Voluntary movement after pallidotomy in severe Parkinson’s disease

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Summary

The mechanisms of improvement in parkinsonian bradykinesia after posteroventral pallidotomy were investigated in 17 patients undergoing unilateral pallidotomy for severe Parkinson’s disease. Clinical ratings of ‘off’ period bradykinesia demonstrated a maximal improvement of 22% 3 months postoperatively. Kinematic assessments of rapid repetitive finger and sequential arm movements were performed after overnight withdrawal of antiparkinsonian medications. There was a bilateral reduction in the inter-onset latency of a two-stage sequential arm movement and a contralateral increase in speed of arm movement after pallidotomy. There was no significant improvement postoperatively in the rhythm, amplitude or speed of repetitive finger movements. The results confirm the clinical impression that pallidotomy improves bradykinesia. This was more evident for complex limb movements, which used attentional strategies and external (visual and auditory) cues, than for repetitive finger-tapping movements, which were largely internally generated. Since ablation of the pallidum can only reduce inhibitory pallidal outflow, it is unlikely to restore the normal pallidal influence on thalamocortical motor circuits. Therefore, any improvement in bradykinesia after pallidotomy must be related to mechanisms other than restoration of pallidothalamic cortical connectivity. Based on the above observations, we suggest that some of the changes in motor control may be explained by the greater efficacy of external cues in facilitating movement after withdrawal of the abnormal pallidal discharge.

Keywords: pallidotomy; Parkinson’s disease; bradykinesia; movement; kinematic

Abbreviations: ADL = activities of daily living; GPi = internal globus pallidus; IOL = inter-onset latency; SMA = supplementary motor area; UPDRS = unified Parkinson’s disease rating scale

Introduction

Stereotactic posteroventral pallidotomy has regained popularity as a treatment for idiopathic Parkinson’s disease, especially in the late stages of disease when drug therapy is complicated by motor fluctuations. An increasing body of evidence indicates that pallidotomy improves both drug-induced dyskinesias and the signs of parkinsonism, such as tremor, rigidity, bradykinesia and akinesia (Lahtinen et al., 1992; Dogali et al., 1995; Lozano et al., 1995; Baron et al., 1996; Fazzini et al., 1997; Kishore et al., 1997; Lang et al., 1997; Ondo et al., 1998; Samuel et al., 1998; Shannon et al., 1998). These studies have mostly used clinical rating scales to demonstrate the improved facility of movement. However, the mechanism and extent of improvement in ‘off’ period bradykinesia after pallidotomy have not been studied in detail.

This study examines the kinematics of unrestrained upper limb movement before and after pallidotomy. The aims of the study were to investigate the extent and nature of changes in quantitative assessments of movement performance after pallidotomy in patients with Parkinson’s disease, and the relationship of any kinematic changes to alterations in clinical motor function and bradykinesia.

Patients and methods

Patients

Seventeen patients (10 males, 7 females) aged 45–75 years (mean age 61 years) underwent unilateral pallidotomy (Table 1). Lesions were left-sided in 11 cases and right-sided in six. Two patients had undergone contralateral pallidotomy approximately 1 year previously and the remaining 15 had undergone no prior neurosurgical procedures. The clinical characteristics of the patients are summarized in Table 1. All had Parkinson’s disease according to the diagnostic criteria of Calne et al. (1992), comprising at least three of the following five features: (i) rigidity; (ii) bradykinesia;
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Fig. 1 Position traces of the index finger during a tapping movement. The position traces were derived from a goniometer placed across the second metacarpophalangeal joint while tapping the index finger on a table top. The amplitude of each tap was measured from each trough to the following peak. The tapping interval was measured from peak to peak. Movement of the parkinsonian patient (lower two panels) is smaller in amplitude than that of the normal subject (top panel). Postoperatively (bottom panel) there is some improvement in movement amplitude. Note that as part of a concerted effort by the parkinsonian patient to maintain a large amplitude movement, the first tap is much larger than those that follow. Note also that in the parkinsonian patient, rhythm is irregular and interrupted by lower-amplitude taps (arrows).

Table 1 Characteristics of patients at time of surgery

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>61.4 ± 8.6</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>12.9 ± 4.9</td>
</tr>
<tr>
<td>Hoehn and Yahr score in off state</td>
<td>3.4 ± 0.6</td>
</tr>
<tr>
<td>UPDRS motor score in off state</td>
<td>38.1 ± 15.1</td>
</tr>
<tr>
<td>Schwab and England ADL score (%)</td>
<td>71.9 ± 11.2</td>
</tr>
</tbody>
</table>

Surgical procedure

Surgery was performed on the side opposite the worst affected limbs (as judged by dyskinesia severity in most cases) or, in the case of symmetrical disease, on the side opposite the dominant hand. Surgery was performed after overnight withdrawal of medication with the patient in the ‘off’ motor state. MRI of the head was performed preoperatively to determine the length of the intercommissural plane. The stereotaxic co-ordinates of the medial segment of the globus pallidus were computed from a computed tomogram of the brain and head. The initial target was located 2–3 mm below the intercommissural plane, 20–22 mm lateral to the midsagittal plane and 3 mm anterior to the mid-commissural plane, as described by Laitinen (1992). Under local anaesthesia, a 1.8-mm diameter electrode with a 2-mm exposed tip was introduced into this target. Electrical stimulation was performed at low (5 Hz) and high (75–100 Hz) frequencies. The site of the lesion was then established by the motor effects observed during macrostimulation. At this target, evoked motor activity in the contralateral arm was frequently observed at low-frequency stimulation. The response to high-frequency stimulation consisted of a variable increase in muscle tone. Visual scintillations indicated that the electrode tip was too caudally placed, in the optic tract, and flexor contraction of the limb indicated proximity to the internal capsule. The first lesion was usually 2 mm below the intercommissural plane. The electrode was then advanced another 2 mm inferiorly and the same procedure was repeated. If the clinical result was favourable after two lesions, the procedure was terminated at this point. In other cases, the electrode was advanced another 1 mm inferiorly and the above procedure was repeated. Lesions were made at 75–78°C for 60 s.

Determination of lesion size and location

Lesion location was determined by CT of the brain 1 day postoperatively, with 2 mm slices through the basal ganglia. Contiguous CT images were reviewed to determine the site and dimensions of the pallidal lesion. Mean location of the centre of the lesions was 2.4 mm below the intercommissural plane (SD 1.4 mm, range 0–5 mm), 3.1 mm anterior to the midsagittal plane (SD 1.9 mm, range 0–7.5 mm) and 22.6 mm lateral to the midsagittal plane (SD 1.7 mm, range 0–5 mm). All patients had long-standing levodopa-responsive Parkinson’s disease with disease duration ranging from 7 to 25 years (mean disease duration 12.9 years). All exhibited significant motor fluctuations on conventional drug therapy, including dyskinesias, wearing-off effects and unpredictable ‘off’ periods. The study was approved by the Ethics Committee of the Royal Adelaide Hospital. Subjects gave informed consent to the studies described in this report.

(iii) tremor; (iv) asymmetrical onset and slow progression; (v) substantial and sustained response to levodopa at some stage during the illness; (vi) absence of other neurological or systemic disease.
Table 2 Results (mean ± standard error) of clinical rating scales, Purdue pegboard tests and levodopa doses at baseline and 2–4 weeks, 3 months and 6 months postoperatively

<table>
<thead>
<tr>
<th></th>
<th>Score range</th>
<th>Baseline (n = 17)</th>
<th>2–4 weeks (n = 14)</th>
<th>3 months (n = 15)</th>
<th>6 months (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>0–176</td>
<td>67.4 ± 4.5</td>
<td>49.9 ± 4.7</td>
<td>53.5 ± 4.9</td>
<td>59.3 ± 5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cognition</td>
<td>0–16</td>
<td>2.8 ± 0.6</td>
<td>3.4 ± 0.6</td>
<td>3.3 ± 0.6</td>
<td>3.8 ± 0.7</td>
<td>0.29</td>
</tr>
<tr>
<td>‘off’ Motor</td>
<td>0–52</td>
<td>18.4 ± 1.2</td>
<td>16.0 ± 1.2</td>
<td>16.5 ± 1.2</td>
<td>19.0 ± 1.3</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Ipsilateral bradykinesia</td>
<td>0–108</td>
<td>38.1 ± 2.6</td>
<td>30.5 ± 2.7</td>
<td>29.5 ± 2.8</td>
<td>33.9 ± 3.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Contralateral bradykinesia</td>
<td>0–6</td>
<td>7.0 ± 0.7</td>
<td>7.3 ± 0.7</td>
<td>6.4 ± 0.7</td>
<td>7.1 ± 0.8</td>
<td>0.324</td>
</tr>
<tr>
<td>Dystrokinesias</td>
<td>0–13</td>
<td>8.1 ± 0.7</td>
<td>6.1 ± 0.7</td>
<td>6.3 ± 0.7</td>
<td>7.1 ± 0.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Clinical fluctuations</td>
<td>0–6</td>
<td>5.7 ± 0.5</td>
<td>2.3 ± 0.5</td>
<td>2.3 ± 0.5</td>
<td>2.4 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral pegboard</td>
<td>0–25</td>
<td>16.4 ± 1.5</td>
<td>18.5 ± 1.4</td>
<td>17.4 ± 1.3</td>
<td>15.2 ± 2.4</td>
<td>0.326</td>
</tr>
<tr>
<td>Contralateral pegboard test</td>
<td>0–25</td>
<td>14.8 ± 1.6</td>
<td>17.5 ± 1.5</td>
<td>18.3 ± 1.7</td>
<td>14.9 ± 2.2</td>
<td>0.102</td>
</tr>
<tr>
<td>Hoehn and Yahr score</td>
<td>0–5</td>
<td>3.4 ± 0.1</td>
<td>2.8 ± 0.1</td>
<td>2.7 ± 0.1</td>
<td>2.8 ± 0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Schwab and England (%)</td>
<td>0–100</td>
<td>71.9 ± 2.4</td>
<td>81.1 ± 2.5</td>
<td>81.8 ± 2.5</td>
<td>78.8 ± 2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Levodopa dose (mg/day)</td>
<td>1041 ± 106</td>
<td>1081 ± 119</td>
<td>1067 ± 127</td>
<td>1097 ± 117</td>
<td></td>
<td>≥0.01</td>
</tr>
</tbody>
</table>

With the exception of the Schwab and England scale, higher scores on the rating scales indicate more severe dysfunction. Significance values are derived from ANOVA across the time intervals shown.

20–25 mm). The mean horizontal extent of the lesions was 10.4 mm (SD 2.2 mm, range 7.5–13.2 mm) and the mean dorsoventral extent was 6.8 mm (SD 2.1 mm, range 4–12 mm). Since the horizontal extent of the lesions was consistently greater than the dorsoventral extent, the lesions were assumed to be spheroidal in shape. Mean lesion volume was 282 mm$^3$ (SD 218, range 74–942 mm$^3$), calculated using the equation for volume of a spheroidal object $[\text{volume} = \frac{4}{3}\pi a b^2]$, where $a$ is half the longer axis of the spheroid and $b$ is half the shorter axis of the spheroid. These measurements overestimate the lesion size by including postoperative oedema. Follow-up scans 1 year postoperatively showed a 50% reduction in lesion size. Accordingly, final lesion size was estimated to be ~100 mm$^3$, comparable to the size of pallidal lesions in other reports (Laitinen et al., 1992; Lozano et al., 1997).

Clinical assessment

Patients were assessed preoperatively, then 2–4 weeks (14 subjects), 3 months (15 subjects) and 6 months (12 subjects) postoperatively using the Unified Parkinson’s Disease Rating Scale (UPDRS) version 3.0 (Fahn et al., 1987), incorporating assessments of (i) mentation, behaviour and mood; (ii) activities of daily living (ADL); (iii) motor examination; and (iv) complications, including separate categories for dyskinesias and clinical fluctuations. Using a method described by previous authors (Lozano et al., 1995; Lang et al., 1997), scores for components 23–26 of the UPDRS motor subset, which assess finger-taps, open–shut hand movements, pronation–supination hand movements and leg agility, respectively, were added to give a clinical bradykinesia score. Apart from dyskinesias and clinical fluctuations, which were given a global score applicable to both ‘on’ and ‘off’ states, UPDRS scores were recorded when patients were examined in the ‘off’ motor state, at least 12 h after withdrawal of antiparkinsonian drugs (Langston et al., 1992). The severity of Parkinson’s disease was also rated using the scale of Hoehn and Yahr (1967). In addition to the ADL score derived from the UPDRS scale, ADL performance was rated by the patient using the scale of Schwab and England (1969). All patients were videotaped at the time of rating for later independent verification of rating scores.

Assessment of upper limb movement

All the studies of upper limb function were conducted when patients were clinically parkinsonian after overnight withdrawal of medication.

Global arm function

The Purdue pegboard test (Tiffin, 1948) was used as an initial assessment of global upper limb and finger movement. Patients were required to place as many pegs as possible into the pegboard in 1 min. Each hand was tested separately. The mean score of three trials was recorded.
Rapid finger movements

Patients were seated at a table with the forearm resting unrestrained on the table top. A single-axis goniometer (model G35; Penny and Giles, Gwent, UK) was attached across the second metacarpophalangeal joint to record changes in finger position. The patient was then asked to tap the index finger as quickly and regularly as possible on the table until at least 20 repetitions had been performed. The aim of this manoeuvre was to examine objectively the amplitude, rhythm and speed of repetitive finger movements. Repetitive tapping finger movements have little or no reliance on external cues and as such are internally generated.
movements. Decay in the amplitude of such movements and slowness in their execution is a cardinal clinical feature of parkinsonian bradykinesia. Right and left hands were examined. Off-line analysis of the goniometer tracing was then performed and measurements were made of the speed, rhythm and amplitude of finger-tapping. Time intervals between the first 10 taps were used in all analyses. The degree of variation among these values was measured from the residual mean square error calculated by fitting a linear regression to the values over time. With regular tapping, individual values would show little variation and the residual mean square error would be small, while irregular tapping

Fig. 3 Mean (± standard error) tapping intervals during repetitive finger-tapping, showing the results for sides ipsilateral and contralateral to pallidotomy. On the contralateral side there was a reduction in mean tapping interval at all assessment times postoperatively compared with preoperatively, but this was not significant (P > 0.01). On both sides and at all assessment times the mean tapping interval declined from the first to the final tap in the sequence. Although this decline was not statistically significant for any single assessment time, when results of all assessment times were pooled and analysed together (top panel) this decline was significant contralaterally (*P < 0.01) but not ipsilaterally (P = 0.04) to pallidotomy.
would be associated with greater variation in tapping interval and a higher residual mean square error. Speed of fingertapping was measured from the length of the intervals between successive taps, the ‘tapping interval’. Shorter tapping intervals during the task indicated more rapid tapping, and longer intervals indicated slower tapping. Amplitude of fingertapping was measured from the goniometer trace of finger position.

Sequential upper limb movement (‘pick-up’ task)

Patients were seated in the same position as for the rapid finger-tapping movement experiment described above. The thumb and index finger were positioned on either side of a small peg standing upright on the table top. In response to an auditory signal, the subject was instructed to grasp the peg between the thumb and index finger, flex the elbow to lift the peg to the nose and then return the peg to the table. A single-axis goniometer (G35; Penny and Giles) was placed over the second metacarpophalangeal joint and a twin-axis goniometer (M180; Penny and Giles) was placed over the elbow joint to record finger and limb position, respectively. The goniometer over the elbow joint measured movements in the flexion-extension axis only. Movement onset and speed of movement at each joint were measured from the position traces. Patients were instructed to carry out the movement as quickly as possible. No other instructions were given and no visual cues were provided about movement trajectory or progress. Prior to recording, patients practised the task until they were proficient at it. At least ten repetitions of the task were then recorded. Reaction time from the auditory signal to movement onset, the interval between the onset of movement at the metacarpophalangeal joint and elbow [inter-onset latency (IOL)] and peak angular speed of elbow movement were measured for each of at least ten trials. The mean value of each measurement was then calculated for each subject.

Statistical analysis

Each variable was analysed separately and in turn. A repeated measures analysis of variance was used for the within-subject factor of time of measurement (preoperatively and on three occasions postoperatively). Separate analyses were performed for the sides ipsilateral and contralateral to surgery. As data were missing for some subjects at certain time points postoperatively, an unbalanced repeated measures analysis of variance was used [program 5V of the BMDP Statistical Software Package (Dixon, 1993)].

Inspection of the pooled data of finger-tapping amplitude and interval indicated that a linear relationship existed between these variables and time during the tapping sequence. For this reason, a model of linear regression was applied to these data.

A $P$ value $<0.01$ was considered significant in all analyses in order to take account of the multiple comparisons performed.

Results

Clinical assessment

Results obtained from the various clinical rating scales and the levodopa dose preoperatively and 2–4 weeks, 3 months and 6 months postoperatively are shown in Table 2. There were maximal improvements of 25–30% in the mean ‘off’-state total UPDRS score ($P < 0.001$) and the mean ‘off’ motor score at 3 months ($P < 0.01$) compared with preoperative values. On the side contralateral to surgery, the mean bradykinesia score improved by 22% at 3 months compared with preoperative values ($P < 0.01$), but did not change on the side ipsilateral to surgery. The total dyskinesia score had improved by 58% 6 months postoperatively ($P < 0.001$). The latter result represented a mean improvement of $\sim$90% in contralateral dyskinesias and 30% in ipsilateral dyskinesias. Scores for mentation, behaviour and mood and clinical fluctuations did not change postoperatively. The total UPDRS score ($P < 0.01$) and the patient-rated ADL performance, measured by the Schwab and England scale ($P < 0.0001$), improved significantly postoperatively, but ‘off’ ADL scores were not significantly different 6 months postoperatively after small improvements at earlier assessments. The Schwab and England scale represents a global assessment of ADL performance in both ‘on’ and ‘off’ states and the greater degree of improvement in this measure is likely to have been influenced by the reduction in dyskinesias. The mean ‘off’-state Hoehn and Yahr score improved from 3.4 preoperatively to 2.8 at 3 and 6 months postoperatively ($P < 0.0001$).

The improvements in total UPDRS, motor and bradykinesia scores had begun to decline at the 6-month follow-up. The improvements in dyskinesia, Hoehn and Yahr score and Schwab and England score remained stable at the 6-month assessment.

Movement kinematics

Global arm function

Slight improvements in mean pegboard scores were seen on both sides postoperatively. However, these changes were not statistically significant on either side (Table 2).

Rapid finger movements

An example of the index finger position trace during rapid finger movements from a normal subject and a patient with Parkinson’s disease (pre- and postoperatively) is shown in Fig. 1. In the patient group, tapping amplitude progressively declined during the course of the task. When all assessment times (pre- and postoperatively) were pooled and analysed together for each side, there was a significant decline in
finger-tapping amplitude during the task on both sides (Fig. 2). On the side ipsilateral to pallidotomy there was a 27% decline in mean tapping amplitude from tap 1 to tap 10 in the sequence ($P < 0.01$), and on the contralateral side there was a 24% decline over this interval ($P < 0.01$). The tapping amplitude was greater on both sides at all three postoperative assessment times than preoperatively. However, when each assessment time was considered independently, this trend was not significant on either side after pallidotomy (Fig. 2).

At each assessment time, mean tapping interval shortened bilaterally during the sequence so that patients tended to tap the index finger more rapidly at the end of the task than at the beginning (Fig. 3). When all assessment times (pre- and postoperative) were pooled and analysed together for each side, the shortening of the mean tapping interval was significant on the contralateral ($P < 0.01$) but not the ipsilateral ($P = 0.04$) side to the pallidotomy. On the contralateral side, mean tapping interval was shorter at all postoperative assessment times compared with preoperatively, but this was not statistically significant (Fig. 3).

Analysis of the degree of variation in tapping interval at each assessment time did not detect any change in postoperative tapping rhythm compared with preoperatively ($P > 0.01$).

**Sequential upper limb movement (pick-up task)**

Inter-onset latency (IOL) during the pick-up task improved significantly on the side ipsilateral to pallidotomy (Figs 4 and 5). On this side, the improvement in mean IOL was maximal 3 months after pallidotomy, with a 36% reduction compared with preoperative values ($P < 0.001$). Six months after pallidotomy, the 21% improvement compared with preoperative values in mean IOL on the ipsilateral side was no longer significant ($P = 0.05$). There was no significant change in auditory reaction time or peak elbow speed on the side ipsilateral to surgery (Fig. 5).

On the side contralateral to surgery, both IOL and peak elbow speed significantly improved postoperatively. Improvement in mean IOL was maximal 3 months after pallidotomy, with a 32% reduction compared with preoperative values ($P < 0.001$) (Fig. 5). At 6 months the improvement in mean IOL on the contralateral side had fallen to 23% compared with preoperative values and was no longer significant ($P = 0.05$). Mean peak elbow speed contralateral to the side of surgery increased by 29% compared with preoperative values ($P < 0.001$) at 3 months (Fig. 5). At 6 months, the increase in mean peak elbow speed had fallen to 19% compared with preoperative values and was no longer significant ($P = 0.05$). There was no significant change postoperatively in auditory reaction time for the arm contralateral to surgery (Fig. 5).

Five of the patients who exhibited the most marked clinical improvement after pallidotomy also showed the most dramatic changes in movement kinematics. However, there was no clear relationship between the degree of clinical improvement in bradykinesia (measured by the change in UPDRS motor score) and IOL and velocity of movement during the pick-up task for the overall group (linear regression: $R^2 = 0.22$, $F = 0.34$, $P = 0.57$).

**Discussion**

**Effects of pallidotomy on clinical assessments of motor performance**

This study has demonstrated a number of changes in both clinical assessments and objective kinematic analyses of motor function after posteroventral pallidotomy in advanced Parkinson’s disease. In keeping with results from other series, the most dramatic effect of pallidotomy was a reduction in drug-induced dyskinesias in the ‘on’ motor state. In addition, ‘off’ motor function, of which bradykinesia is a major feature, also improved. The total UPDRS, motor subset and clinical bradykinesia scores when ‘off’ fell by 20–25%, comparable to the changes reported in clinical rating scales in other studies of pallidotomy in Parkinson’s disease (Lozano et al., 1995; Baron et al., 1996; Fazzini et al., 1997; Kishore et al., 1997; Lang et al., 1997; Samuel et al., 1998; Scott et al., 1998; Shannon et al., 1998). At the 6-month postoperative assessment there was a trend for the total UPDRS scores and the motor subset ratings to return towards baseline values, a finding also evident in other studies (Baron et al., 1996; Samuel et al., 1998; Shannon et al., 1998). However, overall ADL performance, as judged by the Schwab and England scale, improved significantly and was maintained throughout the study period, suggesting that the major functional effects of posteroventral pallidotomy were related to a sustained reduction in drug-induced dyskinesias.

**Effects of pallidotomy on quantitative assessments of movement performance**

The main interest of the present findings lies in the kinematic assessment of upper limb movement as this provides an insight into the mechanism of any changes in ‘off’-period bradykinesia after pallidotomy. When ‘off’, a bilateral improvement of ~35% in IOL during sequential arm movement was evident 3 months postoperatively, corresponding to the 23% improvement in the ‘off’-period UPDRS motor score. The bilateral effect on the quality of movement mirrors the bilateral reduction in dyskinesias and the bilateral improvement in some ‘off’ motor scores after unilateral pallidotomy (Lozano et al., 1995; Baron et al., 1996; Lang et al., 1997). These bilateral effects are in accord with the observations that 10–20% of pallidal efferents project to the contralateral ventral thalamic nuclei (Hazrati and Parent, 1991) and that neurons of the internal pallidal segment in monkeys rendered parkinsonian by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) exhibit responsiveness to both ipsilateral and contralateral limbs (Filion et al., 1988).
Fig. 4 Position traces of movement at the second metacarpophalangeal and elbow joints while subjects picked a peg from a table top, lifted it towards their nose and returned the peg to the table (the pick-up task). Single trials are shown in response to an auditory cue. In A the position traces from a patient with Parkinson’s disease are superimposed on those from a control subject. The reaction times are comparable, but the amplitude of finger movement is smaller and the interval between activation of the finger and elbow movement (inter-onset latency) is longer in the patient (IOL_{PD} = 747 ms) compared with the normal subject (IOL_{N} = 273 ms). Preoperative peak elbow velocity is also slightly lower in the parkinsonian patient (119°/s) than in the normal subject (128°/s). In B the postoperative performance of the same parkinsonian patient 3 months after pallidotomy, using the hand contralateral to pallidotomy, is superimposed on the preoperative traces. Postoperatively, the inter-onset latency (IOL_{post}) shortens to 402 ms and the peak elbow velocity increases to 166°/s.

Fig. 5 Summary of ipsilateral (open columns) and contralateral (filled columns) auditory reaction time, inter-onset latency and peak elbow speed for ipsilateral and contralateral limbs (relative to the side of pallidotomy) during the pick-up task. Results are mean ± standard error. Postoperative values that differ significantly (P < 0.01) from preoperative values are denoted by an asterisk.

The magnitude of change in IOL at 3 months was almost identical on the two sides, yet clinical ratings of bradykinesia and the speed of elbow movement improved only on the contralateral side after pallidotomy. This suggests that the reduction in IOL and increased movement speed may have combined to effect the improvement in bradykinesia on the contralateral side, even though movement speed does not correlate closely with clinical assessments of bradykinesia in Parkinson’s disease (Benecke et al., 1987).

The internal globus pallidus and bradykinesia in Parkinson’s disease

Clinical ratings of bradykinesia and akinesia correlate more with the degree of IOL prolongation than the speed of individual movements, suggesting that prolongation of the IOL may account for much of the slowness of complex movements and bradykinesia in Parkinson’s disease (Benecke et al., 1987). The IOL is derived from the time taken to link a series of individual movements into a complex sequence, which is believed to be a function of the supplementary motor area (SMA) (Benecke et al. 1987). Single-cell recordings in monkeys (Mushiake et al., 1991) and cerebral blood flow studies in humans (Dieber et al., 1991; Samuel et al., 1997a) reveal involvement of the globus pallidus, SMA and dorsolateral prefrontal area in the performance of internally generated complex movements. In the monkey, phasic discharges in internal globus pallidus (GPI) neurons herald the switch from one movement task to another in a movement sequence, and it has been suggested that this pallidal activity is conveyed to the SMA to halt one movement and start another (Brotchie et al., 1991).

Neuronal activity in the GPI is increased in MPTP-induced
parkinsonism in monkeys (Filion and Tremblay, 1991) and in patients with Parkinson’s disease undergoing pallidotomy (Sterio et al., 1994; Lozano et al., 1996). This pattern is reversed by apomorphine (Hutchinson et al., 1997), reinforcing the notion that the abnormal pallidal neuronal activity of parkinsonism is a consequence of dopamine deficiency. Impaired activation of the putamen and SMA during the performance of complex movements in Parkinson’s disease (Playford et al., 1992) is also partly reversed by apomorphine (Jenkins et al., 1992) and levodopa (Rascol et al., 1994). These observations emphasize the central contribution of the abnormal GPi and SMA to bradykinesia in Parkinson’s disease and have encouraged the re-examination of pallidotomy.

**Mechanisms of improvement in bradykinesia after pallidotomy**

The shortening of the IOL and increased speed of movement in the present study, along with the greater facility of movement after pallidotomy in previous reports, appears consistent with the concept that the pallidal lesion disrupts excessive GPi inhibition of the SMA. Functional imaging of the brain during arm movements after contralateral pallidotomy in Parkinson’s disease has shown a relative increase in cerebral blood flow in the SMA and dorsolateral prefrontal cortex (Ceballos-Baumann et al., 1994; Samuel et al., 1997b), and at rest a reduction in thalamic metabolism accompanied by an increase in lateral premotor, dorsolateral premotor and primary motor cortical metabolism (Eidelberg et al., 1996). These findings suggested that pallidotomy may reduce inhibitory pallidothalamic outflow and restore motor control by improving activation of motor cortical areas.

The present results also demonstrate that pallidotomy improves ‘off’ motor performance in Parkinson’s disease, at least in the short term. However, it remains surprising that a lesion of the abnormal pallidum can restore motor performance (Marsden and Obeso, 1994). Partial ablation of the overactive pallidum would be expected to reduce pallidal inhibitory outflow to the ventral thalamus and increase thalamocortical excitatory activity, but is unlikely to restore the normal phasic pallidal activity. Accordingly, the pallidal lesion would not be expected to restore phasic pallidothalamic modulation of SMA activity. Since functional imaging suggests that there is an increase in prefrontal motor cortex activity after pallidotomy, this change and any improvement in facility of movement must occur by mechanisms other than the restoration of pallidal communication with motor cortical areas. Such mechanisms may include the use of auditory, visual, attentional and somatosensory signals, which can act as alternative cues to trigger the execution of movement. The use of such cues in facilitating movement is well recognized in Parkinson’s disease (for example, paradoxical hyperkinesia). This mechanism may also contribute to the relative increase in cerebral blood flow in lateral premotor and inferolateral parietal regions in Parkinsonian patients performing a complex finger keypad task (Samuel et al., 1997a). Indeed, these authors concluded that Parkinsonian patients ‘switch from the use of striatomesial frontal to parietal-lateral premotor circuits in order to facilitate performance of complex finger movements’ (Samuel et al., 1997a). We suggest that this phenomenon may be one explanation for the improvement in sequential movement after pallidotomy in Parkinson’s disease. Various external cues may gain greater access to motor areas once the aberrant pallidal outflow is reduced or eliminated, or they may be used more effectively in the absence of the abnormal pallidal signals.

Accordingly, improvement in ‘off’ motor performance after pallidotomy does not occur by restoring normal function within subcortical–cortical connections. Rather, by attenuating or reducing abnormal pallidal activity, pallidotomy may allow alternative motor strategies to influence the cortical control of movement. There is some support for this hypothesis from functional imaging studies after pallidotomy. Increases in movement-associated regional cerebral blood flow or cortical metabolism in the SMA and dorsolateral prefrontal cortices after pallidotomy are consistent with the restoration of pallidocortical communication (Ceballos-Baumann et al., 1994; Grafton et al., 1995; Samuel et al., 1997b). However, in several of these studies the alterations in cortical function were also evident in the lateral premotor cortex (Ceballos-Baumann et al., 1994; Grafton et al., 1995), parietal association cortex (Ceballos-Baumann et al., 1994) and visual association areas (Samuel et al., 1997b), which do not receive direct inputs from the globus pallidus. Similar changes were present in one study performed at rest (Eidelberg et al., 1996). In this study there was no alteration in resting SMA metabolism after pallidotomy (Eidelberg et al., 1996). One explanation for these findings may be the greater utilization of auditory, somatosensory and visual inputs to the lateral premotor areas to facilitate movement (Goldberg et al., 1985).

**Effects of pallidotomy on different movements**

In contrast to the complex arm movements, there was no change in the speed or rhythm of finger-tapping movements after pallidotomy and the subtle improvement in repetitive finger-tapping amplitude did not reach statistical significance. A comparatively weak effect of pallidotomy on finger-dexterity 1 year postoperatively (Baron et al., 1996) has been noted previously in clinical studies.

The apparent difference in the effect of pallidotomy on these two movements is of interest and may provide further insight into the effects of pallidotomy on Parkinsonian movement. It is necessary first to consider the different qualities of these two motor tasks. The pick-up task consists of two discrete movements, involving anatomically separate...
parts of the limb, linked together as a ‘complex’ movement. In contrast, finger-tapping involves fractionated finger movement alone, the maintenance of which is largely an internal process without external cues. Therefore, it could be argued that finger-tapping is more critically dependent on normal pallidal–SMA function than the complex arm movement. Indeed, decay in the amplitude of repetitive finger-tapping is a robust clinical sign of dyskinesia in Parkinson’s disease. In performing the pick-up task after pallidotomy, compensation for absent pallidal function may be achieved by using the auditory, somatosensory and visual cues inherent to that task. Such cues may also improve movement performance in the absence of the abnormal pallidal output. The finger-tapping task, however, did not use external cues and was more reliant on internal cues and intact basal ganglion function to maintain the rhythm and amplitude of movement. It would be of interest to examine whether this movement, which does not normally involve external factors, could be influenced by an external cue, for example a metronome, to improve performance, and whether this effect would be greater after pallidotomy.

Duration of effects of pallidotomy
The clinical and kinematic improvements in ‘off’ motor function appeared to be declining by 6 months postoperatively in this study, in contrast to the sustained alleviation of dyskinesias. In several other studies of pallidotomy in Parkinson’s disease, the extent of improvement in ‘off’ motor performance also appeared to decline somewhat between 3 and 6 months after surgery (Baron et al., 1996; Shannon et al., 1998), while in others the beneficial effects persisted (Lang et al., 1997; Fazzini et al., 1997). This raises the important question as to whether differences in surgical technique and the final lesion site could influence clinical outcome and motor performance. Differences in surgical technique have not altered the effectiveness in abolishing dyskinesia, while lesion volume does not appear to influence clinical outcome (Eidelberg et al., 1996; Samuel et al., 1998). Those studies in which the site of pallidal ablation was guided by microelectrode recordings of pallidal cell discharge appear to have the most sustained and longest effect on ‘off’ motor function (Lang et al., 1997; Fazzini et al., 1997), though in other studies using comparable techniques varying degrees of decline in ‘off’ motor performance are evident from the published data (Baron et al., 1996; Samuel et al., 1998; Shannon et al., 1998).

Another issue that will potentially influence the localization of the optimal target and therefore contribute to clinical outcome after pallidal surgery is the complexity of the pallidal efferent systems, and whether the critical lesion ablates sensorimotor pallidal neurons or one or more of the pallidal efferent tracts. Two efferent systems emerge from the internal pallidum; the ansa lenticularis from the ventral and outer GPi, and the lenticular fasciculus from the dorsal and inner GPi. Both combine in Forel’s field H and ultimately project to the ventral thalamus. A third pallidal efferent emerges from the external globus pallidus and projects to the subthalamic nucleus (Beck and Bignami, 1968; Kuo and Carpenter, 1973). Recent observations from pallidal stimulation in patients with Parkinson’s disease have suggested these pallidal projections have different functional properties. Stimulation of the dorsal GPi improves mobility and rigidity when ‘off’ but induces dyskinesias. Stimulation of the ventral (posteroventral) GPi reduces dyskinesias but decreases mobility and the response to levodopa (Bejjani et al., 1997; Krack et al., 1998). These differential effects following stimulation of different parts of the pallidum or pallidal outflow tracts may also apply after pallidotomy. Posteroventral pallidal lesions are most effective in abolishing dyskinesia and have a less dramatic impact on voluntary movement, as in the present series. In those series with enduring improvements in ‘off’ motor performance (Lang et al., 1997), the final lesions, guided by microelectrode mapping of the sensorimotor pallidum, have been anterior and dorsal to the original posteroventral target location proposed by Laitinen (1992) [as emphasized by Lozano et al. (1996)]. Further studies are required to investigate whether the emerging functional segregation within the pallidum and pallidal efferents will lead to further refinements in selection of the pallidal target and to greater objective improvements in ‘off’ motor performance after pallidotomy.

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