Improving surgical treatment for movement disorders

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Chapter 5

Pallidotomy suppresses beta power in the subthalamic nucleus of Parkinson’s disease patients

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ABSTRACT

Parkinsonian patients, who have had a unilateral pallidotomy, may require bilateral deep brain stimulation of the subthalamic nucleus (STN), due to disease progression. The current model of the basal ganglia circuitry does not predict a direct effect of pallidotomy on the neuronal activity of the ipsilateral STN. To date, only three studies investigated the effect of pallidotomy on STN overall activity or neuronal firing rate, but not on the spectral content of the neuronal oscillatory activity. Moreover, none of these studies attempted to differentiate the effects to the dorsal (sensory-motor) and ventral (associative-limbic) parts of the STN. We studied the effect of pallidotomy on spectral power in six frequency bands in the STN ipsilateral and contralateral to pallidotomy from seven patients and in 60 control nuclei of patients without prior functional neurosurgery, and investigated whether this effect is different on the dorsal and ventral STN. Our data show that pallidotomy suppresses beta power (13-30 Hz) in the ipsilateral STN. This effect tends predominantly to be present in the dorsal part of STN. In addition, spectral power in the frequencies form 3 to 30 Hz is significantly higher in the dorsal part than in the ventral part. The effect of pallidotomy on STN neural activity is difficult to explain with the current model of basal ganglia circuitry and should be envisioned in the context of complex modulatory interactions in the basal ganglia.
INTRODUCTION

Stereotactic ablative lesions of the Globus pallidus pars interna (GPI) have been used extensively for the treatment of patients with advanced Parkinson’s disease (PD). Postero-ventral pallidotomy effectively reduces parkinsonian symptoms as well as Levodopa-induced dyskinesias in the contralateral hemibody. Due to the increased risk of side effects after bilateral procedures, pallidotomy is usually performed unilaterally only. Patients with unilateral pallidotomy often become candidates for an additional surgical procedure later on in their disease. Cohort studies suggest that bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) is effective in patients with a prior pallidotomy. The current model of basal ganglia circuitry does not predict a direct effect of GPI lesions on the neuronal activity of the ipsilateral STN. To date, only three studies have investigated the possible neurophysiological effects of pallidotomy on STN activity with different methods. Two of these showed significant differences in overall activity or neuronal firing rate in STNs ipsilateral to pallidotomy as compared to controls, while another study did not confirm these findings. None of these studies, however, investigated the spectral content of the neuronal oscillatory activity nor attempted to differentiate the effects to the dorsal (sensory-motor) and ventral (associative-limbic) parts of the STN. Aim of the present study was to investigate the possible effect of a prior pallidotomy on the spectral content of the neuronal oscillatory activity in the ipsilateral and contralateral STN as measured by micro-electrode recordings (MER), and to test whether this effect is different for the dorsal and ventral STN.

METHODS

All data were collected as part of routine treatment procedure and retrospectively analysed. The Medical Ethical Committee of the Academic Medical Center in Amsterdam was officially consulted and denied the need for an official approval for this study.

Patients

All PD patients who underwent STN DBS from March 2003, when we started using MER, until June 2007 were considered for the study. Demographical data and clinical information were retrospectively collected from the patients’ files. The motor part of the Unified Parkinson’s Disease Rating Scale (UPDRS) performed off-medication before STN surgery was used to evaluate parkinsonian symptoms.
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*Surgical procedure and microelectrode recordings*

Unilateral pallidotomies were performed from 1996 to 2004 (prior to STN surgery), contralateral to the most affected side. For target localization, positive-contrast stereotactic frame-based ventriculography was used. In only one patient stereotactic frame-based three-dimensional magnetic resonance imaging (MRI) was used for targeting. The standard GPi coordinates were 22 mm lateral, 2 mm anterior and 5 mm below the midcommissural point. With the exception of one patient, intraoperative MER were not used. Intraoperative low and high-frequency test stimulation was carried out in 2 mm steps starting 6-8 mm above the target with a macroelectrode (2.1 × 4.0 mm bare tip). Radio-frequency thermo-lesions were made with the same electrode used for test stimulation at the 2 adjacent electrode positions with the best therapeutic effect. The final position and volume of all pallidotomies were evaluated on the stereotactic MRI used for STN surgery by two experienced neurosurgeons.

The procedure for STN DBS was a one-stage bilateral stereotactic frame-based approach with intraoperative MER and macro-stimulation as part of a routine procedure. Preoperative frame-based MRI and Leksell Surgiplan® software (Elekta Instrument AB, Stockholm, Sweden) were used for target localization. The standard STN coordinates were 12 mm lateral, 2 mm posterior, and 4 mm below the midcomissural point. Individual adjustments were made based on direct visualization of the STN on T2-weighted MRI. Paths were planned with a 15-20° anterior angulation to the intercommissural line and a 20-30° lateral angulation from the midline, avoiding sulci, vascular structures, and ventricles.

Surgery and MER were performed bilaterally with the patients being awake, without sedatives, and off medication. The dopamine agonists, when used, were gradually reduced and then stopped 3 days before surgery, while Levodopa was stopped at least 12 hours before surgery. Single/multi-unit MER were performed using Medtronic microelectrodes 291 (Medtronic, Minneapolis, Minnesota; 10 µm exposure; impedance ~1.1MΩ at 220Hz), which capture spikes within ~100-200 µm (1-3 neurons) and background activity. Up to five MER needles were placed in a 2-mm interspace array with a central, lateral, medial, anterior, and posterior cannula. Starting from 6-8 mm above target depth, electrodes were advanced simultaneously in 0.5 mm-steps until substantia nigra activity was recognizable or activity significantly decreased in all channels. Signals were amplified by 10,000 (Leadpoint, Medtronic), analog bandpass filtered between 500-5,000 Hz (-3 dB; 12 dB/oct) and sampled at 24 kHz with a 16-bit A/D converter. Clinical testing was performed at several sites by an experienced movement disorders neurologist. The permanent quadripolar DBS electrode (Model 3389) was implanted at the site with the best therapeutic window, i.e., best effect on motor symptoms and higher threshold for side-effects. The final position of all DBS electrodes was verified by co-registration of post-operative CT with pre-operative MRI.
Data analysis
Starting 6 mm above the STN target, all recordings from the trajectory chosen for permanent electrode implantation were retrospectively analyzed. Recordings were visually inspected off-line. Only the longest, artifact-free, stable sections (minimally 3 seconds long) were analyzed. Recordings were assigned a random number and the investigator who performed signal processing and analysis was blinded to any clinical information.
The STN recordings of patients with prior pallidotomy were classified with respect to the pallidotomy side as “ipsilateral” or “contralateral” and compared with STN recordings of patients with no prior pallidotomy (“controls”).

Determination of STN borders
To determine STN borders, we analyzed the root mean square (RMS) of the signal (Moran et al 2006). At each recorded site s, we calculated the RMS(s) of the signal x(s) as:

\[ RMS(s) = \frac{\sum_{i=1}^{n} |x_i(s)|}{n} \]

where \( n \) is the total number of recorded samples at each site and \( i \) is the \( i \)th sample. Since factors like electrode properties or tissue impedance may influence RMS, we calculated a normalized RMS (NRMS) for inter-trajectory comparison. NRMS was defined as

\[ NRMS(s) = \frac{(RMS(s) - RMS_{all\_sites})}{(RMS(s) + RMS_{all\_sites})} \]

where RMS_{all\_sites} is the average of RMS(s) across all sites of the chosen trajectory. Thus, NRMS had a value between -1 and 1. STN MER activity is characterized by an increase of background noise amplitude and an increase of neuronal firing: recordings were defined to be inside the STN if NRMS(s) > 0 and outside the STN if NRMS(s) < 0. All raw recordings were visually inspected to verify this attribution.

Spectral analysis
After recorded MER signals are high-pass filtered, the resulting traces contain high-frequency spike activity, which is modulated by low frequency. We extracted this low frequency information from the signal envelope by means of full-wave rectification.\(^{12,13}\) After artifacts removal and mean subtraction, power spectral density was obtained by computing the power spectrum of the full-wave rectified signal. For each site, the complete signal was divided into non-overlapping disjoint segments of 32768 samples (segment length of 1.3653 seconds). This resulted in a frequency resolution of 0.7324 Hz. Spectral analysis of this signals was performed with MATLAB 7.6 (The Mathworks Inc) using Neurospec 2.0 scripts.\(^{14}\) MER activity was assumed to be a realization of stationary zero mean time series. Discrete Fourier transform and parameters derived from it were used for spectral analysis. The average of the power spectral density of each site was calculated and then averaged across corresponding layers in all the trajectories. Recorded signals were on average 8 seconds long, with a minimum of 3 seconds (7.6% of the signals), which always resulted in 2 or more segments per single site.
Power spectral density was split up into six frequency bands: theta (3-8 Hz), alpha (9-12 Hz), lower beta (13-20 Hz), higher beta (21-30 Hz), lower gamma (31-59 Hz), and upper gamma (60-100 Hz).\textsuperscript{15,16} To compare trajectories, we normalized the absolute power in each frequency band at each site by dividing it by the average absolute total power (3-100 Hz) of all the sites outside the STN in the same trajectory.

**Statistical analysis**
Spectral power in each frequency band was averaged across all recordings inside the STN (Whole STN analysis). In order to analyze the difference between the dorsal and ventral part of the nucleus, each trajectory was divided in two: spectral power was then averaged separately for the dorsal half and the ventral half (Dorso-ventral analysis).
For statistical mean comparison multivariate analysis of variance (MANOVA) was performed with frequencies as dependent variables, and “group” (pallidotomy sides, contralateral sides and controls) and “STN region” (dorsal or ventral) as independent variables. When a significant effect was found, post hoc analysis was run with Bonferroni correction for multiple comparisons. Since disease duration was significantly different between patients with prior pallidotomy and controls, it was used as a covariate in the analysis. Natural logarithmic transformation was applied to data prior to statistical analysis in order to improve normality. Demographical and clinical data were compared with Mann-Whitney test or with z-test when appropriate. For statistical analysis, we used PASW statistics 18 software (former SPSS).

**RESULTS**
Fifty-five PD patients underwent bilateral STN DBS between March 2003 and June 2007. Eight of these had undergone a unilateral pallidotomy prior to STN DBS; one of these patients had also undergone a prior thalamotomy and was excluded from analysis. In another patient, a lacunar infarction was present in the putamen contralateral to the pallidotomy: recordings from that side were also excluded. In the 47 patients without prior pallidotomy (control group), due to MER unavailability (28 nuclei) or suboptimal electrode position (6 nuclei), 34 nuclei were excluded from analysis (Figure 1). Thus, 60 STN trajectories from 35 control patients (10 unilateral and 25 bilateral) and 13 trajectories from 7 patients with prior pallidotomy (7 ipsilateral and 6 contralateral to pallidotomy) were used for analyses.
Clinical and demographical characteristics of the patients are described in table 1. There were no significant differences in total UPDRS motor score off-medication and age at STN surgery between patients with prior pallidotomy and controls. There was also no significant difference in a combined score for gait and postural stability (items 29 and 30 of the UPDRS) between the two groups (data not shown). Patients with prior pallidotomy, however, had significantly longer disease duration at time of STN surgery and tended to use a higher Levodopa equivalents daily dosage.
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Figure 1. Flow diagram of patient inclusion. In brackets the number of sides. MER, microelectrode recordings. *For 3 patients the other side was included, for 3 patients the other side was discarded due to one of the above mentioned reasons.

Table 1. Clinical and demographical characteristics of the patients included in the study, at the time of STN surgery.

<table>
<thead>
<tr>
<th></th>
<th>Pallidotomy (7 patients)</th>
<th>Controls (35 patients)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>5/2</td>
<td>24/11</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.4 ± 3.4</td>
<td>57.5 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>19.4 ± 6.3</td>
<td>10.7 ± 3.7</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Levodopa equivalents daily dosage (mg)</td>
<td>1647.4 ± 967.5</td>
<td>1096.7 ± 431.4</td>
<td>NS</td>
</tr>
<tr>
<td>Total UPDRS motor score off medication</td>
<td>43.4 ± 19.5</td>
<td>39.3 ± 11.3</td>
<td>NS</td>
</tr>
<tr>
<td>Time from pallidotomy to STN DBS (years)</td>
<td>6 (range 3-11)</td>
<td>-</td>
<td>-</td>
</tr>
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</table>

Levodopa equivalents daily dose was calculated according to the following conversion formula: regular levodopa dose × 1 + slow release levodopa × 0.75 + bromocriptine × 10 + apomorphine × 10 + ropinirole × 20 + pergolide × 100 + pramipexole × 100 + [regular levodopa dose + (slow release levodopa × 0.75)] × 0.2 if taking entacapone. Data are means ± Standard Deviation. DBS, Deep brain stimulation; STN, Subthalamic nucleus; UPDRS, Unified Parkinson’s disease rating scale. NS= not significant.

There was no difference in the UPDRS motor score for the contralateral hemibody (UPDRS items 20, 21, 22, 23, 24, 25, and 26) across the three groups.

At the time of pallidotomy, the hemibody contralateral to pallidotomy was the most affected (UPDRS motor score 14.4 ± 4.0 versus 12.0 ± 2.9, for the contralateral and ipsilateral hemibody respectively, data available for 5 patients). At the time of STN surgery, scores on the side contralateral to pallidotomy were still improved (UPDRS motor score 11.8 ± 6.7), although differences did not reach significance. Scores on the hemibody ipsilateral to pallidotomy were not changed (UPDRS motor score before STN DBS 12.2 ± 3.7). Although scores in the hemibody contralateral to pallidotomy were still improved compared to preoperative
condition these patients required bilateral STN DBS to improve motor performance, due to
disease progression. The average volume of the pallidotomies was 0.2 cc (range 0.1-0.4 cc).
All lesions included the GPi, while in five patients the Globus pallidus pars externa (GPe) was
also likely involved (Figure 2).
There was no significant difference in STN trajectory length across the three groups
(pallidotomy sides 4.0 ± 1.4 mm; contralateral sides 4.3 ± 0.6 mm; control sides 4.6 ± 0.8
mm). All trajectories had STN-like activity for more than 2.5 mm (range 2.5-6.5 mm).

![Figure 2. Axial (A and C) and coronal (B and D) T1 MR images of two representative patients with right sided pallidotomy. In one of the patients (A-B) the lesion is probably limited to the GPi; in the other (C-D) the lesion is most likely extended into the GPe as well.](image-url)
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**Analysis of the whole STN recordings**

When averaged across all recordings inside the STN, pallidotomy sides tended to have a reduced spectral power compared to controls in all the six frequency bands, but most clearly in the beta bands. The sides contralateral to pallidotomy had on average only slightly lower power in the frequency bands from 3 to 30 Hz as compared to controls (Figure 3). These differences were not statistically significant (MANOVA, $F = 1.298$, $p = 0.227$).

![Figure 3. Distribution of normalized power across frequency bands in the whole STN in pallidotomy, contralateral and control sides. Columns represent mean, bars represent standard error. Differences in power across groups were not statistically significant.](image)

**Analysis of the dorsal and ventral STN**

In the dorsal part of the STN, power in the pallidotomy sides tended to be smaller than in controls for all frequency bands, while power in the contralateral sides was intermediate between pallidotomy sides and controls. In the ventral STN there was no clear difference in spectral power between the three groups in any of the frequency bands (Figure 4). MANOVA showed a significant main effect of the group ($F = 1.813$, $p < 0.05$). *Post hoc* analysis showed a significant difference in power in the low (13-20 Hz; $F = 3.198$, $p < 0.05$) and the high (21-30 Hz; $F = 3.911$, $p < 0.05$) beta frequencies. Spectral power in these frequencies was significantly lower in the pallidotomy group with respect to controls ($p < 0.05$).

MANOVA showed also a significant main effect of STN region ($F = 4.344$, $p < 0.005$). *Post hoc* analysis showed that power in the frequencies from 3 to 30 Hz was significantly higher in the dorsal STN with respect to the ventral ($p < 0.05$; Figure 4).

In the dorsal part of the STN, power of all frequency bands in the pallidotomy sides appeared lower than in controls, while in the ventral STN there was no clear difference between the three groups. The interaction between group and STN region however did not reach statistical significance and was therefore removed from the model.

We found no correlation between the volume and position of the lesion and power in the lower and higher beta frequency bands in the dorsal STN (data not shown).
**DISCUSSION**

Our data show that beta band spectral power of neuronal oscillatory activity is significantly lower in the STN of PD patients ipsilateral to a prior pallidotomy than in the STN of PD patients without prior pallidotomy. This effect relies particularly on differences in beta band power recorded in the dorsal part of STN. In the dorsal STN power in the frequencies form 3 to 30 Hz is significantly higher than in the ventral part. Contralateral to the pallidotomy side, spectral power in all frequency bands shows no significant differences with the control sides.

In this study, the raw MER data were high-pass filtered and then rectified. After this process, we analyzed the low-frequency modulation of the high-frequency neuronal activity contained in signal envelope. Although this method does not allow frequency analysis of local field potentials, the information gathered from single/multi-unit recordings might be considered as representative for the oscillatory neuronal activity in the basal ganglia-cortical circuitry.

Animal and human studies suggest that the sensorimotor circuit is located in the dorso-lateral region of STN and the postero-ventral region of GPi. In agreement, we found that postero-ventral pallidotomy has a modulatory effect on neuronal oscillatory activity only in the dorsal STN and not in the ventral part, which is more involved in cognitive and associative processes.

Several hypotheses can be made to explain how a prior pallidotomy could influence ipsilateral STN neuronal activity. The suppression of STN beta activity could be due to the presence of an excitatory connection from GPi to STN, which would be interrupted by the pallidotomy. On the other hand, invasive tract tracing in primates has never shown a direct
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efferent connection from the GPI to the STN.\textsuperscript{23} In addition, the GPI efferents are known to be GABAergic and inhibitory.

Based on the currently accepted model of the basal ganglia circuitry however, it is still possible to hypothesize that a reduced activity in the GPI could influence the STN via multisynaptic paths through the pedunculopontine nucleus or the thalamo-cortical loop.\textsuperscript{9,10} Another possible explanation could be that pallidotomy affects STN fibers afferent to the postero-ventral GPI, causing retrograde degeneration and neuronal cell death in the STN. This hypothesis is supported by findings from Mogilner et al.,\textsuperscript{11} who showed a reduced cell density in the STN ipsilateral to pallidotomy with respect to the contralateral STN. Novak et al.\textsuperscript{24} published a case with segmental dystonia and prior pallidotomy who underwent bilateral STN DBS implant. Interestingly enough, also in this patient intraoperative STN MER activity appeared less robust and with lower cell density in the side ipsilateral to pallidotomy as compared to the contralateral side. These processes would selectively affect STN neurons involved in the motor circuitry that are characterized by beta frequency activity, thus explaining the selective suppression of beta frequencies.

It is uncertain whether the observed neurophysiological effects of pallidotomies can be attributed to GPI only. Indeed, a lesion located in the posteroventral GPI might concomitantly affect efferent GPe fibers directed to the STN.\textsuperscript{25} Moreover, pallidotomies could involve to a variable extent the ventral part of the GPe as well.\textsuperscript{26} Postoperative evaluation of MRI confirmed that this was also the case in five of our seven patients (Figure 2). Although GPe efferents directed to the STN are known to be GABAergic and thus suppression of their inhibitory activity would result in increased STN activity, a selective suppression of the beta band power in PD patients could be rather explained in terms of modulation of STN neurons synchronization.\textsuperscript{27}

In this study, pallidotomy patients tended to use higher Levodopa equivalents daily doses compared to controls. Although medication was discontinued in all patients, according to a standard wash-out procedure, we cannot exclude that this difference in daily medication might account, at least in part, for the observed neurophysiological differences by suppression of STN activity. It is of notice, however, that such a difference in medication, would not explain the observed differences between STNs ipsilateral and contralateral to pallidotomy in the same patient, and the fact that the STN activity contralateral to pallidotomy was similar to that of controls.

Patients with prior pallidotomy had significantly longer disease duration than controls. To correct for this difference, we have used disease duration as a covariate in the statistical analysis. One could still hypothesize that longer disease duration is associated to a higher degree of degeneration of the pedunculopontine nucleus, which would in turn affect STN activity to a higher extent. However, more advanced pedunculopontine degeneration would likely be reflected by a worse gait and postural stability and we found no difference in the combined score for gait and postural stability between patients with prior pallidotomy and controls.
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The modulatory effect of a prior pallidotomy on neuronal activity of the ipsilateral STN is supported by data from other studies.\textsuperscript{6,11,12} These studies investigated the overall activity in terms of RMS of the signal or the neuronal firing rate, while in our study the emphasis was on the spectral content of the neuronal oscillatory activity. Zaidel et al.\textsuperscript{12} showed that normalized RMS activity in multi-unit recordings was on average lower in STN ipsilateral to pallidotomy than in controls. Moreover, they showed that RMS was more regularly distributed across successive depths with respect to the controls. The authors suggest that their findings could be a reflection of a reduced synchrony in STNs ipsilateral to pallidotomy. Mogilner et al.\textsuperscript{11} showed that pallidotomy reduced the firing rate of single STN neurons ipsilaterally. Kleiner-Fisman et al. reported a similar trend toward a lower mean firing rate, although the difference was not statistically significant.\textsuperscript{6} In these studies, however, recordings where analyzed across the whole STN only. Also in our study, when we considered the STN as a whole, the trend toward lower beta values did not reach significance. This could be due both to the small sample sizes of the pallidotomy groups in these studies and to the fact that beta suppression is evident in the dorsal STN but is absent in the ventral part, and a modulatory effect of pallidotomy can be missed when averaging data across the whole nucleus.

In the patients presented here, the hemibody contralateral to pallidotomy was more affected at the time of pallidotomy. At the time of STN surgery, three to 11 years after pallidotomy, the UPDRS scores for the hemibody contralateral to pallidotomy were still lower than before pallidotomy. This indicates that pallidotomy still exerted a contralateral anti-parkinsonian effect, which would be in line with a persisting effect on STN activity. At the time of STN surgery, UPDRS motor scores in the hemibody contralateral to pallidotomy were on average comparable to controls. This suggests, in line with previous studies,\textsuperscript{28,29} that power in the beta frequency band does not reflect the absolute severity of motor symptoms. Rather, the suppression of beta frequencies might reflect the clinical improvement of motor symptoms produced by pallidotomy, in the same way as the symptomatic improvement produced by Levodopa and STN DBS correlates with depression of the beta frequencies as measured by local field potentials.\textsuperscript{16,28-33}

In conclusion, our findings show that pallidotomy affects neuronal activity in the ipsilateral STN by modulating beta activity, especially in the dorsal part. The effect of pallidotomy on STN neural activity is difficult to explain based on the current knowledge of the pathophysiology of the basal ganglia and should be considered in the context of the complex modulatory interactions in the basal ganglia circuitry.

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