Subthalamic stimulation modulates cortical control of urinary bladder in Parkinson’s disease

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Subthalamic nucleus deep brain stimulation (STN-DBS) is an effective therapy for off-period motor symptoms and dyskinesias in advanced Parkinson’s disease. Clinical studies have shown that STN-DBS also ameliorates urinary bladder function in Parkinson’s disease patients by delaying the first desire to void and increasing bladder capacity. This study aimed at investigating the effect of STN-DBS on the neural mechanisms underlying cerebral bladder control. Using PET to measure changes in regional cerebral blood flow (rCBF), 11 patients with bilateral STN-DBS were studied during urodynamic bladder filling in STN-DBS ON and OFF condition. A filled bladder led to a significant increase of rCBF in the anterior cingulate cortex, which was further enhanced during STN-DBS OFF. A significant interaction between bladder state and STN-DBS was observed in lateral frontal cortex with increased rCBF when the bladder was filled during STN-DBS OFF. The data suggest that STN-DBS ameliorates bladder dysfunction and that this modulation may result from facilitated processing ofafferent bladder information.

Keywords: deep brain stimulation; Parkinson’s disease; subthalamic nucleus; urinary bladder

Abbreviations: ACC = anterior cingulate cortex; LFC = lateral frontal cortex; rCBF = regional cerebral blood flow; ROI = region of interest; STN-DBS = subthalamic nucleus deep brain stimulation


Introduction
A large proportion of patients suffering from Parkinson’s disease presents with urinary dysfunction including urgency, increased frequency or incontinence as predominant symptoms (Lemack et al., 2000). Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been established as a surgical treatment of motor symptoms in Parkinson’s disease patients (Krack et al., 2003). However, data from experimental urodynamic measures in men (Finazzi-Agro et al., 2003; Seif et al., 2004) and animal models (Dalmose et al., 2004) have also demonstrated a significant influence of STN-DBS on urinary bladder function. In these studies, the main effect of STN-DBS appeared to be a normalization of urodynamic parameters in the storage phase with a delayed first desire to void and an increased bladder capacity. The neural basis of the impact of STN-DBS on urinary functions remains to be elucidated.

Based on anatomical connectivity and electrophysiological studies STN-DBS influences the activity of the internal globus pallidus (Parent et al., 1989; Yelnik et al., 1996) and the substantia nigra pars reticulata (Lynd-Balta and Haber, 1994; Parent and Hazrati, 1994). Both structures transfer striatal information to downstream thalamic nuclei (VA/VL) (DeVito and Anderson, 1982; Parent et al., 1983) and from there to the frontal cortex (Barbas et al., 1991), supplementary motor area (SMA) (Inase et al., 1996) and dorsolateral prefrontal cortex (DLPFC) (Ilinsky et al., 1985). Functional imaging studies have supported the view that STN-DBS profoundly influences the function of the basal ganglia circuitry in Parkinson’s disease patients and subsequently modulates thalamo-cortical projections. Most remarkably in motor paradigms, PET investigations have shown that STN-DBS affects the regional cerebral blood flow (rCBF) in
The mean age of patients was 57.7 years (mean ± standard deviation), the mean disease duration 15.2 years. In all patients quadripolar electrodes (3389, Medtronic, Minneapolis, MN) have been implanted bilaterally into the STN (for stimulation of the forebrain structures including the cingulate and frontal cortical regions including the SMA (Limousin et al., 1997; Ceballos-Baumann et al., 1999; Thobois et al., 2002; Strafella et al., 2003), DLPC (Limousin et al., 1997; Thobois et al., 2002) as well as the anterior cingulate gyrus (Limousin et al., 1997; Strafella et al., 2003). In addition, STN-DBS leads to changes in neural activation of frontotemporal (Schroeder et al., 2003) and anterior cingulate (Schroeder et al., 2002) cortical areas during cognitive tasks. Notably, these forebrain structures including the cingulate and prefrontal cortex may also play a role in withholding of urine as has been revealed by lesion studies (Andrew and Nathan, 1966; Andrew et al., 1966; Duffau and Capelle, 2005) as well as PET (Blok et al., 1997, 1998; Nour et al., 2000; Athwal et al., 2001; Matsuura et al., 2002; Dasgupta et al., 2005) and MRI (Kuhlzu-Buschbeck et al., 2005) studies.

We aimed to assess changes in brain activation during bladder filling in Parkinson’s disease patients with STN-DBS. We expected that STN-DBS changes afferent bladder information processing and thus the perception of first desire to void and urge to void thereby modulating bladder function. We furthermore hypothesized that this STN-DBS effect is associated with a modulation of neural activity in frontal cortical structures previously shown to be involved in micturition. A UTT screening kit. Subjects were comfortably positioned in the PET scanner with an intravenous cannula placed in their right cubital vein for injection of the radioactive tracer. The patient’s bladder was catheterized with a two lumen, fluid-filled pressure catheter (6F). A one lumen catheter was inserted into the rectum to monitor intra-abdominal pressure and calculate intra-vesical pressure. For the empty-bladder conditions, the bladder was emptied by the pressure catheter before the PET measurement. For the filled-bladder conditions, the bladder was filled with body warm isotonic saline solution at an infusion velocity of 25–50 ml/min. After initiation of infusion, the patients were asked to report their first bladder sensation, first desire to void and urge to void (the latter corresponding to the situation when they usually would use the bathroom). When the patients reported urge to void, filling was stopped, a bolus of [15O] water was intravenously injected and the PET measurement was started. While STN-DBS was switched OFF in half of the empty-bladder and filled-bladder conditions, respectively, STN-DBS was effective in the other half of the empty-bladder and filled-bladder conditions, respectively.

To allow adequate time for STN-DBS to become effective and ineffective, respectively, the order of conditions was counterbalanced across patients in the following way: In six patients STN-DBS was switched OFF at least 20 min before the first PET examination and concomitant urodynamic measurements were performed in the medication OFF condition at least 12 h after withdrawal of anti-parkinsonian medication. The experimental design was factorial, with the factors ‘stimulation’ (STN-DBS ON versus STN-DBS OFF) and ‘bladder state’ (empty versus filled). Each of the resulting four conditions (ON-empty, ON-filled, OFF-empty, OFF-filled) was replicated three times per patient, giving a total of 132 observations (12 scans, 11 patients).

### Material and methods

#### Subjects

The study included 11 patients (6 female and 5 male) with idiopathic Parkinson’s disease according to the UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria (see Table 1). The mean age of patients was 57.7 ± 10.9 years (mean ± standard deviation), the mean disease duration 15.2 ± 3.6 years. In all patients quadripolar electrodes (3389, Medtronic, Minneapolis, MN) have been implanted bilaterally into the STN (for stimulation parameters see Table 2). The surgical procedure has been described elsewhere in detail (Schrader et al., 2002). In all patients STN-DBS led to a significant reduction of the UPDRS motor part (UPDRS III) in the medication OFF condition [STN-DBS turned OFF (STN-DBS OFF): 44.4 ± 9.6; STN-DBS turned ON (STN-DBS ON): 16.5 ± 9.8, P < 0.05 Wilcoxon-test] as well as Hoehn and Yahr ratings (STN-DBS OFF: 3.7 ± 0.7; STN-DBS ON: 2.3 ± 0.7, P < 0.05, Wilcoxon-test). Patients were randomly selected for the PET study irrespective of urinary dysfunction.

All patients gave informed consent. The study was approved by the Ethics Committee of the Department of Medicine of the Christian Albrechts University Kiel (no. A146/04). Permission to administer radioactive substances was obtained from the regulatory authorities (Bundesamt für Strahlenschutz).

#### Experimental design and urodynamic measurements

PET examinations and concomitant urodynamic measurements were performed in the medication OFF condition at least 12 h after withdrawal of anti-parkinsonian medication. The experimental design was factorial, with the factors ‘stimulation’ (STN-DBS ON versus STN-DBS OFF) and ‘bladder state’ (empty versus filled). Each of the resulting four conditions (ON-empty, ON-filled, OFF-empty, OFF-filled) was replicated three times per patient, giving a total of 132 observations (12 scans, 11 patients).

In each patient urinary tract infection (UTI) was excluded by a UTI screening kit. Subjects were comfortably positioned in the PET scanner with an intravenous cannula placed in their right cubital vein for injection of the radioactive tracer. The patient’s bladder was catheterized with a two lumen, fluid-filled pressure catheter (6F). A one lumen catheter was inserted into the rectum to monitor intra-abdominal pressure and calculate intra-vesical pressure. For the empty-bladder conditions, the bladder was emptied by the pressure catheter before the PET measurement. For the filled-bladder conditions, the bladder was filled with body warm isotonic saline solution at an infusion velocity of 25–50 ml/min. After initiation of infusion, the patients were asked to report their first bladder sensation, first desire to void and urge to void (the latter corresponding to the situation when they usually would use the bathroom). When the patients reported urge to void, filling was stopped, a bolus of [15O] water was intravenously injected and the PET measurement was started. While STN-DBS was switched OFF in half of the empty-bladder and filled-bladder conditions, respectively, STN-DBS was effective in the other half of the empty-bladder and filled-bladder conditions, respectively.

To allow adequate time for STN-DBS to become effective and ineffective, respectively, the order of conditions was counterbalanced across patients in the following way: In six patients STN-DBS was switched OFF at least 20 min before the first PET measurement.

### Table 1 Patient characteristics, medication and response to STN-DBS

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Disease duration (years)</th>
<th>Medication (mg/day)</th>
<th>UPDRS III (max 108)</th>
<th>Hoehn and Yahr (max 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Med OFF/ Stim OFF</td>
<td>Med OFF/ Stim ON</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>49</td>
<td>14</td>
<td>750 L-Dopa; 200 amantadine</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>61</td>
<td>17</td>
<td>100 L-Dopa; 4 cabergoline; 200 amantadine</td>
<td>57</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>39</td>
<td>10</td>
<td>450 L-Dopa; 4 cabergoline; 100 amantadine</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>57</td>
<td>17</td>
<td>500 L-Dopa</td>
<td>50</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>75</td>
<td>22</td>
<td>500 L-Dopa; 2.1 pramipexole; 100 amantadine</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>69</td>
<td>18</td>
<td>200 L-Dopa; 0.54 pramipexole; 150 amantadine</td>
<td>53</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>63</td>
<td>10</td>
<td>100 L-Dopa; 1 cabergoline</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>65</td>
<td>17</td>
<td>800 L-Dopa; 2 cabergoline</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>49</td>
<td>12</td>
<td>500 L-Dopa; 200 amantadine</td>
<td>59</td>
<td>21</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>47</td>
<td>15</td>
<td>700 L-Dopa</td>
<td>45</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>61</td>
<td>15</td>
<td>300 L-Dopa</td>
<td>43</td>
<td>12</td>
</tr>
</tbody>
</table>
rCBF measurement and switched ON again directly after the sixth rCBF measurement. Before starting the seventh rCBF measurement (after at least 20 min), the effectiveness of STN-DBS was documented clinically. In these patients, STN-DBS remained ON during the second six (seventh to twelfth) rCBF measurements and, of course, thereafter. In the other five patients, the first six rCBF measurements were performed with STN-DBS ON. Right after the sixth rCBF measurement, STN-DBS was switched OFF. After at least 20 min, the decay of the stimulation effect was documented clinically and the seventh rCBF measurement was started. STN-DBS remained OFF in these patients until the end of the twelfth rCBF measurement and was switched ON directly after the PET scanning. Finally, the order of the bladder state conditions within each block of six STN-DBS ON or OFF rCBF measurements was pseudo-randomized within patients.

The mean volumes of first desire to void and urge to void in STN-DBS OFF and ON as well as the difference of these volumes between STN-DBS OFF/stim OFF and ON were compared using a paired t-test. In the other five patients, the first six rCBF measurements were performed with STN-DBS ON. Right after the sixth rCBF measurement, STN-DBS was switched OFF. After at least 20 min, the decay of the stimulation effect was documented clinically and the seventh rCBF measurement was started. STN-DBS remained OFF in these patients until the end of the twelfth rCBF measurement and was switched ON directly after the PET scanning. Finally, the order of the bladder state conditions within each block of six STN-DBS ON or OFF rCBF measurements was pseudo-randomized within patients.

PET scanning
rCBF was measured by recording the regional distribution of cerebral radioactivity after the intravenous injection of $^{15}$O water. The PET measurements were carried out using an ECAT EXACT HR+ scanner (CTI Siemens, Knoxville, TN) with a total axial field of view of 155 mm covering the whole brain. Data were acquired in 3D mode with inter-detector collimating septa removed and a Neuro-Insert installed to limit the acceptance of events originating from out-of-field-of-view activity (i.e., the whole body).

For each measurement of rCBF, 555 MBq of $^{15}$O water was given intravenously as a bolus injection. The whole study (12 scans) caused a radiation dose of 4.1 mSv (effective dose) per subject. Twelve consecutive PET scans were collected, each beginning when the brain activity exceeded a threshold of 5% of the background level. Emission data were thereafter collected sequentially over 40 s. This process was repeated for each emission scan, with 10 min between scans to allow for adequate decay of radioactivity. All emission scan data were corrected for scattered events and for radiation attenuation by means of a transmission scan taken prior to the first emission measurement. The corrected data were FORE rebinned and reconstructed into 63 transverse images (separation 2.4 mm) of $128 \times 128$ pixels ($2.0 \times 2.0$ mm$^2$) by 2D filtered back projection (DIFT) using a Shepp filter with a width of 6 mm. The reconstructed PET images had a resolution of 7 mm and were regarded to represent rCBF qualitatively.

Table 2

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Stimulation parameters, right electrode (V; µs; Hz)</th>
<th>Stimulation parameters, left electrode (V; µs; Hz)</th>
<th>Cumulative charge of right and left electrode (µC)</th>
<th>First desire to void (ml) Med OFF/stim OFF, Med OFF/stim ON</th>
<th>Urge to void (ml) Med OFF/stim OFF, Med OFF/stim ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.2; 60; 180</td>
<td>4.2; 60; 180</td>
<td>0.504</td>
<td>80</td>
<td>140</td>
</tr>
<tr>
<td>2</td>
<td>2.8; 60; 130</td>
<td>2.8; 60; 130</td>
<td>0.336</td>
<td>80</td>
<td>140</td>
</tr>
<tr>
<td>3</td>
<td>3.2; 60; 130</td>
<td>4.2; 60; 130</td>
<td>0.444</td>
<td>110</td>
<td>240</td>
</tr>
<tr>
<td>4</td>
<td>3.3; 60; 130</td>
<td>3.0; 60; 130</td>
<td>0.396</td>
<td>110</td>
<td>240</td>
</tr>
<tr>
<td>5</td>
<td>3.0; 60; 130</td>
<td>3.0; 60; 130</td>
<td>0.360</td>
<td>110</td>
<td>240</td>
</tr>
<tr>
<td>6</td>
<td>3.0; 60; 130</td>
<td>3.0; 60; 130</td>
<td>0.450</td>
<td>110</td>
<td>240</td>
</tr>
<tr>
<td>7</td>
<td>3.9; 60; 130</td>
<td>3.3; 60; 130</td>
<td>0.432</td>
<td>110</td>
<td>240</td>
</tr>
<tr>
<td>8</td>
<td>2.0; 60; 130</td>
<td>2.0; 60; 130</td>
<td>0.240</td>
<td>110</td>
<td>240</td>
</tr>
<tr>
<td>9</td>
<td>2.6; 60; 130</td>
<td>3.7; 60; 130</td>
<td>0.378</td>
<td>110</td>
<td>240</td>
</tr>
<tr>
<td>10</td>
<td>3.4; 60; 130</td>
<td>3.4; 60; 130</td>
<td>0.480</td>
<td>110</td>
<td>240</td>
</tr>
<tr>
<td>11</td>
<td>2.8; 60; 180</td>
<td>4.7; 60; 180</td>
<td>0.450</td>
<td>110</td>
<td>240</td>
</tr>
</tbody>
</table>

Based on the stimulation parameters of each patient with amplitude (V), pulse width (µs) and frequency (Hz) we determined the stimulation charge (µC) in each electrode according to the following equation: amplitude (V) × pulse width (µs) × impedance (Ω) of the respective stimulation contact. Subsequently we calculated the sum of both (right and left cumulative charge (µC)) as a marker of stimulation intensity.

Image processing
All calculations and image manipulations were performed on a Transtec Linux cluster using MATLAB version 6.5 (The Mathworks Inc., Natick, MA). Statistical parametric mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm2) was used for image realignment, image normalization, and smoothing and to create statistical maps of significant relative rCBF changes.

To correct for interscan head movement, all PET scans were realigned to the first emission scan using SPM2 software. A mean relative rCBF image was then created for each subject. This PET mean image was normalized to the standard SPM2 PET template in MNI space (Evans et al., 1994) using linear proportions as well as a non-linear sampling algorithm (Friston et al., 1995a). The resulting normalization parameter set was used to spatially normalize all PET images. The PET images were thereafter smoothed using a low-pass Gaussian filter of 12 mm to reduce the variance due to individual anatomical variability, to improve signal-to-noise ratio, and to meet the statistical requirements of the theory of Gaussian fields presupposed by the General Linear Model employed in SPM2 (Friston et al., 1995b). The resulting voxel size in stereotactic space...
Table 3 Relative increases in neural activity associated with STN-DBS ON and OFF as well as with the different bladder states and the interaction of the two factors

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>T-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main effect of STN-DBS ON: (ON-empty + ON-filled) &gt; (OFF-empty + OFF-filled)</td>
<td>STN</td>
<td>R</td>
<td>+18</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>16</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Sensorimotor cortex</td>
<td>R</td>
<td>44</td>
<td>14</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>10</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>SMA</td>
<td>R</td>
<td>16</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>26</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Main effect of filled-bladder: (ON-filled + OFF-filled) &gt; (ON-empty + OFF-empty)</td>
<td>ACC</td>
<td>L</td>
<td>16</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Interaction between STN-DBS and bladder state: [(OFF-filled &gt; OFF-empty) &gt; (ON-filled &gt; ON-empty)]</td>
<td>ACC</td>
<td>L</td>
<td>16</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Simple effect of bladder state during STN-DBS ON: (ON-filled &gt; ON-empty)</td>
<td>ACC</td>
<td>L</td>
<td>16</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Simple effect of bladder state during STN-DBS OFF: (OFF-filled &gt; OFF-empty)</td>
<td>ACC</td>
<td>L</td>
<td>12</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>LFC</td>
<td>L</td>
<td>12</td>
<td>34</td>
<td>34</td>
</tr>
</tbody>
</table>

Brain regions showing relative rCBF increases associated with each comparison of interest. For each region of activation, the coordinates in MNI space are given referring to the maximally activated voxel within an area of activation as indicated by the highest T-value. x, distance (mm) to right (+) or left (−) of the mid sagittal plane; y, distance anterior (+) or posterior (−) to vertical plane through the anterior commissure; z, distance above (+) or below (−) the intercommissural (AC–PC) plane. STN = subthalamic nucleus, SMA = supplementary motor area, ACC = anterior cingulate cortex, LFC = lateral frontal cortex; *P < 0.05, corrected for multiple comparisons across the whole brain; **P < 0.05, corrected for region-of-interest (ROI)/small volume correction (SVC); †P < 0.001, uncorrected.

was 2 × 2 × 2 mm³. Data were subsequently expressed in terms of MNI coordinates (x, y, z) as defined in Table 3.

Statistical analysis

Following stereotaxic normalization and image smoothing, statistical analysis was performed. The main effects of the factors ‘stimulation’ and ‘bladder state’ and their interactions were estimated on a voxel-by-voxel basis using SPM2. Condition-related differences in global CBF, within and between patients, were removed by treating global activity as a covariate (Friston et al, 1995b). This removed systematic state-dependent differences in global blood flow associated with the different conditions which can obscure condition-related regional alterations in activity. For each voxel in stereotactic space the ANCOVA (analysis of covariance) generated a condition specific adjusted mean rCBF value (arbitrarily normalized to 50 ml/min) and an associated adjusted error variance. This allowed the planned comparisons of the mean blood flow distributions across all sets of conditions. For each voxel, across all subjects and all scans, the mean relative rCBF values were calculated separately for each of the main effects. The means were compared with the t statistic and thereafter transformed into normally distributed Z statistics. The resulting set of Z-values constituted a statistical parametric map (SPM[Z] map). SPM[Z] statistics were interpreted in light of the theory of probabilistic behaviour of Gaussian random fields (Friston et al, 1995b). For the contrasts of interest, the significance of these statistical parametric maps was assessed by comparing the expected and observed distribution of the t statistic under the null hypothesis of no differential activation effect on rCBF. Only activations that exceeded a statistical threshold of P < 0.05 (corrected for multiple comparisons, corresponding to T = 4.79) were considered significant (no extent threshold was applied).

In addition, region-of-interest (ROI) analyses based on previous findings (Dasgupta et al, 2005; Kuhtz-Buschbeck et al, 2005) were applied for the interaction terms and the simple effects (Worsley et al, 1996). Here the statistical threshold was set at P < 0.05 (small-volume correction) (Friston, 1997). ROIs were created by computing a spherical volume of interest with a radius of 12 mm (corresponding to the effective image resolution of 12 mm following the low-pass Gaussian filter procedure used for smoothing the single subject data, see above) centred on the respective activation peaks of Dasgupta et al (Dasgupta et al, 2005) for the anterior cingulate cortex (ACC; − 4, 18, 28) and of Kuhtz-Buschbeck et al (2005) for the left lateral frontal cortex (LFC; −18, 27, 39).

Localization of activations

The stereotaxic coordinates of the voxels of local maximum significant changes in relative rCBF within areas of significant relative rCBF change associated with the different factors were determined. The anatomical localization of these local maxima was assessed by reference to MNI space (Evans et al, 1994). Additional validation of this method of localization was obtained by superimposition of the SPM[Z] maps on the single subject MRI template (in MNI space) provided by SPM2.

Results

Urodynamic data

STN-DBS led to significant changes in first desire to void and urge to void (Fig. 1 and Table 2). In STN-DBS ON the mean volume associated with first desire to void was 140 ± 65.1 ml, while it decreased to 78.9 ± 36.6 ml in STN-DBS OFF (P < 0.011, Wilcoxon test). Correspondingly, the
bladder capacity at urge to void was 135.5 ± 64.6 ml in STN-DBS OFF and increased to 199.5 ml ± 72.1 ml in STN-DBS ON (P < 0.016, Wilcoxon test). Pearson correlation analyses did not reveal any significant relationship between the stimulation intensity (as measured by stimulation charge) and volumes at first desire to void and urge to void or differences in these volumes due to STN-DBS (P > 0.05).

In 4 patients, we urodynamically recorded hyperactivity of the detrusor muscle irrespective of the stimulation state. A two-group analysis which compared the neural activations of the 7 patients with an unremarkable urodynamic profile to that of the 4 patients with urodynamically recordable hyperactivity of the detrusor muscle (i.e. pathologically increased bladder sensitivity) revealed that there were no significant differences in neural activation between the two groups. This result confirmed that the reported group PET data are related to an effect in all 11 patients and not in one subgroup only.

It has to be kept in mind, however, that the temporal resolution of the PET method is limited (acquisition time per scan: 40 s). Therefore, the rCBF measurements by PET are less sensitive to transient effects like the detrusor muscle hyperactivity, which usually last about 5–15 s, than methods like functional MRI (fMRI) with a higher temporal resolution of about 1 s. However, in patients with metallic implants like STN-DBS electrodes, fMRI is not applicable, since the gradient changes may induce currents in the implants like STN-DBS electrodes, fMRI is not applicable, especially to the detrusor muscle irrespective of the stimulation state.

In these volumes due to STN-DBS (P > 0.05).

**Neural activations measured by PET**

**Main effect of STN-DBS: STN-DBS ON versus STN-DBS OFF and vice versa**

STN-DBS ON (relative to STN-DBS OFF) led to significantly increased neural activity in the basal ganglia bilaterally (P < 0.05, corrected for whole brain) independent of bladder state (see Table 3). The MNI coordinates of the maximally activated voxels in the current study (left: −16, −10, −4; right: +18, −10, −8) were in good accordance with the coordinates published previously by Hershey et al. (2003) in Talairach and Tournoux space: ±21, −14, −4, converted to MNI space using the tal2mni-function in SPM2 by Matthew Brett (http://www.mrc-cbu.cam.ac.uk/): ±11, −14, −6.

Associated with the clinical symptoms of the patients resulting from STN-DBS OFF (see Table 1), there were bilateral significant increases of neural activity in the sensorimotor cortex (predominantly right-sided), the SMA, and (predominantly left-sided) in the cerebellum (P < 0.05, corrected for whole brain) in STN-DBS OFF (relative to STN-DBS ON).

**Main effect of bladder state: filled bladder versus empty bladder and vice versa**

Contrasting the filled-bladder conditions with the empty-bladder conditions (independent of STN-DBS) yielded significantly increased neural activity in the ACC only (−6, +36, +22, P < 0.05, corrected for whole brain) (Fig. 2A). The inverse contrast (empty bladder > filled bladder) did not reveal any significant changes in neural activity.

**Interactions between STN-DBS and bladder state**

We performed hypothesis-driven ROI-analyses (see Material and methods) of the following interaction term: (OFF-filled > OFF-empty) > (ON-filled > ON-empty). This term mainly represents the influence of the stimulation OFF condition on the contrast between filled and empty bladder. This analysis yielded significantly increased neural activity in the left LFC (P < 0.01, small volume correction) (Fig. 2C and D). This area within the LFC (activation peak at −16, +36, +32) corresponds well to the left lateral frontal area which has been described before (activation peak at −18, +27, +39), when healthy female volunteers voluntarily suppressed their urge to void (Kuhtz-Buschbeck et al., 2005).

The inverse interaction term [(OFF-empty > OFF-filled) > (ON-empty > ON-filled)] did not reveal any significant changes in neural activity.

**Simple effect of bladder state during STN-DBS ON or OFF**

A filled bladder (compared with an empty bladder) was associated with only sub-threshold activation (P < 0.001, uncorrected) of the ACC (−6, +38, +20) in STN-DBS ON (Fig. 2B). On the contrary, in STN-DBS OFF the filled-bladder condition (in contrast to the empty-bladder condition) yielded significant increases in neural activity in the ACC (−4, +34, +26, P svc < 0.05, ROI analysis with the ACC coordinates (−4, +18, +28); Fig. 2B) and left LFC (−12, +36, +32, P svc < 0.01, ROI analysis with the LFC coordinates (−18, +27, +39) corresponding to areas of
activation reported by other groups to be associated with bladder filling.

This pattern of the simple effects confirmed that the significant increase of neural activation in the left LFC associated with the interaction term \([\text{OFF-filled} > \text{OFF-empty}] > (\text{ON-filled} > \text{ON-empty})\) was mainly due to the contrast between the filled and empty bladder in STN-DBS OFF.

Possible medication effects

PET examinations were performed in the medication OFF condition at least 12 h after withdrawal of anti-parkinsonian medication. It should be noted that 12 h of medication withdrawal might not be sufficient to completely wash out dopamine agonists due to their pharmacokinetic characteristics. Therefore, to examine the effect of the potentially remaining dopamine agonists on our findings, we performed a two-group analysis which compared the neural activations of the 6 patients with dopamine agonists to that of the 5 patients without dopamine agonists, which revealed that there were no significant differences in neural activation between the two groups for the main effects of bladder status and the interaction, i.e. the contrasts of main interest. There was, however, a difference between the patients with versus without dopamine agonists for the main effect STN-DBS OFF. Two activation foci in the left sensorimotor cortex showed a significant increase in neural activity in the patients without dopamine agonists under STN-DBS OFF versus ON compared to the patients with dopamine agonists. This result of an increase in sensorimotor activity in situations of combined medication and STN-DBS OFF is fully compatible with previous reports (Ceballos-Baumann et al., 1999).

Furthermore, if at all, the remaining dopamine agonists should have attenuated the rCBF changes observed. Thus, the fact that (using a factorial design) we find consistent and stringent changes of rCBF despite possible remains of dopamine agonists in our patients further supports the strength of our findings.

Discussion

The present study demonstrates, for the first time, that STN-DBS specifically modulates forebrain cortical centres involved in urinary bladder control. At the same time this is, to our knowledge, a leadoff neuroimaging study which highlights the impact of STN-DBS on control of autonomic function in Parkinson’s disease patients. As the main finding of our study we observed a differential reduction of the bladder volume at the perception of first desire to void and urge to void (i.e. bladder dysfunction) resulting from STN-DBS OFF which was associated with an increase of LFC activity during filled-bladder conditions compared with empty-bladder conditions. In contrast, STN-DBS ON ameliorated bladder dysfunction (by increasing the bladder volumes at the perception of first desire to void/urge to void) and this amelioration was associated with a ‘normalization’ of the neural activity in the network underlying cerebral bladder control.

The LFC has previously been identified to play a role in the cerebral control of urinary bladder function. In lesion studies, the frontal superior gyrus was found to be involved in the inhibition of micturition (Andrew and Nathan, 1964; Sakakibara et al., 1996). Lesions in that area, extending laterally to the tip of the frontal horn of the ventricle and medially to the anterior part of the cingulate gyrus, caused clinical syndromes of neurogenic bladder with lack of bladder sensation, uninhibited sphincter relaxation and inability to suppress the micturition reflex. Case series
(Lang et al., 1996; Sekido and Akaza, 1997) have confirmed similar correlations between frontal lesion sites and occurrence of bladder dysfunction with preponderating symptoms of incontinence. A recent MRI study (Kuhtz-Buschbeck et al., 2005) demonstrated that the left LFC may likewise be of particular importance in the physiological process of continence maintenance in healthy subjects. Using fMRI in young women, instruction to voluntarily suppress the desire to void was shown to lead to significant activation of the left frontal cortex. The coordinates of that activation are in good accordance with the area we found in association with bladder fullness in STN-DBS OFF. Based on that data, it might be hypothesized that LFC activation in STN-DBS OFF reflects cortical effort to suppress unwanted bladder activity triggered early at reduced bladder capacity.

The neural pathway of the proposed impact of LFC on sustaining continence is not yet known. Data from rodents (Beckstead, 1979; Kita and Oomura, 1981; Sesack et al., 1989) and non-human primates (Arnsten and Goldman-Rakic, 1984; Ongur et al., 1998) support the existence of direct fibre connections between prefrontal areas and subcortical structures such as hypothalamic nuclei and the periaqueductal grey (PAG) which are involved in urinary bladder control. The hypothalamus and PAG are supposed to essentially influence the pontine micturition centre (PMC) (Holstege, 1987; Blok and Holstege, 1994) and determine the beginning of micturition. Consistent with experimental data in animals, PET studies have shown that the hypothalamus and PAG appear to be more active during micturition than during withholding of urine (Blok et al., 1997, 1998; Nour et al., 2000). Similarly, the withholding-paradigm in our study did not reveal any significant activation in the hypothalamus, PAG or PMC. The LFC activation during STN-DBS OFF may therefore reflect an inhibitory influence of the frontal lobe onto downstream micturition control centres. Alternatively, one may argue that the rCBF increase in LFC does not reflect a top-down modulation by non-pyramidal corticofugal projections but rather increased demands on cortical executive control mechanisms localized in (dorso-) lateral prefrontal cortex. The LFC activation may therefore reflect cortical monitoring of the discrepancy between actual bladder volume and inappropriate perception of bladder volume in STN-DBS OFF. In this respect, the reported activation in the LFC is functionally part of the DLPFC known to be involved in monitoring of (conflicting) sensory percepts (Fink et al., 1999).

Comparable to findings in healthy volunteers (Nour et al., 2000; Athwal et al., 2001; Matsuura et al., 2002; Dasgupta et al., 2005; Kuhtz-Buschbeck et al., 2005), the present study revealed that bladder filling (irrespective of STN-DBS) was associated with rCBF increases in the ACC. The role of the ACC in monitoring bladder filling is not conclusively defined. However, neuroimaging studies allocate general cognitive processes such as demand of attention and executive control to the ACC (Stephan et al., 2003) and, more specifically with respect to the context of our study, also autonomic control (Critchley et al., 2003). Additionally, the ACC has been implicated in bioregulatory processes including nociception (Buchel et al., 2002), respiration (Liotti et al., 2001), processing of somatosensory (Buchel et al., 2002) and viscerosensory (Aziz et al., 2000) information as well as autonomic arousal (Critchley et al., 2000). In view of these findings, some authors have argued that the ACC does not simply monitor bladder volume. They rather suggested a role in integrating afferent information and internal motivational states, evaluation of responses as well as guiding compensatory strategies (Athwal et al., 2001; Blok, 2002; Dasgupta et al., 2005). It therefore might be hypothesized that the ACC activation observed in our study represents appraisal of afferent urinary information in the context of additional external or internal cues as well as evaluation of behavioural strategies.

In this context it is noteworthy that STN-DBS ON was associated with only weak ACC activation in the filled-bladder condition while STN-DBS OFF led to a stronger increase of rCBF in the ACC although that difference in ACC activation between STN-DBS OFF and ON did not reach statistical significance (as assessed by the interaction term). Nevertheless, the different ACC activity levels in the simple contrasts suggest a qualitative modulation of the ACC by STN-DBS during bladder filling. Similarly, it has been shown that ACC activity is modulated by STN-DBS (Limousin et al., 1997; Schroeder et al., 2002; Strafella et al., 2003) in motor and cognitive tasks. The data thus add to previous evidence that the ACC is a target structure of the basal ganglia-thalamo-cortical circuitry affected by STN-DBS. Alternatively, based on the standard basal ganglia model of DeLong (1990), STN-DBS may cause adjustment of cerebral activation resulting from urinary sensory input at the level of the basal ganglia with subsequent altered activation of output cortical regions. In this context, the qualitative differences in ACC activation would probably correspond to the significant change in urodynamic parameters in the stimulation OFF and ON condition. Increased ACC activation in STN-DBS OFF may then result from earlier perception of urge to void compared to the STN-DBS ON with only weak ACC activation at greater bladder capacity.

A confounding factor in our study might be that it was not referenced to the same absolute bladder filling volumes in each individual patient but instead referred to the subjective feeling of the urge to void. The former procedure would have allowed assessing the differential cerebral response to the same physical condition (i.e. the same absolute bladder volume) depending on the STN-DBS condition. However, due to the limited number of scans per patient it was not possible to include such additional conditions in this study. Therefore, we focused on the urge to void, since most studies hitherto also used the sensation of urge to void as an appropriate parameter. Furthermore, it
has to be taken into account that the retrograde bladder filling at an infusion velocity of 25–50 ml/min (as used in our study) does not correspond to the physiological bladder filling which is usually within the range of <20 ml/min (Abrams et al., 2002). Therefore, our paradigm with high infusion rates may not reflect the naive bodily state and may have modulated the neural mechanisms involved in the physiology of bladder monitoring. Comparably to our study, previous PET investigations have been based on urodynamic bladder filling with infusion rates of 50 ml/min (Nour et al., 2000; Matsuura et al., 2002) or even of 200 ml/min (Athwal et al., 2001). Contrariwise, other functional imaging studies have provided physiological bladder filling by water drinking and confirmation of bladder fullness by transabdominal ultrasound (Bloek et al., 1997, 1998; Dasgupta et al., 2005; Kucht-Buschbeck et al., 2005). In all studies, irrespective of the filling method, there was a substantial modulation of frontal and partly of subcortical centres known to be involved in the cerebral control of the urinary bladder. We decided to use retrograde bladder filling in order to provide reproducible urinary bladder states for each of 12 PET scans and allow a short as possible investigation period for the severely affected Parkinson’s disease patients. Future studies may more precisely elucidate the influence of the method of bladder filling on neural activations involved in the cerebral control of the urinary bladder.

As a conceptual model, we propose that STN-DBS influences the integration of afferent bladder information within the basal ganglia circuits resulting in different appraisal of sensory information by cortical areas. An influential suggestion (Kaji and Murase, 2001) is that basal ganglia structures play an important role in association of sensory cues to motor commands and thus reinforcing pattern of cortical activity during movement preparation and execution. It has been proposed that disturbances of this sensory gating in striatal diseases result in inadequate motor programmes (Abbruzzese and Berardelli, 2003). In Parkinson’s disease, neurophysiological observations (Flowers, 1976; Baroni et al., 1984) suggest that changes in the process of sensorimotor integration do not occur at peripheral level but depend on abnormal central processing of sensory input. Concomitantly, it has been shown that STN-DBS leads to improved sensorimotor integration in patients (Gerschlager et al., 1999; Devos et al., 2003). Based on these findings, one may argue that increased ACC activity implies that the

Fig. 3 Influence of STN-DBS on cortical centres of urinary bladder control in stimulation OFF condition (A) and stimulation ON condition (B). In STN-DBS OFF, errant processing of urinary bladder input, which is relayed to the higher centres by the PAG, in the basal ganglia (BG) loop may lead to an increase in activation of the ACC. As a compensatory mechanism, the LFC is activated and exerts its inhibitory influence on the PMC. This allows maintenance of continence. In STN-DBS ON, sensory information processing in the BG loop may be restored, which consecutively results in normalization (i.e. a relative decrease) of ACC activity. As a consequence, inhibitory influence of the LFC on the PMC is no longer necessary for maintenance of continence. Thal = Thalamus.
ACC attributes increased relevance to bladder fullness due to errant sensory processing in the basal ganglia in STN-DBS OFF. Eventually, the activation of LFC in STN-DBS OFF may be regarded as a compensatory strategy for maintenance of continence influenced by the ACC (Fig. 3A). Contrary, partial restoration of the physiological basal ganglia state by means of STN-DBS may induce normalization of the sensory gating process and consecutively regularize impact of afferent bladder information on ACC. This leads to decreased ACC in STN-DBS ON and consequently reduces the need for increased LFC activity for maintaining continence (Fig. 3B).

In summary, we offer a physiological explanation for the influence of STN-DBS on bladder function in Parkinson’s disease patients and show that STN-DBS modulates activation of LFC and ACC during bladder filling. The underlying neural mechanism might be a more effective integration of afferent bladder information in the basal ganglia circuitry as a consequence of STN-DBS.

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