The effects of posteroventral pallidotomy on the preparation and execution of voluntary hand and arm movements in Parkinson’s disease

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Summary

We studied the effect of posteroventral pallidotomy on movement preparation and execution in 27 parkinsonian patients using various motor tasks. Patients were evaluated after overnight withdrawal of medication before and 3 months after unilateral pallidotomy. Surgery had no effect on initiation time in unwarned simple and choice reaction time tasks, whereas movement time measured during the same tasks was improved for the contralesional hand. Movement times also improved for isometric and isotonic ballistic movements. In contrast, repetitive, distal and fine movements measured in finger-tapping and pegboard tasks were not improved after pallidotomy. Preparatory processes were investigated using both behavioural and electrophysiological measures. A precued choice reaction time task suggested an enhancement of motor preparation for the contralesional hand. Similarly, movement-related cortical potentials showed an increase in the slope of the late component (NS2) when the patients performed joystick movements with the contralesional hand. However, no significant change was found for the early component (NS1) or when the patient moved the ipsilesional hand. The amplitude of the long-latency stretch reflex of the contralesional hand decreased after surgery. In summary, the data suggest that pallidotomy improved mainly the later stages of movement preparation and the execution of proximal movements with the contralesional limb. These results provide detailed quantitative data on the impact of posteroventral pallidotomy on previously described measures of upper limb akinesia in Parkinson’s disease.

Keywords: Parkinson’s disease; pallidotomy; motor function

Abbreviations: CRT = choice/complex reaction time; IT = initiation time; MRCP = motor-related cortical potential; MT = movement time; pcCRT = precued complex reaction time; SMA = supplementary motor area; SRT = simple reaction time

Introduction

Limitations of drug therapy in the long-term medical management of Parkinson’s disease have led to a renewal of interest in functional neurosurgery for severely disabled parkinsonian patients. At the present time, posteroventral pallidotomy is one of the most widely used techniques, and there are already many reports of its clinical effects on the major symptoms of Parkinson’s disease (Svennilson et al., 1960; Laitinen et al., 1992; Dogali et al., 1995; Lozano et al., 1995; Baron et al., 1996; Lang et al., 1997; Samuel et al., 1998; Scott et al., 1998). Virtually all confirm the dramatic reduction in drug-induced dyskinesias. However, many of the other symptoms respond less well. Off-period akinesia and rigidity show a more modest improvement of ~30%, whilst gait, balance and other axial signs are largely unchanged. The effect can be bilateral even after unilateral lesions, although the improvement is generally greater on the side contralateral to the lesion.

The aim of the previous studies has been to quantify the effectiveness of pallidotomy as a medical treatment, and as such, in virtually all of them investigators have assessed function with clinical rating scales. However, clinical scales often hide much of the complexity of the underlying motor dysfunction. The aim of the present study was to provide some insight into this complexity by measuring the effect of pallidotomy using various of the physiological and psychomotor techniques that have been used previously to
study akinesia in patients with Parkinson’s disease. We have focused on akinesia/bradykinesia for two reasons. First, akinesia is the symptom of Parkinson’s disease most closely related to striatonigral dopamine depletion (Vingerhoets et al., 1997). Secondly, the rationale for posteroventral pallidotomy comes directly from the physiological model of basal ganglion function that deals mainly with symptoms of hyper- and hypomobility (Alexander et al., 1986, 1990; Alexander and Crutcher, 1990; DeLong, 1990; Wichmann and DeLong, 1996). This model predicts that in Parkinson’s disease, lesions of the overactive pallidal output to primary, premotor and supplementary motor areas (SMAs) should lead to an improvement in the processes of movement preparation, initiation and execution.

The tests we have used can be divided broadly into two main categories: (i) tests of preparation and initiation of movement, and (ii) tests of movement execution. The former included a series of reaction time tests and recordings of the premovement EEG activity. For the latter we measured movements that were aimed or non-aimed, simple or complex, proximal or distal. Finally, to test the possible contribution of excessive stretch reflexes, we measured the size of the EMG response to phasic stretch in wrist flexor muscles.

**Patients**

Twenty-seven patients with idiopathic Parkinson’s disease (19 men and 8 women) were evaluated before and 3 months after unilateral pallidotomy. Ten patients were operated on the right globus pallidus internus and 17 on the left, as indicated by clinical need. Their mean age (the right globus pallidus internus and 17 on the left, as after unilateral pallidotomy. Ten patients were operated on (19 men and 8 women) were evaluated before and 3 months after surgery, all suffered from a severe form of Parkinson’s disease with motor fluctuations. The range of the Hoehn and Yahr score before surgery was 2.5–5 in the off-drug state and 2–4 in the on-drug state. The target was located using CT scanning and microrecordings. The surgical technique is detailed elsewhere (Samuel et al., 1998). Owing to patient disability and practical constraints of the tests, not all tests could be performed on every patient. The clinical characteristics of the patients who took part in each experiment are given in Table 1. All patients gave informed consent prior to participating in the study and the combined

### Table 1 Clinical characteristics of the patients for each task

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<th>Task</th>
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<td><strong>n</strong></td>
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<tr>
<td>Task 1: SRT and CRT</td>
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<td>Task 5: MRCP</td>
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Mean ± SEM. 

*Ethical Committee of The Institute of Neurology and The National Hospital for Neurology and Neurosurgery approved the procedures.*

**Method**

Patients were evaluated in the morning on successive days, after overnight withdrawal of medication. Both upper limbs were studied and results concerning the limb ipsilateral and that contralateral to surgery were averaged separately.

### Unwarned simple reaction time and choice reaction time (n = 16)

Patients performed an unwarned visual simple reaction time (SRT) task and choice reaction time (CRT) task as described previously (Brown et al., 1993a). The response apparatus had six buttons, each 2.5 cm in diameter. The two central buttons served as the ‘home’ keys for the left and right hands and two pairs of response keys were situated 20 cm above and below the central keys. In the SRT task, one home key and one of the upper response keys were exposed. In the CRT task, all six keys were exposed. Stimuli were presented on a computer screen. A central cross acted as a fixation point. The patient initiated each SRT trial by placing the index finger of either the right or the left hand on the home key. After a random and variable delay of 2–6 s, the imperative stimulus appeared. This was a 1-cm solid square, which appeared at the fixation point. The patient had to respond as quickly as possible by moving the finger from the home key to the appropriate response key. The time from the appearance of the target to the lifting of the finger from the home key was the response initiation time (IT). The time from this to the pressing of the response key was the movement time (MT). Patients received auditory feedback that a response had been made. The patients then returned, in their own time, to the home key, thus initiating the next trial. The time until the next imperative stimulus varied randomly between 2 and 5 s. Patients received 40 SRT trials with each hand, the order counterbalanced across patients. Median IT and MT were calculated for each hand.

In the CRT task, patients placed the index fingers of their right and left hands on the two home keys. The imperative
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Fig. 1 Simple and complex reaction time tasks before and 3 months after surgery. SRT = simple reaction time (or initiation time); SMT = simple movement time; CRT = complex reaction time (or initiation time); CMT = complex movement time (see text for statistics).

stimulus was a square appearing above or below and to the right or left of the fixation point in pseudorandom order. Patients had to respond by moving their index finger to the upper or lower response keys with the appropriate hand. Median IT and MT for each hand were measured as before. Patients received 80 trials, half with the left hand and half with the right. Equal numbers of responses were made to the upper and lower keys.

Precued choice initiation time (n = 17)
To determine the precued choice initiation time (pcCRT), the task was similar to the unwarned CRT task with the exception that the patients were provided with a precue that informed them in advance about where the imperative stimulus was going to appear (Jahanshahi et al., 1992a). The precue was the outline of a square in the stimulus location. After a variable delay (S1–S2 interval) the outline was filled, at which point the patient had to respond as before. The duration of the S1–S2 interval was 200, 800, 1600 or 3200 ms. A control condition was recorded with the precue at the same time as the ‘go’ signal. Eighty trials were given: 16 for each interval in pseudorandom order, with an equal number of responses to each of the four response keys. Median IT was calculated for the two hands for each of the five S1–S2 intervals.

Pegboard and finger-tapping (n = 21)
These two tasks were administered as described previously (Brown et al., 1993b; Brown and Jahanshahi, 1998). The pegboard task involved peg placement using the Purdue pegboard (Purdue Research Foundation, 1948). Patients had to pick up metal pegs (3 × 25 mm) one by one from a well in front of them, and place the pegs in a vertical row of holes drilled into a board. Patients performed the task three times, once with the right hand, once with the left hand and once with both hands simultaneously. On each occasion, the patients had to place as many pegs as possible in a 30-s period. Unimanual and bimanual peg scores were calculated for each hand for each 30-s period.

In the tapping task, patients were required to tap a response button repetitively using the index finger for 30 s. The button had full travel of ~4 mm and activated a standard 150 g microswitch. The tapping task was performed three times, once with the left hand, once with the right and once bimanually. Unimanual and bimanual tapping scores were calculated for each hand for each 30-s period.

In addition to performing the tapping and pegboard tasks individually, the patients also performed a combined task. In this, they tapped with one hand while placing pegs with the other. Both hand combinations were assessed. Patients were instructed to do both tasks as well as they could, and not to concentrate on one to the exclusion of the other. As before, scores for the two hands were calculated for each of the combined tasks. One patient was unable to perform this combined task preoperatively.

Flex and squeeze (n = 18)
Patients were comfortably seated on a chair, the forearm was flexed through 90°, resting on a manipulandum, and the hand held a vertical grip containing a strain gauge. Patients performed two types of movement, a 20° flexion of the elbow and an isometric 30 N hand squeeze (Benecke et al., 1986, 1987a, b). The position of the manipulandum and the strength developed were displayed by means of two vertical bars on an oscilloscope screen, placed 1.5 m in front of the patient, allowing visual control of the amplitude of the movement. Patients were instructed to execute a self-paced movement, as fast as possible, and were informed that the end-point accuracy was less important. Different tasks using these two movements were studied: (i) isolated flexion of the elbow (simple flex); (ii) isolated hand squeeze (simple squeeze); (iii) simultaneous flexion of the elbow and hand squeeze (complex flex and complex squeeze).

After three to five training runs, patients performed 10–15 movements in each condition. The two hands were studied successively. Movement data were recorded and analysed off-line. Movement times were determined by visual
inspection from the point where the position trace deflected reliably from the baseline to the end-point of the task, when the speed of the movement reached a zero level.

Movement-related cortical potential (n = 12)
To determine movement-related cortical potential (MRCP), patients were seated in a comfortable chair and required to perform self-initiated joystick movements at the rate of ~1 per 5–10 s, in a randomly chosen direction, either left, right, forwards or backwards. They held the joystick between the thumb and the index finger. Sixty to 80 movements without eye movement or other artefacts were recorded for each hand.

Twelve EEG channels were recorded, using silver–silver chloride electrodes fixed with collodion, in a monopolar configuration with a linked earlobe reference. Electrodes were placed in three sagittal rows, according to the 10–20 international system and three additional electrodes in FC (F3, FC3, C3, P3 in the left side, Fz, FCz, Cz, Pz on the midline and F4, FC4, C4, P4 on the right side). EMG activity of the first dorsal interosseous and the abductor pollicis brevis was recorded with surface electrodes. EEG and EMG signals were amplified and filtered using Digitimer D 150 amplifiers (Digitimer Ltd, Welwyn Garden City, Herts, UK). A 5-s time constant and 100 Hz high-frequency cut-off were used for EEG signals and a 3-ms time constant and 3 kHz high-frequency cut-off for EMG signals. EEG activity was recorded on a PC computer via an analogue/digital converter.

Fig. 2 Initiation time according to the interval between the cue and the go signal in the precued choice reaction time task before and 3 months after surgery (see text for statistics).
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Fig. 3 Finger-tapping and pegboard tasks before and 3 months after surgery. uni = task executed with one hand; bi = task executed with both hands; PEG + tap = number of pegs picked up when the other hand is tapping; TAP + peg = number of taps when the other hand is picking up pegs (see text for statistics).

(CED1401 Plus, Cambridge Electronic Design, Cambridge, UK) using SigAvg software (Cambridge Electronic Design) to collect data sweeps of 4 s (3 s before and 1 s after joystick movement) at a sampling rate of 250 Hz.

EEG activity was back-averaged off-line after manual realignment of the traces to movement onset. A grand average was calculated for each hand. As some patients were operated in the left and others in the right globus pallidus internus, channels were arranged in order to obtain an average for the channels of the hemisphere ipsilateral to surgery and an average for the channels of the hemisphere contralateral to surgery. The early (NS1) and the late (NS2) components of the averaged MRCP were identified by visual inspection. The onset of the early component was set at the onset of the rise of the slope from baseline and the end at the point of change of the slope, which corresponded to the onset of the late component. The end of the late component corresponded to the time of onset of EMG activity. The slopes of each component were measured.

Forearm flexors stretch reflex (n = 11)

Stretch reflex of the forearm flexors was measured in both arms. Patients were seated on a chair with the forearm secure in position, and the hand was placed in a wrist manipulandum, which could induce extensions of the wrist by means of a torque motor attached to the underside of the manipulandum. The patient was instructed to keep the hand in a rest position between the stretches, with a slight extension of the wrist, helped by the visual display of the hand position on an oscilloscope screen. The torque motor applied a constant strength of 8 N and the patient had to develop a basal steady contraction of the forearm flexors to keep the hand in the rest position. Additionally, every 3–5 s the motor induced a sudden extension of the wrist with three levels of force (13, 26, 39 N) in random order, each lasting 200 ms. Rectified EMG activity of the forearm flexors was recorded with surface electrodes by back-averaging to the wrist position, with a 3-ms time constant and a 3-kHz high-frequency cutoff. Data were recorded for 300-ms sweeps 50 ms before and 250 ms after the movement using the same equipment as described for MRCP recordings. Sixteen responses were averaged in each condition. The latency and duration of the responses were measured using visual inspection. The amplitude of the response was defined as the ratio of the average amplitude of the response to the average background activity. We log-transformed the ratio before statistical analysis.

Statistics

Analysis of variance for repeated measures was carried out using the GLM (general linear model) procedure of SPSS (SPSS Inc., 1996). Time (pre-/postsurgery) and hand (ipsilesional/contralateral) were within-subject factors in all analyses. Other within-subject factors were used as detailed below for individual measures. Statistics for non-significant
results

Unwarned SRT and CRT task

Hand, time and task (SRT/CRT) were within-subject factors. Initiation time (IT) and movement time (MT) were analysed separately.

For IT, patients were reliably slower in the CRT task than in the SRT task, as expected (Fig. 1) \[F(1,15) = 146.9, P < 0.001\]. However, the effect of neither hand nor time was significant, although there was a trend for patients to show a greater preoperative–postoperative difference for the contralesional hand \[F(1,15) = 4.3, P < 0.06\]. Average IT across tasks for the ipsilesional hand decreased from 543 ± 28 ms preoperatively to 526 ± 29 ms postoperatively (Fig. 1), while the contralesional hand showed a larger decrease, from 559 ± 29 to 511 ± 28 ms. None of the interaction terms were significant.

A similar analysis was carried out on the MT data. None of the interactions involving task were significant, and so averaged MT across tasks was considered. Analysis revealed a significant hand × time interaction \[F(1,15) = 6.6, P < 0.05\]. Average MT for the contralesional hand improved from 581 ± 55 to 426 ± 35 ms \[F(1,15) = 7.1, P < 0.05\], while the ipsilesional hand improved non-significantly from 497 ± 47 to 433 ± 33 ms.

A final analysis was performed to compare the relative improvements in IT and MT, averaged across the two tasks. The average improvement in MT was significantly greater than the improvement in IT \[F(1,15) = 12.1, P < 0.01\]. However, there was no differential effect of hand relative to surgery \[time × IT/MT × hand, F(1,15) < 1\].

Precued choice initiation time

As with the above analyses, hand and time were two of the within-subject factors in the ANOVA (analysis of variance). The third factor was S1–S2 interval. Only the IT data are reported here (Fig. 2). Because the main purpose of the analysis was to look for differential effects of time and hand at the various S1–S2 intervals, the interactions will be considered first. Analysis revealed a significant three-way (task × hand × interval) interaction \[F(4,13) = 3.6, P < 0.05\]. With the exception of the expected effect of S1–S2 interval on IT \[F(4,13) = 16.9, P < 0.001\], none of the other main effects or interactions were significant.

To help interpret the three-way interaction term, the two hands were considered separately. The ipsilesional hand showed no time × interval interaction, with a similar decrease in IT with increasing S1–S2 interval on the two occasions. However, a significant interaction was found for the contralesional hand \[F(4,13) = 4.3, P < 0.05\]. Further post hoc \(t\) tests comparing pre- and postsurgery data revealed that the patients were significantly faster after surgery, with an 800 ms precue interval \(t(1,16) = 3.9, P < 0.01\), but no difference was found with shorter or longer S1–S2 intervals.

Finger-tapping and pegboard tasks

For the simple tasks (finger-tapping and the pegboard task performed alone), task (unimanual/bimanual) was used as a within-subject factor. Patients tapped more in the unimanual than in the bimanual condition (average taps ± SEM across hand and time: 89.3 ± 5.7 for the unimanual task and 77.3 ± 5.9 for the bimanual) \[task, F(1,20) = 34.3, P < 0.001\] (Fig. 3). None of the other main effects were significant. There was no difference between the hands or across time. None of the two-way or three-way interaction effects were significant.

Similar results were found for the pegboard task. Patients performed better with the unimanual task than with the bimanual \[task, F(1,20) = 72.8, P < 0.001\] (average across hands and time, 6.9 ± 0.8 for the unimanual task and 4.5 ± 0.6 for the bimanual task) (Fig. 3). The main effect of hand just reached significance \[F(1,20) = 4.2, P = 0.05\]. The contralesional hand was more impaired than the ipsilesional hand before the operation and remained so.
Table 2  Slope of the early and the late part of the MRCP (µV/s) (mean ± SEM) before (t0) and 3 months after surgery (t3)

<table>
<thead>
<tr>
<th>Electrode location</th>
<th>Hand contralateral to surgery</th>
<th>Hand ipsilateral hand to surgery</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Early t0  Early t3  Late t0  Late t3</td>
<td>Early t0  Early t3  Late t0  Late t3</td>
</tr>
<tr>
<td>FCc</td>
<td>2.32 ± 0.88  3.88 ± 1.12  4.76 ± 1.29  8.14 ± 1.31</td>
<td>1.46 ± 0.65  2.23 ± 0.78  5.68 ± 1.22  2.85 ± 1.80</td>
</tr>
<tr>
<td>Cc</td>
<td>3.71 ± 0.77  3.21 ± 0.97  5.99 ± 1.67  8.80 ± 1.01</td>
<td>2.76 ± 0.90  1.42 ± 0.93  5.77 ± 1.19  5.01 ± 1.78</td>
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<tr>
<td>Fz</td>
<td>3.69 ± 0.97  3.62 ± 1.10  3.77 ± 1.09  7.57 ± 1.60</td>
<td>1.68 ± 0.54  1.39 ± 0.50  5.81 ± 1.53  3.52 ± 1.72</td>
</tr>
<tr>
<td>FCz</td>
<td>4.56 ± 1.00  4.58 ± 0.96  5.89 ± 1.61  9.80 ± 1.76</td>
<td>3.03 ± 0.75  3.03 ± 0.83  8.10 ± 1.10  6.36 ± 1.60</td>
</tr>
<tr>
<td>Cz</td>
<td>5.54 ± 1.00  4.61 ± 1.17  7.89 ± 1.91 13.00 ± 1.99</td>
<td>4.20 ± 1.28  3.03 ± 0.91 11.55 ± 1.63 11.54 ± 2.50</td>
</tr>
<tr>
<td>Pz</td>
<td>4.06 ± 1.17  1.57 ± 1.39  2.94 ± 1.59  7.44 ± 1.58</td>
<td>2.40 ± 0.84  0.57 ± 0.52  4.61 ± 1.45  4.66 ± 1.63</td>
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<tr>
<td>FCi</td>
<td>2.75 ± 0.82  2.35 ± 0.84  2.99 ± 1.16  7.06 ± 1.05</td>
<td>2.86 ± 0.97  1.84 ± 0.88  6.90 ± 1.13  4.72 ± 1.66</td>
</tr>
<tr>
<td>Ci</td>
<td>4.26 ± 1.02  2.88 ± 0.78  4.52 ± 1.47  9.35 ± 1.28</td>
<td>3.52 ± 1.33  2.93 ± 0.97  9.20 ± 1.58  8.57 ± 2.01</td>
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* = hemisphere contralateral to the hand moving; i = hemisphere ipsilateral to the hand moving.

Fig. 5 Movement-related cortical potentials before (grey curve) and after pallidotomy (black curve). Mean data from all patients performing a joystick movement with the contralesional hand (A) or the ipsilesional hand (B) (see text for statistics).

was no significant effect of the simultaneous tapping performance on the number of pegs placed (Fig. 3). In contrast, tapping performance deteriorated substantially when performed with the pegboard task compared with tapping performed alone \(F(1,19) = 313.9, P < 0.001\). However, none of the main effects and interactions involving time or hand were significant and there was no differential effect of time on the combined relative to unimanual task.

**Flex and squeeze task**
Analyses were performed as above, with hand, time, task (flexion/squeeze) and complexity (simple movement/complex movement) as within-subject factors. As previously reported, movement time to perform the complex task was longer than movement time to perform the simple task (Benecke et al., 1986, 1987a, b) [complexity, \(F(1,17) = 11.8, P < 0.005\)]. Contralesional arm and ipsilesional arm were differently influenced by surgery, as shown by a significant time × hand interaction \(F(1,17) = 6.8, P < 0.05\). In addition there was a significant task × time × complexity interaction \(F(1,17) = 8.4, P < 0.05\).

To help interpret these interactions, the two sides were then considered separately. For the ipsilesional arm, there was no significant change in MT after surgery (Fig. 4). For the contralesional arm, MT was significantly faster after surgery \(time, F(1,17) = 11.0, P < 0.005\) (Fig. 4). In addition, for the contralesional arm the improvement in flex MT was greater in the complex than in the simple task \(time × complexity interaction, F(1,17) = 9.1, P < 0.01\). This time × complexity interaction was not significant for the squeeze task.

**Movement-related cortical potential**
The MRCPs recorded when patients performed joystick movements are presented in Fig. 5 and the slopes of the central and frontocentral electrodes in Table 2. The slopes of the early and the late components were analysed separately. Because of the sample size it was necessary to consider sets of electrodes in separate analyses.
The first analysis considered the four midline channels. Hand, time and site (Fz/FCz/Cz/Pz) were the within-subject factors. The analysis of the late slope showed a significant hand × time interaction [$F(1,11) = 8.9, P < 0.05$]. To help interpret this interaction we considered the two hands independently. For movements made by the contralesional hand, the slope of the late component increased significantly after surgery [time, $F(1,11) = 5.8, P < 0.05$], whereas the ipsilesional hand showed no significant change (Table 2). For the slope of the early component, none of the interactions were significant (Table 2).

The second analysis considered the three central channels. Hand, time and side (C ipsilesional side/Cz/C contralesional side) were the within-subject factors. For the late slope, the only significant interaction was hand × time [$F(1,11) = 5.99, P < 0.05$]. To help interpret this interaction we considered the two hands independently. The slope of the late component increased significantly after surgery when movements were made by the contralesional hand [time, $F(1,11) = 6.1, P < 0.05$]. There was no significant difference in the effect of surgery according to the side. The ipsilesional hand showed no significant change.

**Forearm flexor stretch reflex**

The latency, duration and amplitude ratio (see Method) were analysed separately for the early and the late components of the stretch reflex. Level (of torque), side and time were within-subject factors. The amplitude increased with the level of torque applied both for the early [$F(2,8) = 16.41, P < 0.005$] and the late [$F(2,8) = 131.41, P < 0.001$] components. The early component ratio did not change with time. Considering the late component, the ratio decreased in both arms after surgery (Fig. 6). The time × level interaction was significant only for the contralesional arm when analysed separately [$F(2,8) = 7.62, P < 0.05$]. Further post hoc $t$ tests revealed that the effect of time was significant for the highest level of torque [$t(1.9) = 2.30, P < 0.05$]. The duration of the late component was decreased after surgery [$F(1,6) = 8.13, P < 0.05$], independently of the hand, from $57.05 \pm 2.92$ ms before surgery to $53.28 \pm 4.33$ ms after surgery (average across torques and hands). The duration of the early component did not change significantly ($18.60 \pm 1.36$ ms before surgery and $20.8 \pm 1.63$ ms after surgery). The latency of the late component was increased from $54.67 \pm 2.00$ ms before to $56.82 \pm 1.80$ ms after surgery and the increase was close to statistical significance [$F(1,6) = 5.35, P = 0.06$]. The latency of the early component did not change significantly ($27.33 \pm 1.04$ ms before surgery and $28.01 \pm 2.21$ ms 3 months after surgery).

**Discussion**

In the discussion, we will consider the effect of pallidotomy on the processes involved in both the preparation and execution of voluntary upper limb movement. The results will be discussed in relation to patterns of impairment previously described in patients with Parkinson’s disease and the known effects of dopaminergic therapy. Finally, we will consider the implications for current pathophysiological models of akinesia in Parkinson’s disease.

**Movement preparation**

Three measures in the present results give some insight into the effects of pallidotomy on movement preparation: simple versus choice reaction time, precued reaction times and premovement EEG activity.

**Simple versus choice reaction time**

Simple reaction times are faster than choice reaction times in part because subjects have the chance to prepare in advance the movement they will have to make at the time of the ‘go’ signal. Several authors have reported a selective impairment in SRT relative to CRT in patients with Parkinson’s disease in comparison with healthy subjects, and concluded that patients do not prepare as well as normal subjects for forthcoming movements (Evarts et al., 1981; Bloxham et al., 1984; Sheridan et al., 1987; Pullman et al., 1988; Goodrich et al., 1989). However, patients may also have difficulty in keeping a prepared motor response in store, and this may be an additional factor which could affect simple more than choice reaction time. The present study did not include a control group, but we were able to compare our data with data from previous studies using the same procedures. The patients of the present study were more severely affected (Hoehn and Yahr range, 2.5–5; mean, 3.6) than the patients of the previous study (Hoehn and Yahr range, 1–3; mean, 2.1) (Brown et al., 1993a). Preoperatively, the patients’ SRT was slower than data obtained in our previous study in parkinsonian patients (Brown et al., 1993a) (previous data mean IT, 390 ms), but their preoperative CRTs were similar to previous data (previous data mean IT, 670 ms). This suggests that the more severe disease of the patients in the present study was reflected in a differential slowing of SRT, the condition in which advance preparation is possible. However, while pallidotomy led to a modest, non-significant improvement in IT there was no differential effect on the two tasks.

**Precued reaction times**

Whilst simple and choice reaction times reflect the ability of patients to prepare and maintain preparation for a forthcoming movement, the precued task investigates the time needed to use advance information to speed up response initiation. A cue about the next movement is given at different times in advance of a reaction signal. Healthy subjects can use the cue to speed CRT to the level of SRT if information is presented 800 ms before the reaction signal (Jahanshahi et al., 1992a). In contrast, our patients needed 3200 ms to...
achieve the full benefit of the advance information when they were tested before the operation, confirming the result of our previous study (Jahanshahi et al., 1992a). Postoperatively, marked benefit was seen at 800 ms, but only for responses with the contralesional hand. The patients had become more like normal subjects in terms of the speed with which they could incorporate advance information into their movement plan. However, they remained slow in the time needed to translate this plan into movement.

The fact that this effect was restricted to the contralesional hand is of interest. The use of cues to prepare movements in advance is considered to depend on conscious, attention-demanding processes (Goodrich et al., 1989). If pallidotomy had improved these, we might have expected both sides to be affected. A more likely explanation is that the cue was used to improve later, purely motor stages of movement preparation, which are more lateralized. Requin (1992) divided motor preparation into three stages. First, a decision is made on the goal of the movement (e.g. reach for a glass). This is held to be non-motoric and symbolic. Next, there is the motor programme, which is also non-motoric and specifies relatively abstract response parameters. Finally, there is the formulation of the motor commands necessary to perform the specific action. The present results suggest that pallidotomy decreases the time needed to incorporate cue information into this last stage.

**Premovement potentials**

The average EEG activity preceding self-paced voluntary movements is usually divided into two phases, the NS1 (or BP) and the NS2 (or NS’, MP) components. Subdural recordings indicate that the early part of the potential is generated in the bilateral supplementary and primary motor cortices, whilst later activity is more lateralized and dominant in the primary motor cortex (Ikeda et al., 1992). Previously, some reports have shown differences between parkinsonian patients and controls mainly in the early portion of the MRCP (Dick et al., 1989; Feve et al., 1992; Jahanshahi et al., 1995; Touge et al., 1995). This was also true of the present sample in their preoperative condition compared with data in normal subjects obtained in previous studies (mean amplitude at Cz: normal subjects, 4.9 µV in Touge et al., 1995; patients in the current study, 3.3 µV for movements of the contralesional hand). However, perhaps because of their advanced clinical state, we also found that the NS2 component was smaller than normal (normal subjects, 8.1 µV in Touge et al., 1995; patients in the current study, 4.3 µV).

Pallidotomy resulted in a selective increase in the amplitude of the later, NS2 component of the potential. In the context of the reaction time results, this is consistent with the idea that the lesion produces its effect by enhancing the later stages of movement preparation rather than any earlier preparatory processes.

**Movement execution**

Movement execution was measured in both simple and repetitive tasks. Within the former group we employed three measures: (i) the time to move the hand from one button to another in a jump reaction time task, the buttons providing fixed start and end points for the movement; (ii) the time to make a self-terminated elbow flexion (isotonic movement) or hand squeeze (isometric movement); and (iii) the time.....
to perform simultaneous elbow flexion and hand squeeze. Preoperatively, all of these movements were slower than normal, with values within the same range as previous studies on Parkinson’s disease from this laboratory (Benecke et al., 1986, 1987a, b). Pallidotomy decreased movement time, but the effect was much greater in the button-pressing tasks than for the self-terminated movements. The greater effect in the button-pressing task might be related to the fact that it has an end-point, whereas the flex and squeeze is a self-terminated task. According to a previous study, parkinsonian patients have more difficulty in executing self-terminated movements (Flowers, 1976).

Although simple, single-joint ballistic movements are slow in Parkinson’s disease, they offer a poor reflection of the patient’s clinical akinesia (Berardelli et al., 1986). Rather, it is with complex movements that the deficits are most clearly seen (Berardelli et al., 1986). Benecke et al. (1986, 1987a, b) clearly demonstrated that making a flexion movement either simultaneously with or following a squeeze led to an increased deficit compared with flexion performed alone. The same pattern was seen in the present patients preoperatively. Postoperatively, however, this deficit was improved, at least for the contralesional hand. In other words, pallidotomy improved complex movements more than simple movements.

The repetitive tasks that we used were pegboard and finger-tapping. Both involved distal movements, the pegboard requiring substantial sensorimotor co-ordination. Preoperatively the movements were slow, but, surprisingly, there was little change in either task after pallidotomy. Additionally, there was no differential impact when the same movement was performed bimanually or when two different movements were performed simultaneously. We can only speculate on the possible reasons for this lack of effect. The movements involved fractionated distal finger movements that were not tested in the SRT, CRT and flex and squeeze tasks. This suggests that pallidal lesions have a larger effect on proximal than distal muscles. Alternatively, perhaps the highly fractionated nature of the finger movements was the crucial factor that made them resistant to change with pallidotomy.

**Stretch reflexes**

The long-latency component of the EMG response to muscle stretch is known to be enhanced in patients with Parkinson’s disease (Rothwell et al., 1983; Cody et al., 1986). In contrast, the short-latency response is the same size as in healthy controls. The same was true of the present patients in their preoperative state. Pallidotomy selectively decreased the amplitude of long-latency responses in the contralesional arm, which may contribute to the reduction of rigidity that has been reported in many clinical studies. The mechanism of the effect is less clear. The long-latency component of the stretch reflex in wrist flexor muscles may result from activity in two separate nervous pathways, one involving a transcortical relay of fast-conducting (group I) muscle afferents, the other reflecting activity in slower-conducting (group II) muscle afferents in a shorter spinal pathway. Pallidotomy could affect the transcortical pathway through its effect on pallidothalamicocortical projections. The reported change in excitability of motor cortex inhibitory circuits detected in magnetic stimulation studies after pallidotomy would be consistent with this idea (Strafella et al., 1997; Young et al., 1997). Alternatively, pallidotomy might reduce the sensitivity of the secondary muscle spindle endings through an action on the fusimotor system. As yet, this notion is unexplored, but could involve pallidal outputs to brainstem nuclei.

**Comparison of the effects of pallidotomy and levodopa**

In some respects, the effects of pallidotomy and levodopa are remarkably similar. Both improve movement time and lead to an additional improvement in complex versus simple arm movements (simultaneous flex and squeeze compared with each alone) (Benecke et al., 1987b). Both have little effect on initiation times in the SRT and CRT tasks used in this study (Jahanshahi et al., 1992b).

However, there are some aspects of akinesia that improve following administration of levodopa but which show little change following pallidotomy, and vice versa. Thus, pallidotomy increased the speed with which patients could incorporate cue information to speed up reaction time whereas levodopa has been previously shown to have no effect (Jahanshahi et al., 1992b). In addition, pallidotomy improved the late part of the MRCP just prior to movement onset, whereas levodopa appears to enhance only the early component (Dick et al., 1987; Feve et al., 1992). Simple repetitive movements, such as finger-tapping, and tasks involving fine distal co-ordination, such as the pegboard task, have provided very sensitive measures of levodopa effectiveness in treating Parkinson’s disease (Meier and Martin, 1970; Hughes et al., 1994). In contrast, pallidotomy led to no appreciable change. The greater effect of levodopa in some tasks could be explained by the more diffuse action of levodopa. Pallidotomy was unilateral and was positioned to have maximum effect on the motor component of the cortex–basal ganglia–thalamocortical loops. Levodopa acts diffusely on the striatum and can modify the activity of both direct and indirect pathways. It also affects the substantia nigra pars reticulata, the other major output structure of the basal ganglia. There are even dopaminergic receptors in the globus pallidus internus, the subthalamic nucleus and some cortical areas which could play a role in mediating some of the effects of levodopa. Indeed, clinically also, levodopa and pallidotomy can have opposite effects. For example, pallidotomy improves levodopa-induced dyskinesias. It is more difficult to explain why premed CRT and the late MRCP were more affected by pallidotomy. Perhaps the effect of levodopa on other structures could prevent these improvements.
Implications and conclusions

The current model of basal ganglion anatomy envisages several parallel striatopallidocortical loops, among them an associative or complex loop and a motor loop (Alexander et al., 1986, 1990; Alexander and Crutcher, 1990; DeLong, 1990; Wichmann and DeLong, 1996). Some aspects of this model have been reconsidered, but it is still useful to discuss the mechanisms of action of basal ganglion surgery (Levy et al., 1997; Parent and Cicchetti, 1998). The motor loop includes the putamen, the posteroverentralateral globus pallidus internus, the ventrolateral thalamus and, at cortical level, the primary motor cortex, the premotor cortex and the SMA proper. The associative loop includes the caudate nucleus, part of the putamen, the anterodorsal globus pallidus internus, the substantia nigra reticulata, the ventroanterior and some mediodorsal thalamus and frontal association cortical areas, including the dorsolateral prefrontal cortex and the pre-SMA. In our study, the target for pallidotomy was the ventroposteralateral part of the globus pallidus internus, which is part of the motor loop. This procedure is more effective against parkinsonian motor symptoms than anterior pallidotomies (Svennilson et al., 1960). The increase in globus pallidus internus activity found by microelectrode recordings during pallidotomy is mainly localized to the posteroverentral part (Hutchinson et al., 1994). Consequently, the primary motor cortex, premotor cortex and SMA proper should be the main areas modified by pallidotomy, while the dorsolateral prefrontal cortex and pre-SMA should be less influenced.

The role of these various cortical areas can be summarized as follows. Early preparatory processes, decision and selection of movement may involve the pre-SMA and dorsolateral prefrontal cortex (Brinkman and Porter, 1979; Matsuzawa et al., 1992; Jahanshahi et al., 1995). Following this, the motor cortex needs to be set in the state required for movement initiation, processes which involve mainly the SMA proper, the premotor cortex and the motor cortex according to electrophysiological and metabolic studies in animal models and humans (Brinkman and Porter, 1979; Roland et al., 1980; Tanji and Kurata, 1985; Mushiake et al., 1991; MacKinnon et al., 1996). Finally, movement execution may be the domain of the motor cortex, and of the SMA also (Mushiake et al., 1991).

Our results are consistent with most aspects of this organization. Posteroverentral pallidotomy improved the last stages of movement preparation and execution, presumably by acting on the motor loop to improve function in the primary motor cortex, premotor cortex and SMA proper. Early preparatory processes, characteristic of projection targets of the frontal, associative basal ganglion loops were unaffected. Studies on regional CBF and glucose metabolism have also noted a consistent change in SMA activation after pallidotomy (Ceballos-Baumann et al., 1994; Grafton et al., 1994, 1995; Eidelberg et al., 1996; Samuel et al., 1997). However, changes are also seen in regions including the dorsolateral prefrontal cortex (Ceballos-Baumann et al., 1994; Samuel et al., 1997).

The significance of this prefrontal change is unclear, as there are no reports of any consistent changes following surgery in cognitive functions known to involve this region. If anything, there is a suggestion that some abilities may deteriorate, such as aspects of working memory (Troster et al., 1997; Jahanshahi et al., 1997).

It is acknowledged that the present study is largely descriptive. We deliberately chose tasks for which we already had empirical data, allowing us to compare the results of surgery with known patterns of impairment in medicated and unmedicated patients. The way is now open for further experimental studies to test specific hypotheses about the role of the basal ganglia–thalamocortical circuitry in akinesia in Parkinson’s disease and voluntary movement in general.

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