A revival of Spiegel’s campotomy: long term results of the stereotactic pallidothalamic tractotomy against the parkinsonian thalamocortical dysrhythmia

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The over-inhibition of thalamic relay cells by hyperactivity of the internal part of the globus pallidus is a cornerstone of the parkinsonian pathophysiology that leads to a distortion of the thalamocortical dynamics called thalamocortical dysrhythmia (TCD). Here, we present the results of the stereotactic pallidothalamic tractotomy (PTT), which interrupts selectively the enhanced pallidal output to the thalamus in a restricted location in the fields of Forel. This operation represents a reactivation of Spiegel’s campotomy. PTT was offered to 41 patients (66.1 ± 8.5 years) suffering from chronic, therapy-resistant Parkinson’s disease. It was performed bilaterally in 21 patients. Forty patients displayed mixed, i.e. tremulant and akinetic parkinsonian signs, and seven had drug-induced dyskinesias. One patient had only rest tremor. The evaluation was based on the Unified Parkinson’s Disease Rating Scale (UPDRS) scores, comparing the patients’ preoperative medicated state with the state at the last postoperative follow-up. We, thus, tested surgical success in terms of superiority to drug treatment. Mean follow-up was 22.4 months with 15 patients followed for ≥ 2 years. Mean improvement was 60% (P < 0.001) for UPDRS III and 51% (P < 0.001) for UPDRS II. Significant improvement (P < 0.01) appeared in subscores for tremor (87%), limb akinesia (58%) and axial akinesia (33%). Improvement of postural stability and gait was at the limit of significance (P < 0.05). Improvement of hypomimia and hypophonia did not reach statistical significance. Increase of dysarthria was significant (P < 0.01). Intake of L-DOPA was reduced significantly and 21 patients were able to stop intake. Median improvement of the Quality of Life score was 67%. Improvement remained, independent of follow-up length. In conclusion, PTT provides a high, stable level of relief to parkinsonian patients whose condition cannot be controlled with pharmacotherapy. The rationale of the surgical therapy is based on a selective extrathalamic regulation of the parkinsonian TCD.

Keywords: neurosurgery, subthalamotomy, pallidofugal fibres, thalamus, thalamocortical system

INTRODUCTION

Pharmacological therapy of Parkinson’s disease (PD) based on L-DOPA and dopamine agonists is well established, specific and effective. However, therapy resistance, fluctuations and dyskinesias can appear over time (Marsden and Parkes, 1976; Ahlskog and Muehner, 2001). To provide therapy to these patients, surgical approaches were developed in the 1950s and 1960s. Among these, operations at the level of the motor thalamus have been shown to be effective mainly or exclusively against tremor and have, therefore, become secondary in the treatment of parkinsonian symptoms (Walter and Vitek, 2004). Current surgical procedures against chronic therapy-resistant PD are radiofrequency lesion (RFL) and high frequency stimulation (HFS) at the level of the subthalamic nucleus (STN) or the internal part of the globus pallidus (GPI). Several studies have reported on GPI RFL (Baron et al., 2000; Fine et al., 2000; Parkin et al., 2002; Valldeoriola et al., 2002; Hamani et al., 2005) and HFS (Kumar et al., 2000; PD-study-group, 2001; Visser-Vandewalle et al., 2003), as well as on STN RFL (Alvarez et al., 2001; Su et al., 2002; Vilela Filho and da Silva, 2002; Patel et al., 2003) and HFS (PD-study-group, 2001; Herzog et al., 2003; Kleiner-Fisman et al., 2003; Krack et al., 2003; Pahwa et al., 2003; Ford et al., 2004; Rodriguez-Oroz et al., 2005; Deuschl et al., 2006).

The pathophysiology that underlies parkinsonian symptomatology has been traced back to a chain reaction between the substantia nigra and frontal cortex (Albin et al., 1989; DeLong, 1990; Hutchison et al., 1994; Lozano et al., 1998). As a consequence of complex, partially elucidated events within the basal ganglia, the GPi becomes hyperactive (Hutchison et al., 1994; Sterio et al., 1994; Beric et al., 1996; Lozano et al., 1998) and causes a tonic over-inhibition of the pallidal-recipient thalamic relay cells (Magnin et al., 2000; Anderson et al., 2003). This over-inhibition is thought to initiate the development of the thalamocortical dysrhythmic (TCD) process (Llinás and Jahnsen, 1982; Jahnsen and Llinás, 1984; Jeanmonod et al., 1996; Llinás et al., 1998; Llinás et al., 1999; Sarnthein et al., 2003), which provides the pathophysiological framework for our surgical approach.

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In this context and also on the basis of the anatomical and historical evidence discussed below, we chose to reactualize the ‘campotomy’ of Spiegel et al. (Spiegel et al., 1963) and propose the term ‘pallidothalamic tractotomy’ (PTT) to indicate selectively the targeted subarea centered on the field H1 of Forel (or fasciculus thalamicus), through which the pallidothalamic fibres of the fasciculus lenticularis (or H2 field of Forel) and of the ansa lenticularis are funneled into the thalamus (Nauta and Mehler, 1966; Magnin et al., 2001a).

Here, we report the long term results of PTT in 41 patients suffering from chronic, therapy-resistant PD. An earlier study described the first results of PTT in a group of 21 patients (Magnin et al., 2001a). At variance with most reports in the literature, we judge the surgical outcome against the preoperative, medicated (ON) state only, this being the only relevant measure to test surgical success in terms of superiority to drug treatment. PTT is an efficient surgical alternative to HFS and avoids the device-related complications and maintenance costs of HFS.

METHODS

Patients

The magnetic resonance (MR) and microelectrode-guided stereotactic PTT was approved by the University Hospital ethics committee. All patients were fully informed of the risks and benefits of the procedure and gave informed consent. Selection criteria for stereotactic treatment were as follows:

1. Idiopathic PD as defined primarily by the presence of tremor at rest, akinesia (or rather hypobradykinesia) and rigidity (Marsden and Obeso, 1994);
2. At least one of the two clinically most relevant symptoms, tremor at rest and akinesia (Hughes et al., 1993), reaches intensity 3/4 or 4/4. They have resisted to optimal pharmacological treatment including L-DOPA and other antiparkinsonian drugs for at least 1 year;
3. Absence of dementia;
4. Strongly diminished quality of life.

Resistance to medication was documented repeatedly by neurologists during the years of the disease. At the time of the surgical indication, the evidence of a progressive, more or less rapid, drug resistance was highly relevant because it demonstrates the physiopathological strength of the idiopathic PD and, thus, the need for its surgical control. Typically, resistance was related to loss of efficiency (OFF-phenomenon), fluctuations (ON-OFF phenomenon) and chorea (ON-dyskinesias).

Clinical evaluation

Considering the large variations over time and the multiplicity of symptoms and signs that are characteristic of PD, their evolution is classically assessed by the neurological examination as part of the Unified Parkinson’s Disease Rating Scale (UPDRS III) and the patient’s report (UPDRS II). These two measures provide a test of mutual cross-validation.

We consider surgery to be justified ethically if it can provide relief that is significantly superior to that obtained by non-invasive approaches. The success of surgery must, therefore, be judged against the preoperative medicated (ON) state. In this context we view the OFF medication state before the operation as not directly relevant to the surgical decision and did not analyze it. This had the advantage of avoiding exposing patients to the stress of preoperative drug suppression. Thus, the clinical results presented in this paper refer to medicated (ON) clinical states. The postoperative follow-ups document the reduction of L-DOPA intake compared with preoperative values.

The neurological state of the patients was assessed by two examiners pre- and postoperatively in the optimal medicated state. The patients were examined at least twice preoperatively. Follow-up assessments took place after 3, 6 and 12 months and later at a minimum of 1 examination per year. Assessment of motor symptoms was rated from 0–4 according to the UPDRS III (Weiner and Lang, 1989). It included rest tremor (item 20), postural and kinetic tremor (item 21a posture b kinetic), global akinesia (item 31), fine and alternating limb akinesia (item 23 + 25), axial akinesia (item 27), rigor (item 22), postural stability (item 30), gait (item 29), hypophonia and dysarthria (item 18a + b), mimic (item 19), and chorea. UPDRS II assessment involved tremor (item 16a rest, 16b kinetic), limb akinesia (item 8), axial akinesia (item 12), postural stability (item 13), gait (item 15), voice (item 5), dressing (item 10), hygiene (item 1), eating (item 9), dyskinesias (item 33) and mimic. Salivation, swallowing, freezing and sensory complaints were not evaluated. In terms of UPDRS III, item 24 is covered by items 23 and 25, and items 26 and 28 are functionally less relevant than 27, 29 and 30, and so were not assessed. Similar adaptations of the UPDRS assessment have already been proposed (Rabey et al., 1997), with the goal of reducing redundancy.

Considering limb motricity, the UPDRS score was assessed pre- and postoperatively on the extremities with the strongest symptomatology in case of bilateral surgery, and on contralateral limbs for unilateral surgery.

Furthermore, patients were asked for their quality of life before surgery and at each follow up, rated as normal (0/4), slightly (1/4), moderately (2/4), strongly (3/4) or massively (4/4) reduced.

Surgery

Operations were performed under local anaesthesia in fully awake patients (Magnin et al., 2001a; Magnin et al., 2001b). The stereotactic system consisted of a base ring compatible with MR, a Cosman Roberts Well frame, a custom-made, radiofrequency thermocouple electrode, a radiofrequency generator and the Stereocalc software (Radionics).

To plan the lesion target, we localized anterior and posterior commissures on stereotactic T1-weighted MR images.
Based on the position of the commissures, the target was determined using our stereotactic atlas (Morel et al., 1997; Bourgeois et al., 1999). The PTT target was centered on the pallidothalamic fibers before they enter the thalamus through the ventral medial thalamic nucleus (coordinates: anteroposteriorly, at the midcommissural point; dorsoventrally, 2 mm below the horizontal intercommisural plane; mediodorsally, 7–8 mm lateral to the ventricular border; anteroposterior angle, 60–65°; and mediolateral angle, 15–20°). Peroperative physiology comprised thalamic single unit and local field potential (LFP) recordings, scalp electroencephalographic (EEG) recordings and macrostimulation.

The lesion was produced by radiofrequency thermocoagulation, with a final average lesion size 4 mm diameter and 7 mm length, between the ventral thalamic border and the dorsal border of the subthalamic nucleus, centered on the fasciculi thalamicus and lenticularis in the H1 and H2 fields of Forel, respectively (Fig. 1). The lesion, thus, aimed to leave untouched the more posterior prerubral field H of Forel that contains the cerebellothalamic tract (fasciculus cerebellothalamicus). The lesion also involves an anterior portion of the ventral medial thalamic nucleus and a small dorsomedial caudal portion of STN. Because the part of STN that is related to motor function lies more lateral, we assume that the PTT lesion achieves its therapeutic effect dominantly by interruption of the pallido-thalamic tract.

On day 2, a postoperative MRI examination allowed us to visualize the lesion and reconstruct its position by projection onto the stereotactic atlas (Morel et al., 1997). The percentage of overlap of the PTT lesion with the pallidothalamic fibers was estimated as >50% in all patients in this study, and 51 out of 64 lesions reached 75–100% overlap.

Statistical analysis

Outcome measures were scores on UDPRS II and UDPRS III, quality of life and L-DOPA intake. We report preoperative scores $S_{\text{pre}}$ and postoperative scores $S_{\text{post}}$ at last follow-up.

We define $I_p = (1 - S_{\text{post}}/S_{\text{pre}}) \times 100$ as improvement in scores of an individual patient. Since our follow-ups varied in length from 3 to 64 months, and since the length of follow-up might be assumed to be independent of the outcomes $S_{\text{post}}$, investigation of the relationship between improvement $I_p$ and length of follow-up should also inform us about the stability of improvement over time.

The statistical significance of pairwise comparisons between $S_{\text{pre}}$ and $S_{\text{post}}$ was evaluated with Wilcoxon signed-rank tests using SPSS (version 10.0; SPSS Inc). Although we employ a non-parametric test, Tables 3 and 4 present means rather than medians for comparison with other studies. Spearman correlation (Matlab version 7.04; The Mathworks) was used to assess relationships between variables, in particular the relationship between improvement $I_p$ and length of follow-up.

RESULTS

General clinical and demographic data

Patients characteristics are listed in Table 2. Forty of our 41 patients suffered from mixed forms of the disease (i.e. displayed different combinations of tremulous and akinetic manifestations). This patient group is, thus, in agreement with the definition of idiopathic PD, in which most patients display a combination of tremor and akinesia (Hughes et al., 1993), in accordance with the original description of ‘shaking palsy’ by James Parkinson.

In this patient group, the mean Hoehn & Yahr staging was $3 \pm 1$, and 14 patients had a rating of 4 and 5. Nineteen bilateral procedures were performed with a minimum interval of 3 months in between, and two were performed simultaneously. In two cases, an additional complementary PTT procedure had to be performed because of insufficient effect of the first surgery due to partial coverage of the PTT target. Before surgery, the average L-DOPA intake was 589 mg day $^{-1}$, not including DOPA-agonist equivalents. This dose

Fig. 1. Site of the PTT lesion in the pallidothalamic tract. A. Postoperative T1-weighted MR image of a PTT radiofrequency lesion in a patient with PD (tremulo-akinetis). The MRI was taken 3 days after surgery and shows oedema around the lesion. B. Projection of the targeted (grey oval) and effective (interrupted lines) lesions on a sagittal section of the thalamic atlas (Morel et al., 1997). The two lesions (represented without oedema) are close to each other (90% overlap) and interrupt the pallidothalamic tract (blue in B) through the fasciculi lenticularis (f) and thalamicus (t). These two tracts are distinct from the fasciculus cerebellothalamicus (ft), represented in red. Horizontal, interrupted lines in A and B represent the intercommisural level (DV O).

Abbreviations: CL, central lateral nucleus; CM, centre médian nucleus; Li, limitans nucleus; MDpc, mediodorsal nucleus, parvocellular division; ML, medial lemniscus; Pf, parafascicular nucleus; R, reticular nucleus; RN, red nucleus; SN, substantia nigra; STh, subthalamic nucleus, VLPv, ventral lateral posterior nucleus, ventral division; VA (pc, mc), ventral anterior nucleus (parvo- and magnocellular divisions); VM, ventral medial nucleus, VPMpc, ventral posterior medial nucleus, parvocellular division; ZI, zona incerta; PTT, pallidothalamic tractotomy. Scale bars: A, 5 mm; B, 1 mm between graduations.
Table 2. General characteristics of the patient group.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Mean ± s.d.</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Age at disease onset (years)</td>
<td>56.2 ± 10.8</td>
<td>31–75</td>
</tr>
<tr>
<td>Age at first surgery (years)</td>
<td>66.1 ± 8.5</td>
<td>48–85</td>
</tr>
<tr>
<td>Age at last follow-up (years)</td>
<td>68.1 ± 8.2</td>
<td>52–86</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>9.8 ± 6.0</td>
<td>1–24</td>
</tr>
</tbody>
</table>

Principal outcome measures

After PTT, the total score for UPDRS III improved significantly \((P < 0.001, Z = -5.5)\) (Fig. 2 and Table 4), with a median improvement of 61%. The median preoperative UPDRS II score was reduced by 55% \((P < 0.001, Z = -4.7)\), and the patients’ assessment of their quality of life improved by 67% \((P < 0.001, Z = -5.0)\). There were no significant changes of the UPDRS III improvements with respect to the follow-up length, the patients’ age at last follow-up, the disease duration and the UPDRS III state before surgery (Fig. 3). We correlated the postoperative improvement of UPDRS II with follow-up length after removing two outliers and found a non-significant decline. Similarly, improvements in quality-of-life score were small and not significant with respect to follow-up length. These results indicate that improvement is stable over time.

Table 3 displays the means of UPDRS II and UPDRS III scores and additional subscores. UPDRS III improvement was highly significant for all forms of tremor \((P < 0.001)\), for global \((P < 0.005)\), axial \((P < 0.001)\) and distal (or limb) akinesias \((P < 0.001)\), and for rigor \((P < 0.001)\). P value was <0.05 for postural stability and gait. Mean values improved also for hypophonia and hypomimia, although these postoperative improvements did not reach statistical significance. For all items except dysarthria, the number of patients who benefited from surgery \((n+)\) was larger than the number of patients whose score deteriorated \((n-)\) in all items.

A summary of the data in Table 3 is presented in Table 4 for easier comparison with data from the literature. This includes means pre- and post-operative with standard deviations and percentages of improvement for UPDRS III and UPDRS II scores, UPDRS III tremor, axial and limb akinesia subscores, dyskinesias and drugs.

All patients had L-DOPA treatment preoperatively (median 600 mg day\(^{-1}\), range 300–1300 mg day\(^{-1}\)). We have not converted doses of dopaminergic drugs into L-DOPA equivalents. L-DOPA intake could be reduced (median 0 mg day\(^{-1}\)) with high significance \((P < 0.005)\), and 21 patients completely stopped L-DOPA intake postoperatively. Changes in L-DOPA intake are shown in Fig. 4. Preoperatively, 21 patients received dopamine agonists, 14 COMT inhibitors, eight amantadine, 11 selegline, 23 anticholinergic drugs, 13 benzodiazepines, five antidepressants, four neuroleptics, 7 antiepileptics, eight beta-blockers. At the last follow-up, three patients still took a DOPA agonist, three a COMT inhibitor, two an anticholinergic drug, five a benzodiazepine, eight an anti-depressant and one a neuroleptic drug.

Side-effects

Two clinically irrelevant bleedings were seen on the postoperative MR examination, one in the subthalamic nucleus, the other in the caudate nucleus. There was one postoperative pulmonary embolus that was treated with anticoagulation, without complications. There were two, acute, short-lived \((1–2 \text{ days})\) postoperative hypertensive phases, and two reversible pupillary asymmetries.

Acute postoperative reversible psychoemotional phenomena were observed in eight patients (one anxiety, one libido loss, four hyperphagias and two hypomaniac states). More protracted, context-sensitive and often patient-specific psychoemotional phenomena were also seen (one libido loss, six patients with slight to moderate anxiodepressive elements, four slight to moderate reduced activity states). A detailed study of the cognitive, executive and memory functions is...
underway. Obvious deficits in these domains were observed in three patients, but improvements also occurred. In the case of cognitive deterioration, we observed variable degrees of slowing of some executive functions unrelated to the unilaterality or bilaterality of PTT.

Postoperative dynamics

Oscillations of clinical symptoms in the early postoperative phase were observed generally. These are characterized by (1) the presence of tremor waves that recede over 2–3 months with progressive reduction of intensity, duration and frequency, (2) in two patients with preoperative on-dyskinesias, chorea unrelated to L-DOPA intake that receded over a few days, (3) fluctuations, immediately after the radiofrequency lesion, of consciousness, with increased sleepiness, fully regressive over 24 hours (19 patients), and (4) the temporary, short-lived (24 hours) appearance of a corticospinal syndrome (paresis with Babinski sign) without MR abnormalities (10 patients). These observations are in agreement with the highly complex and subtle oscillatory thalamocortical dynamics on which the TCD is based. In contrast, rigor was reduced immediately and without fluctuations, and we observed a steady reduction of akinetic manifestations, extending over days to months. There was no instance of postoperative ballism.

DISCUSSION

The present study is based on a group of 41 patients with a mean follow up of 22 ± 18 months. Improvement of UPDRS II and III exceeded 50% compared with the preoperative ON state (Fig. 2). Of the 25 subscores in Table 3, 15 improved with high significance. Axial symptomatology (postural stability, gait, mimic and voice) was more resistant than the distal one, as often described in the literature. PTT provided full protection against postoperative ballism. This might be because (1) PTT protects against the development of this complication, and/or (2) the PTT lesion involves only a small dorsomediocaudal portion of STN (Fig. 1). Furthermore, from the present results, clinical improvement is independent of the length of follow-up (Fig. 3).

History and rationale of the target

In the 1960s and 1970s, different groups (Spiegel et al., 1963; Mundinger, 1965; Bertrand, 1973) described the results of Spiegel’s campotomy on both akinesia and tremor, and suggested that this approach might combine the therapeutic effects of pallidotomy and thalamotomy. Our choice for a reactualization of this approach was additionally guided by the fact that (1) a prethalamic operation leaves the thalamocortical network intact, and (2) the interruption of the overinhibitory output of GPi onto thalamus (Hutchison et al., 1994; Sterio et al., 1994; Beric et al., 1996; Lozano et al., 1998) might be best controlled by a small, selective lesion in the H1/H2 fields of Forel. These fields give passage to most of the pallidothalamic fibers on an area of ~4 mm diameter (Nauta and Mehler, 1966; Magnin et al., 2001a), and an operation at this location is less invasive than the multiple, internal, pallidal penetrations necessary to provide an equivalent thalamic desinhibition.
Table 4. Summary of improvements in means.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Items</th>
<th>Range of possible scores</th>
<th>Mean, Pre-</th>
<th>Mean, Pre-</th>
<th>Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS III</td>
<td>18a + b, 19, 20, 21a + b, 22, 23, 25, 27, 29, 30, 31</td>
<td>0–52</td>
<td>15.1 ± 7.1</td>
<td>6.1 ± 3.4</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>5, 8, 9, 10, 11, 12, 13, 15, 16a + b</td>
<td>0–40</td>
<td>11.8 ± 6.3</td>
<td>5.9 ± 3.6</td>
<td>51</td>
</tr>
<tr>
<td>Tremor</td>
<td>0–12</td>
<td>4.6 ± 1.9</td>
<td>0.6 ± 1.0</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Axial</td>
<td>18a + b, 19, 27, 29, 30</td>
<td>0–24</td>
<td>5.2 ± 4.3</td>
<td>3.5 ± 2.7</td>
<td>33</td>
</tr>
<tr>
<td>Limb akinesias</td>
<td>23, 25</td>
<td>0–8</td>
<td>3.0 ± 1.7</td>
<td>1.3 ± 1.2</td>
<td>58</td>
</tr>
<tr>
<td>Dyskinesias</td>
<td>33</td>
<td>0–4</td>
<td>2.1 ± 0.8</td>
<td>0.4 ± 0.8</td>
<td>80</td>
</tr>
<tr>
<td>Drugs (mg)</td>
<td>589 + 710 to 1300</td>
<td>410 + 35</td>
<td>190 ± 241</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

Scores describe patients’ pre- and postoperative state at best medication. Numbers in brackets indicate single UPDRS items. In addition we present scores for chorea, mimic, Quality of Life and drugs. \( n \) indicates how many patients in each subgroup had a non-zero subscore for a specific symptom. Columns \( n^+ \) and \( n^- \) show the number of patients in each subgroup whose subscore improved or deteriorated, respectively. \( P \)-values were calculated with paired Wilcoxon signed-rank test, compared with before surgery.

This table presents the improvements in means of pre- and postoperative scores for comparison with data from the literature. Numbers of respective UPDRS items are indicated.
The thalamocortical dysrhythmia

We integrate the treatment of PD in the context of a pathophysiological framework globally described as thalamocortical dysrhythmia (TCD) (Llinás et al., 1998; Llinás et al., 1999). Based on conceptual foundations laid by Llinás et al. (Llinás, 1984; Volkman et al., 1992; Llinás and Pare, 1994; Volkman et al., 1996), the following mechanism was proposed to explain how thalamic overinhibition leads to parkinsonian symptoms.

1. Reduced dopamine input to the striatum results in increased pallidothalamic inhibition (Hutchison et al., 1994; Sterio et al., 1994; Beric et al., 1996; Lozano et al., 1998), which, in turn, results in thalamic relay cell membrane hyperpolarization in thalamic nuclei VLa and VA. In this state, a deactivation of calcium T-channels causes thalamic relay neurons to fire low-threshold calcium spike (LTS) bursts at 4 Hz interburst frequency (Llinás and Jahnsen, 1982; Jeanmonod et al., 1996; Magnin et al., 2000; Llinás and Steriade, 2006). In experimental animals free of TCD some authors report very few spontaneous LTS bursts (Woody et al., 2003; Ramcharan et al., 2005; Ruiz et al., 2006), whereas others observe sizeable numbers in high order thalamic nuclei (Ramcharan et al., 2005). Nevertheless, compared to the later, LTS bursts occur over twice as often in the central lateral and VLa/VA thalamic nuclei of PD patients (Magnin et al., 2000).

2. Bursting thalamic relay neurons exert a rhythmic influence on thalamocortical loops in the theta (4–9 Hz) frequency band, shown by high theta power in thalamic LFP (Sarnthein et al., 2003). The tight functional coupling between thalamus and cortex is confirmed by the high theta coherence between the two (Sarnthein et al., 2005; Sarnthein et al., 2005). This coupling is sustained by thalamocortical, thalamoreticulothalamic and corticoreticulothalamic recurrent projections. The high functional relevance of the corticoreticulothalamic feedback projection has been shown experimentally (Steriade, 2001), as well as the tendency of the thalamocortical network to maintain a given functional modality, in this case the hyperpolarized state (Pedroarena and Llinás, 2001).

3. Divergent thalamocortical, corticothalamic and reticulothalamic projections (Jones, 2001) provide the anatomical substrate for the coherent diffusion of low frequency activity to an increasing number of neighboring thalamocortical modules. After recruitment of a sufficiently large number of thalamocortical loops, theta power increase becomes measurable on the scalp with either EEG or magnetoencephalography (MEG) (Soikkeli et al., 1991; Llinás et al., 1999; Tanaka et al., 2000; Salenius et al., 2002; Sarnthein et al., 2003) and negative symptoms such as hypobradykinesia can arise. Note that increased low-frequency oscillations also occur during sleep and cognitive tasks (Klimesch, 1999; von Stein and Sarnthein, 2000; Kahana et al., 2001), where they are considered normal. It is the long-lasting, widespread and uncontrolled overproduction of slow rhythms in the awake brain that characterizes TCD.

4. Finally, positive symptoms like tremor are produced by activation of high frequency cortical domains in the vicinity of low frequency theta areas: constraining corticocortical GABAergic inhibitory interneurons to theta rhythmicity might indeed reduce lateral inhibitory drive, leading to disinhibition and, thus, activation of neighboring cortical domains (‘edge effect’ (Llinás et al., 2005)). MEG (Llinás et al., 1999) and LFP power correlation studies and bicoherence data (Sarnthein et al., 2003) provide evidence for such a phenomenon, showing a high interfrequency covariation between theta and beta domains and, thus, indicating a coupling of high and low frequency activities.

The postoperative fluctuations observed after PTT may be understood to result from a temporary state of thalamic relay cell desinhibition that causes a rebound wave of reticulothalamic overinhibition.

Comparison of clinical outcomes

The data in Table 5 were collated from several recent, sizable studies on different surgical prethalamic approaches for PD. Only ON-medication results are included, for direct comparison with the present study. We only consider the ON-medication score during a drug therapy. The mean UPDRS III improvement in the eight HFS STN studies that we selected amounts to 8.7%. The review of Hamani et al. (Hamani et al., 2005) on 38 studies on the same procedure provides a mean ON-medication UPDRS III improvement of 18%, and the only available reviewed study with a 5-year follow-up gave no improvement. The report with the UPDRS III improvement closest to that observed in our study (61%) is that of Su et al. (Su et al., 2002) with RFL in STN, and an improvement of 59%.

Most studies evaluate the ON-medication score during a DOPA-challenge, which we did not perform formally. This might cause a discrepancy because, potentially, our UPDRS
Table 5. Comparison of the results of different neurosurgical therapies for PD.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Age at Surgery</th>
<th>Uni/Bi</th>
<th>Follow Up</th>
<th>UPDRS</th>
<th>III</th>
<th>II</th>
<th>Tremor</th>
<th>Limb Akinesia</th>
<th>Axial</th>
<th>Dyskinesias</th>
<th>Drugs (mg)</th>
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<tr>
<td><strong>GPI</strong></td>
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<td>Baron et al.</td>
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<td>10</td>
<td>58</td>
<td>Uni</td>
<td>4 years</td>
<td>pre-op</td>
<td>30.6</td>
<td>10.2</td>
<td>2*</td>
<td>7.3</td>
<td>1</td>
<td>1.7</td>
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<td>Fine et al.</td>
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<td>Uni</td>
<td>13 months</td>
<td>post-op</td>
<td>17.7</td>
<td>14.6</td>
<td>0*</td>
<td>6.6</td>
<td>6.9</td>
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<td>Parkin et al.</td>
<td>2002</td>
<td>45</td>
<td>64</td>
<td>0/25</td>
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<td>post-op</td>
<td>17.9</td>
<td>11.1</td>
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<tr>
<td>Valdeolmuela et al.</td>
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<td>post-op</td>
<td>21.7</td>
<td>12.3</td>
<td>0.1</td>
<td>4.9</td>
<td>8.4</td>
<td>5.8</td>
<td>993</td>
</tr>
</tbody>
</table>

| **HFS**        |      |    |                |        |           |          |     |    |        |                |       |             |            |
| Visser-Vandewalle et al. | 2003 | 28 | 56             | Uni    | 33 months | pre-op   | 10.6| 1.2 | 2.5   | 1.5             | 3.7    | 7.11         | 718        |
| PD-study-group | 2001 | 36 | 56             | Bi     | 6 months  | pre-op   | 18.5| 8.8 | 0.3   | 6.9             | 3.5    | 0.7          | 1120       |
| Kumar et al.   | 2000 | 21 | 53             | 4/17   | 6 months  | post-op  | 17.5| 13.2| 0.5   | 4.8             | 0.5    | 0.9          | 1132       |
| Patil et al.   | 2003 | 18 | 60             | Uni    | 24 months | pre-op   | 17.7| 9.3 | 0.1   | 3.7             | 1.1    | 1.3          | 319        |
| Prados et al.  | 2001 | 91 | 59             | Bi     | 6 months  | post-op  | 21.6| 11.2| 1.6   | 9.5             | 4.2    | 1.9          | 1218       |
| Palomo et al.  | 2003 | 19 | 58             | Bi     | 28 months | post-op  | 26.1| 11.8| 2.7   | 8.4             | 4.4    | 1.4          | 518        |
| Klein-Fisman et al. | 2003 | 25 | 57             | Bi     | 30 months | post-op  | 22.8| 12.1| 2.7   | 8.2             | 4.8    | 1.9          | 1155       |
| Ford et al.    | 2005 | 30 | 59             | Bi     | 12 months | post-op  | 21.9| 10.5| 0.2   | 4.1             | 6.8    | 4.3          | 1155       |
| Rodriguez-Oroz et al. | 2005 | 30 | 49             | Bi     | 3.8 years | post-op  | 22.8| 10.6| 2.5   | 8.9             | 3.3    | 1.91         | 1109       |
| Deuschl et al. | 2006 | 78 | 61             | Bi     | 6 months  | post-op  | 18.9| 9.0 | 0.9   | 6.7             | 3.1    | 0.7          | 597        |

| **PD**         |      |    |                |        |           |          |     |    |        |                |       |             |            |
| Su et al.      | 2002 | 7  | 61             | Uni    | 18 months | pre-op   | 43.6| 15.8| 5.7   | 8.3             | 13.6   | 8.4          | 874        |
| Vilas-Filho et al. | 2002 | 23 | 56             | Uni    | 14 months | pre-op   | 25.8| 5.8 | 0.5   | 3.4             | 0.4    | 0.8          | 406        |
| Alvarez et al. | 2001 | 10 | 60             | Uni    | 12 months | pre-op   | 23.5| 14.1| 5.4*  | 12.8             | 10.2   | 1.5          | 967        |
| Patil et al.   | 2003 | 18 | 60             | Uni    | 24 months | pre-op   | 14.7| 9.3 | 0.7*  | 8.6             | 4.6*   | 1.6          | 797        |
| Heresz et al.  | 2003 | 20 | 60             | Bi     | 24 months | post-op  | 19.3| 13.4| 1.3   | 6.8             | 3.5    | 2.4          | 522        |
| PD-study-group | 2001 | 91 | 59             | Bi     | 6 months  | post-op  | 21.6| 11.2| 1.6   | 9.5             | 4.2    | 1.9          | 1218       |
| Palomo et al.  | 2003 | 19 | 58             | Bi     | 28 months | post-op  | 26.1| 11.8| 2.7   | 8.4             | 4.4    | 1.4          | 518        |
| Kleiner-Fisman et al. | 2003 | 25 | 57             | Bi     | 30 months | post-op  | 22.8| 12.1| 2.7   | 8.2             | 4.8    | 1.9          | 1155       |
| Ford et al.    | 2005 | 30 | 59             | Bi     | 12 months | post-op  | 21.9| 10.5| 0.2   | 4.1             | 6.8    | 4.3          | 1155       |
| Rodriguez-Oroz et al. | 2005 | 30 | 49             | Bi     | 3.8 years | post-op  | 22.8| 10.6| 2.5   | 8.9             | 3.3    | 1.91         | 1109       |

The results of four surgical procedures (GPI of GPI, RFL of STN, HFS of GPI and HFS of STN) are compared with those of the present study. Listed are patients’ best state of UPDRS II and UPDRS III scores and subscores, as well as scores for dyskinesias and drugs: preoperative medication ON (pre); postoperative medication ON (post); and stimulation ON for HFS. If ON values are not available, OFF values are listed (marked with ‘*’). We used the scores Spre and Spost from the longest follow-up with complete data set and calculated improvement percentages (100s × Spost/Spre)100 whenever available. Tremor, limb akinesia and dyskinesias were analysed contralateral to the operation. Drugs are listed as L-DOPA equivalents and exclude agonist equivalents if possible.

Abbreviations: b, bilateral procedures; n, number of patients included in follow-up report; u, unilateral procedures. The column ‘axial’ contains the items 5, 12, 15, 18, 19, 27, 29, 30 of UPDRS.
III ON-values are higher than if a DOPA-challenge was done. The UPDRS II score, however, is entirely anamnestic and, thus, independent of the DOPA-challenge. Our UPDRS II improvement might, thus, be compared directly with that of other studies. Because UPDRS II and UPDRS III correlate highly in all publications, including our own, they indeed serve to cross-validate each other.

RFL compared to HFS

In the past few years HFS has gained a dominant position in the field of neurosurgery for PD. Current arguments in its favour are its reversibility and the possibility of adjusting stimulation parameters with time. Nevertheless, we propose arguments that favor a lesional approach:

(1) The mechanisms of action of HFS are unclear. However, an experimental setup close to the clinical HFS conditions has shown that stimulation frequencies >100 Hz are non-physiological (Urbano et al., 2002). Although cell bodies and, particularly, axons can follow such frequencies, HFS quickly causes synaptic transmission failure, which remains as long as the stimulation is applied.

The most efficient STN HFS site is at the dorsal border of the STN at the level of the H2 field of Forel where part of the pallido-thalamic tract travels (Herzog et al., 2004; Zonnenshain et al., 2004; Breit et al., 2006). We propose that stimulation at this site amounts to a functional block of the pallidothalamic synapses and contributes at least partly to the therapeutic effect of STN HFS. The limited efficiency of HFS might be due to the fact that HFS STN stimulation sites are localized in the H2 field of Forel (fasciculus lenticularis) and not in H1, which is more medial and contains fibers from both the fasciculus and ansa lenticularis (Nauta and Mehler, 1966). Another possible mechanism of action is based on the increased activity of Gpi during STN HFS (McIntyre et al., 2004). This might be caused by disfacilitation of the external part of the globus pallidus (Gpi) and then a reduced inhibition of the Gpi. This Gpi increased activity and the resulting increased inhibition of thalamic relay neurons might promote a low frequency production large enough to reduce the cortical edge effect (thalamotomy-like effect). This is another possible explanation for the partial improvements obtained by STN HFS.

(2) A major argument in favor of HFS is its reversibility. However, patients wish that correction of their problem is as complete and definitive as possible. Although reversibility would be a valid argument in the case of significant uncertainties, the wealth of current anatomophysiological knowledge and the precision obtainable with modern technology (Bourgeois et al., 1999) allow, and even require, that a complete and definitive surgical therapy is considered.

(3) HFS practicality factors are also important. At best, patients should be as independent as possible, and free of the frequent hospital stays that are required for stimulator care (parameter adaptations and battery changes) and treatment of complications like hardware dysfunctions, cable breaks and disconnections, electrode displacements, infections, and skin erosions. These complications have an 8% cumulative rate per year (Oh et al., 2002), thus, representing a significant and increasing time consideration for patients, caregivers and health-care systems.

Neurodegeneration in PD

The neurodegeneration concept dominates the current view of the parkinsonian state, supported by a host of neuropathological data. The assumption is that the loss of dopaminergic neurons in the substantia nigra together with cell losses all over the brain hemispheres and brainstem are caused by a single degenerative process.

At variance with the neurodegeneration concept, we propose the TCD process to be responsible for cell losses in thalamus and cortex. TCD may indeed lead to excitotoxic calcium overload in cortical and thalamic cells (Bertolino and Llinás, 1992; Pivovarova et al., 2004). The cortical atrophy observed in patients suffering from idiopathic PD would, thus, be secondary to the TCD. In this case, cortical atrophy and its resulting progressive symptomatology could be stopped by proper surgical control. The stability of our results (Fig. 3) and those of others (Alvarez et al., 2005) speak for this possibility. The surgical treatment would then have to be offered in due time (i.e. after 1 year of dopamine resistance), and would have not only a symptomatic, but also a causal and protective role. Such an approach would give parkinsonian patients at least a chance to seize in the context of an otherwise widely accepted disease concept that leaves little hope against the progressive, relentless and irreversible brain damage that affects their bodily and mental capacities.

The cognitive factor

Our clinical experience and recent evidence in the literature (Goetz et al., 2000; Benedetti et al., 2004) speak for prominent, consistent influences of cognitive and emotional factors on parkinsonian, particularly akinetic, symptomatology. These influences are thought to arise in associative and mesocortical thalamocortical domains and intermingle with primary, bottom-up nigrostriatopallidothalamic pathogenetic events. There is evidence that low frequency generation is also related to cognitive activation (Klimesch, 1999; von Stein and Sarnthein, 2000; Kahana et al., 2001), thus, providing a basis for psychogenic disorders. That cognitive and emotional factors have significant, even massive, inhibitory influence on motricity is demonstrated by the general observation of the blocking effect of acute fear on body movements. This is reminiscent of the akinetic pattern seen in PD patients, which is less improved in our and other surgical and pharmacological experiences. This observation, coupled with our evidence of stably improved motor functions after PTT, leads us to envisage that resistance is due to potentially reversible ideofactorial factors, and not, as generally assumed, as a manifestation of neurodegeneration.

Pure akinesia (i.e. without tremor) is present in only ~20% of parkinsonian patients (Hughes et al., 1993). Some patients display initially tremor, losing it later in favor of akinesia. We interpret this observation as a sign that the TCD, under the pressure of ideofactorial factors, has extended into the prefrontal cortices, anterior to precentral/premotor areas. This hypothesis is supported by preliminary observations of MEG and EEG TCD source localizations in paralimbic
and associative cortical domains in parkinsonian patients. In this context, some pure akinetic patients might need primarily a treatment that is centered on psychotherapy more than on surgery (Shima et al., 1996), and others be at best helped by an integrated surgical and psychotherapeutic approach. In addition, prominent placebo effects described in PD (Goetz et al., 2000; Benedetti et al., 2004) might be at the source of at least part of the results of the HFS technique. The trend, which is visible in Table 5, for lower preoperative rates of tremor compared with the other symptoms, makes this observation all the more relevant. The evolution of the patients in our series demonstrates long-term stability, whereas STN HFS does not seem to provide this stability despite continuous placebo exposition. This might be related to an insufficient TCD control by the STN HFS (see above), thus, allowing disease mechanisms to develop further.

The classical observation of neuropsychological deficits in patients suffering from depression and anxiety (Cummings and Mega, 2003) poses the same question as for axial akinesia: a possible relationship with ideoffective factors and not with degeneration. Our observations speak for neuropsychological difficulties, essentially characterized by a highly variable slowing of prefrontal functions that is fully compatible with this cognitive/emotional hypothesis. In any case, these observed detrimental cognitive effects are clearly outweighed by the postoperative improvements of parkinsonian symptoms, with a 67% median improvement of Quality of Life score after PTT.

Last, but not least, the recent evidence that apoptotic cell death (Lucassen et al., 2001), atrophies of different brain areas (Lyons et al., 2002; Sandi, 2004), telomeric length (Epel et al., 2004) and neurogenesis (Mirescu et al., 2004) are influenced by chronic psychosocial stress, gives additional weight to our proposal that ideoffective events must be tightly integrated into a more complete understanding of the parkinsonian disease state.

CONCLUSIONS

This study provides evidence that PTT, a reactualization of Spiegel’s campotomy, is a valuable surgical option in the treatment of patients suffering from therapy-resistant PD. Its efficiency is demonstrated clearly in comparison with the preoperative medicated (ON) state, and clinical improvements are independent of follow-up length. Compared to all HFS procedures, PTT avoids device-related complications, maintenance measures and costs, and provides a high, stable level of relief to parkinsonian patients whose condition cannot be controlled by pharmacotherapy.

PTT surgery obeys the requirements imposed by the physiopathological framework of the thalamocortical dysrhythmia, for which evidence has been collected at pallidal, thalamic and cortical levels.

Our data indicate that sufficient surgical control of the TCD might provide a causal and, even, protective effect on the brain. The TCD does, indeed, promote thalamic and cortical cell death. In addition, we propose that the regularly observed resistance of axial signs might require a larger view of the situation of the PD patient, including analysis of the relevance of ideoffective factors.

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