = thalamus; Put = putamen; GP = globus pallidus. (**C**) This section has been stained with oil red O and viewed with polarized light, to demonstrate birefringent products of fibre degeneration. An asterisk marks the lesion cavity. Products of fibre degeneration can be seen to extend between the arrowheads, across the internal capsule and towards the GPi. There is further evidence of fibre degeneration extending dorsolaterally (upper arrow) towards the reticular nucleus of the thalamus, and ventromedially (lower arrow) towards the brainstem.

pronounced immediately after surgery, probably related to the contributory effect from perilesional oedema. The three cardinal signs of parkinsonism—bradykinesia, rigidity and tremor—were decreased contralateral to the lesion, with the effect being greatest and significant for parkinsonian tremor. Dyskinesia duration and disability were reduced and motor fluctuations attenuated. Overall, the L-dopa equivalent daily intake was approximately halved. Total daily 'ON' time, without significant dyskinesia, was increased 4-fold. The benefits were maintained throughout the follow-up period, as noted in many of the patients of Alvarez *et al*. (2001). However, unlike Alvarez and colleagues, we found little ipsilateral benefit in our patients, and in fact subscores for bradykinesia confirmed disease progression.

Cognitive testing in a subgroup of the patients suggested that subthalamotomy does not have a wide-ranging adverse effect on cognition. Patients who had undergone left-sided or bilateral surgery had slightly reduced scores for certain aspects of cognition, predominantly verbal memory and aspects of attention. Further studies on larger numbers of patients and comparison with non-operated controls are required to validate these findings and ascertain if 'deterioration' in cognition is a true effect of surgical intervention independent of the effects of disease progression. Although this study demonstrates the efficacy and supports the use of unilateral subthalamotomy for the treatment of asymmetric tremor-dominant Parkinson's disease, some limitations apply. The first concerns the interpretation of clinical scores in patients who had DBS electrodes inserted contralateral to the subthalamotomy. These patients were assessed in the OFF state following overnight withdrawal of medication and stimulation, and despite this, any residual effects of stimulation influencing their general condition cannot be entirely excluded. The second concerns the use of the UPDRS to score performance unilaterally; however, this seemed the most reasonable way to assess laterality of effect, and has been used in other studies (Alvarez *et al*., 2001).

Unilateral STN DBS, like subthalamotomy, results in major improvement in contralateral tremor (Krack *et al*., 1997; Kumar *et al*., 1999) and can also be helpful in patients with highly asymmetrical tremor-dominant Parkinson's disease. Thalamic lesions or stimulation are as effective as subthalamotomy or STN stimulation in reducing parkinsonian tremor, but do not produce meaningful improvement in other motor aspects of the disease (Ondo *et al*., 1998). Unilateral pallidotomy has comparable effects on contralateral drug-induced dyskinesias, rigidity and bradykinesia, with similar limited effects on gait, balance and speech. The effects of pallidotomy on tremor are more variable than those of subthalamotomy, and unlike pallidotomy, STN stimulation and lesioning allow a reduction in L-dopa intake by ~50% and consequent reduction in generalized dyskinesia. The effects of bilateral STN DBS have been more extensively documented (Limousin *et al*., 1998); patients demonstrate substantial improvement in most aspects of OFF-state parkinsonism, including gait and postural stability. Bilateral STN DBS has been shown to improve parkinsonism considerably more than does unilateral STN DBS (Limousin *et al*., 1995; Kumar *et al*., 1999).

The abnormal patterns of high frequency neuronal activity of the STN, which are a feature of the parkinsonian state, drive the inhibitory output of nuclei of the basal ganglia, leading to oversuppression of thalamocortical and brainstem nuclei. Loss of this excitatory drive is presumed to be the reason for the beneficial effect of STN lesioning and DBS. Experimental lesions of the STN in MPTP-treated monkeys reverse contralateral akinesia, rigidity and postural tremor, but may also induce hemichorea/ballism (Bergman *et al*., 1990; Aziz *et al*., 1991, 1992; Guridi *et al*., 1994). This occurs more often and is more likely to persist after excitotoxic (Bergman *et al*., 1990; Guridi *et al*., 1994) than thermolytic lesions (Aziz *et al*., 1991, 1992), possibly because excitotoxins cause selective damage to neurons within the nucleus (Olney, 1974; Hammond, 1979), whereas thermolytic lesions also destroy traversing or adjacent pallidofugal fibre tracts (Aziz *et al*., 1991, 1992). We and others have found that lesioning of the STN for treatment of Parkinson's disease rarely induces hemichorea/ballism (Gill and Heywood, 1997, 1998; Alvarez *et al*., 2001; Barlas *et al*., 2001). This may be due in part to the reduction in L-dopa, possible after STN lesioning, which presumably reduces the susceptibility of primed direct pathway striatal neurons to fire inappropriately and suppress abnormal patterns of GPi neurons leading to the expression of dyskinesia. On the other hand, it is interesting to note that our two patients with lesions confined to STN and not involving H2/ZI had problems with ballism and dyskinesia, and in one of the patients with a lesion confined to the STN (Fig. 6) dyskinesia was subsequently ameliorated by DBS in the H2/Z1/STN region. Indeed, lesions of H2/Z1 have been used to treat hemiballism (Krauss and Mundinger, 1996). H2 pallidofugal fibres carry inhibitory efferent information from the GPi to thalamocortical and brainstem nuclei. The role of the ZI remains uncertain; in animal models it becomes hyperactive after nigrostriatal denervation (Perier *et al*., 2000). Interestingly, we also found at *post mortem* that a small lesion confined predominantly to the H2/ZI region (Fig. 5) resulted in a profound effect on contralateral motor UPDRS scores with predominant effect on tremor (Table 2). Perhaps some of the effectiveness of subthalamotomy is attributable to a combination of disconnecting the dorsolateral STN from its cortical and thalamic (centromedian/parafascicular nuclei) inputs and its outputs from GPi and the pars reticulata of the substantia nigra; to a reduction in ZI hyperactivity; and to the antidyskinetic and antiparkinsonian effects of lesioning the H2 pallidofugal fibres. Furthermore, DBS has shown that the most effective contact of the quadripolar electrode is in the upper part of the STN recording area or immediately above it, suggesting a role of this region in the clinical effectiveness of the STN electrical stimulation (Lanotte, 2002).

DBS is rapidly gaining favour for the treatment of medically intractable Parkinson's disease. It allows modifi-

cation of stimulation parameters and of the target of influence, by selecting different active contacts. Perhaps most importantly, DBS is reversible and would therefore not preclude patients from receiving emerging restorative therapies. However, there are drawbacks associated with DBS, such as the need for intensive, specialized medical assistance to achieve optimal clinical benefit, and for periodic surveillance to ensure the correct functioning of the system. Stimulators are bulky, can be uncomfortable for the patient, and need replacement every 3–5 years. Complications of DBS include electrode migration, electrode fracture, electrical/mechanical problems with the pulse generator, and potential hazards associated with induction by external electromagnetic fields. There is also a risk of infection. In addition, both the placement and maintenance of stimulators remains an expensive option. It is likely that economic and geographical pressures will dictate that STN lesioning continues to be used in many parts of the world. We conclude from this study that unilateral subthalamotomy is a safe and effective alternative to unilateral DBS, mainly in the treatment of asymmetrical tremor-dominant Parkinson's disease; however, expertise for accurate target localization remains a prerequisite and further careful outcome studies are essential.

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