

# 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 of afferent 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

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## 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

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

Patient no.	Sex	Age	Disease duration (years)	Medication (mg/day)	UPDRS III (max 108)		Hoehn and Yahr (max 5)	
					Med OFF/ Stim OFF	Med OFF/ Stim ON	Med OFF/ Stim OFF	Med OFF/ Stim ON
1	M	49	14	750 L-Dopa; 200 amantadine	38	9	2.5	1.5
2	F	61	17	100 L-Dopa; 4 cabergoline; 200 amantadine	57	41	4.0	3.0
3	M	39	10	450 L-Dopa; 4 cabergoline; 100 amantadine	39	10	3.0	2.0
4	F	57	17	500 L-Dopa	50	21	4.0	3.0
5	M	75	22	500 L-Dopa; 2.1 pramipexole; 100 amantadine	29	17	5.0	3.0
6	F	69	18	200 L-Dopa; 0.54 pramipexole; 150 amantadine	53	21	4.0	3.0
7	F	63	10	100 L-Dopa; 1 cabergoline	42	15	4.0	2.0
8	M	65	17		33	6	3.0	1.0
9	F	49	12	800 L-Dopa; 2 cabergoline	59	21	4.0	3.0
10	F	47	15	700 L-Dopa	45	8	4.0	2.0
11	M	61	15	300 L-Dopa	43	12	4.0	2.0

frontal cortical regions including the SMA (Limousin *et al.*, 1997; Ceballos-Baumann *et al.*, 1999; Thobois *et al.*, 2002; Strafella *et al.*, 2003), DLPFC (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 lesional studies (Andrew and Nathan, 1964; 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 (Kuhntz-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.

## 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  $57.7 \pm 10.9$  years (mean  $\pm$  standard deviation), the mean disease duration  $15.2 \pm 3.6$  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):  $44.4 \pm 9.6$ ; STN-DBS turned ON (STN-DBS ON):  $16.5 \pm 9.8$ ,  $P < 0.05$  Wilcoxon-test] as well as Hoehn and

Yahr ratings (STN-DBS OFF:  $3.7 \pm 0.7$ ; STN-DBS ON:  $2.3 \pm 0.7$ ,  $P < 0.05$ , 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 [ $^{15}\text{O}$ ] 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

**Table 2** Stimulation parameters, cumulative stimulation charge of the right and left electrode, and mean volume of first desire to void and urge to void of each patient

Patient no.	Stimulation parameters right electrode (V; $\mu$ s; Hz)	Stimulation parameters left electrode (V; $\mu$ s; Hz)	Cumulative charge of right and left electrode ( $\mu$ C)	First desire to void (ml)		Urge to void (ml)	
				Med OFF/stim	Med OFF/stim ON	Med OFF/stim	Med OFF/stim ON
1	4.2; 60; 180	4.2; 60; 180	0.504	80	140	130	200
2	2.8; 60; 130	2.8; 60; 130	0.336	80	140	160	285
3	3.2; 60; 130	4.2; 60; 130	0.444	130	160	180	195
4	3.3; 60; 130	3.0; 60; 130	0.396	110	240	140	250
5	3.0; 60; 130	3.0; 60; 130	0.360	40	150	50	185
6	3.0; 60; 180	3.0; 90; 180	0.450	40	100	80	130
7	3.9; 60; 130	3.3; 60; 130	0.432	115	220	205	310
8	2.0; 60; 130	2.0; 60; 130	0.240	45	85	60	90
9	2.6; 60; 130	3.7; 60; 130	0.378	100	150	200	250
10	3.4; 60; 130	3.4; 60; 130	0.480	60	45	210	160
11	2.8; 60; 180	4.7; 60; 180	0.450	30	70	70	140

Based on the stimulation parameters of each patient with amplitude (V), pulse width ( $\mu$ s) and frequency (Hz) we determined the stimulation charge ( $\mu$ C) in each electrode according to the following equation: amplitude (V)  $\times$  pulse width ( $\mu$ s)/impedance ( $\Omega$ ) of the respective stimulation contact. Subsequently we calculated the sum of both [right and left cumulative charge ( $\mu$ C)] as a marker of stimulation intensity.

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 the stimulation parameters (amplitude, pulse width, frequency) of each patient are displayed in Table 2. We determined the stimulation intensity by calculating the stimulation charge ( $\mu$ C) of each DBS electrode based on the following expression: [amplitude (V)  $\times$  pulse width ( $\mu$ s)]/impedance of stimulation contact ( $\Omega$ ). We were interested in the dose–response relationship between stimulation intensity and urodynamic parameters. Therefore, we performed Pearson correlation analyses between the cumulative stimulation charge of both DBS electrodes and the mean volumes at first desire and urge to void as well as the difference of these volumes between STN-DBS ON and OFF.

## 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 (size 2.0  $\times$  2.0 mm<sup>2</sup>) 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.

## 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

Region	Side	x	y	z	T-value
Main effect of STN-DBS ON: (ON-empty + ON-filled) > (OFF-empty + OFF-filled)					
STN	R	+18	−10	−8	8.03*
	L	−16	−10	−4	9.54*
Main effect of STN-DBS OFF: (OFF-empty + OFF-filled) > (ON-empty + ON-filled)					
Sensorimotor cortex	R	+44	−14	+44	10.13*
	L	−44	−10	+36	6.76*
SMA	R	6	−12	50	8.51*
Cerebellum	R	+14	−60	−12	5.99*
	L	−8	−52	−16	6.08*
Main effect of filled-bladder: (ON-filled + OFF-filled) > (ON-empty + OFF-empty)					
ACC	L	−6	+36	+22	4.99*
Interaction between STN-DBS and bladder state: [(OFF-filled > OFF-empty) > (ON-filled > ON-empty)]					
LFC	L	−16	+36	+32	3.95**
Simple effect of bladder state during STN-DBS ON: ON-filled > ON-empty					
ACC	L	−6	+38	+20	4.05 <sup>#</sup>
Simple effect of bladder state during STN-DBS OFF: OFF-filled > OFF-empty					
ACC	L	−4	+34	+26	3.95**
LFC	L	−12	+36	+32	3.96**

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 midsagittal 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); <sup>#</sup> $P < 0.001$ , uncorrected.

was  $2 \times 2 \times 2 \text{ mm}^3$ . 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 stereotaxic 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

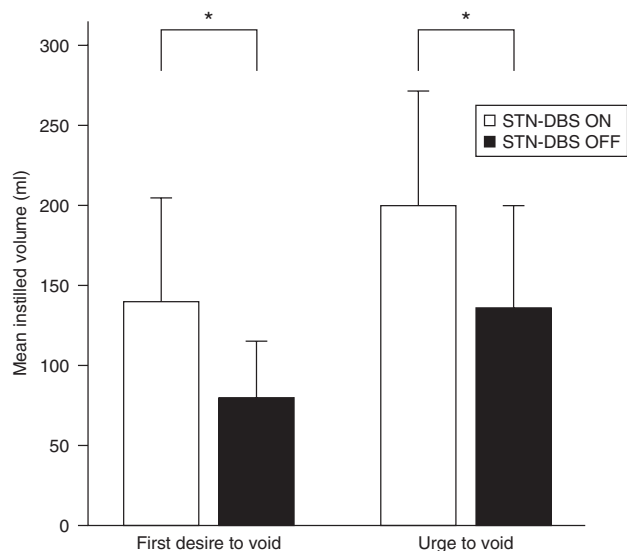
The stereotaxic coordinates of the voxels of local maximum significant changes in relative rCBF within areas of significant relative rCBF change associated with the different factors were determined. The anatomical localization of these local maxima was assessed by reference to MNI space (Evans *et al.*, 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  $140 \pm 65.1 \text{ ml}$ , while it decreased to  $78.9 \pm 36.6 \text{ ml}$  in STN-DBS OFF ( $P < 0.011$ , Wilcoxon test). Correspondingly, the





**Fig. 1** Influence of STN-DBS on perception of first desire to void and urge to void. \* =  $P < 0.05$  (Wilcoxon test).

bladder capacity at urge to void was  $135.5 \pm 64.6$  ml in STN-DBS OFF and increased to  $199.5 \text{ ml} \pm 72.1$  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 electrodes, which may harm the patients.

## 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:  $\pm 11, -14, -4$ , converted to MNI space using the tal2mni-function in SPM2 by Matthew Brett (<http://www.mrc-cbu.cam.ac.uk/>):  $\pm 11, -14, -6$ ].

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 (predominately 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.

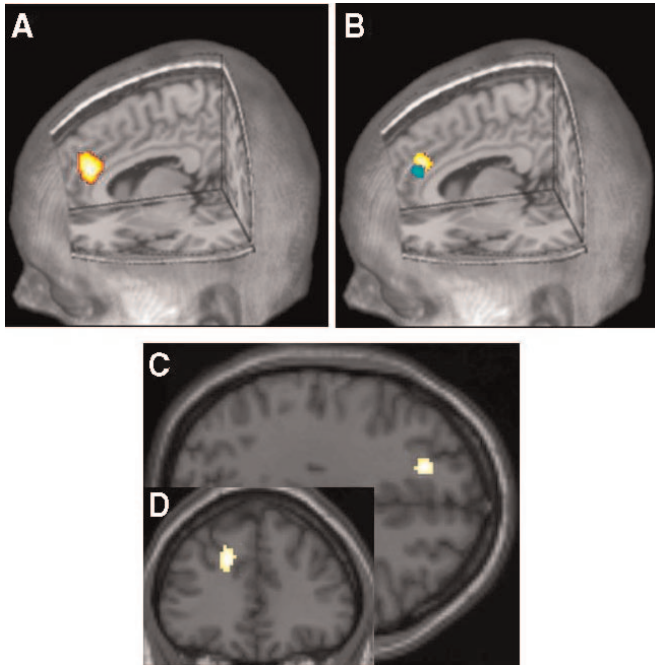
### Interactions between STN-DBS and bladder state

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 (Kuitz-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 ( $-4, +34, +26$ ,  $P_{\text{svc}} < 0.05$ , ROI analysis with the ACC coordinates ( $-4, +18, +28$ ); Fig. 2B] and left LFC [ $-12, +36, +32$ ,  $P_{\text{svc}} < 0.01$ , ROI analysis with the LFC coordinates ( $-18, +27, +39$ )] corresponding to areas of



**Fig. 2** Upper row: Modulation of neural activity in ACC by bladder fullness and STN-DBS. (A) Strong ACC activation for the main effect of bladder filling (ON-filled and OFF-filled) > (ON-empty and OFF-empty). (B) The simple effects of bladder state for the STN-DBS ON conditions displayed in blue/green (ON-filled > ON-empty) and for the STN-DBS OFF conditions (OFF-filled > OFF-empty) shown in yellow/red. Note, the two clusters associated with the simple effects are distinct and that the simple effect OFF-filled > OFF-empty activates the ACC more strongly than the contrast ON-filled > ON-empty. The activation clusters are superimposed on a 3D section of a single subject MRI template provided by MRIcro (Rorden and Brett, 2000). Lower row: The left lateral frontal cortex (LFC) is differentially modulated by STN-DBS and bladder status as expressed by the interaction term [(OFF-filled > OFF-empty) > (ON-filled > ON-empty)]. Depicted is the differential increase of neural activity in the LFC under STN-DBS OFF versus STN-DBS ON when the bladder is filled versus when it is empty. The activation cluster in the LFC is shown in two different views: superimposed on an axial slice at  $z = +32$  mm (C) and a coronal section at  $y = +36$  mm (D) of the standard SPM2 single subject MRI template in MNI space. For display purposes the threshold was set to  $P < 0.001$ , uncorrected, for all figures.

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 [(OFF-filled > OFF-empty) > (ON-filled > 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 lesional 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 (Kuhntz-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.

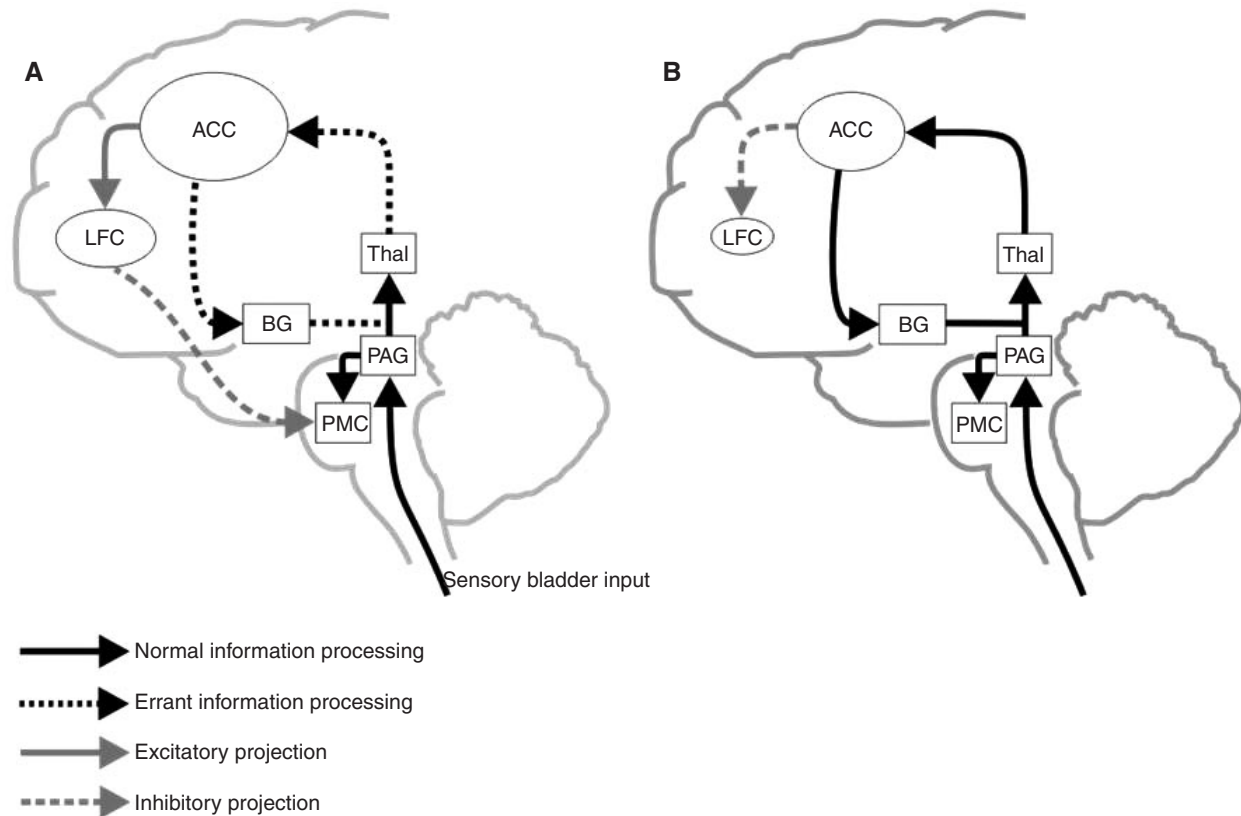
The neural pathway of the proposed impact of LFC on sustaining continence is not yet known. Data from rodents (Beckstead, 1979; Kita and Oomura, 1981; Sesack *et al.*, 1989) and non-human primates (Arnsten and Goldman-Rakic, 1984; Ongur *et al.*, 1998) support the existence of direct fibre connections 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 cognitive control processes (Koechlin *et al.*, 2003) and 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; Kuhntz-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



**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.

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 (Blok *et al.*, 1997, 1998; Dasgupta *et al.*, 2005; Kuhtz-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 (Gerschlag *et al.*, 1999; Devos *et al.*, 2003). Based on these findings, one may argue that increased ACC activity implies that the



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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## Reference

- Abbruzzese G, Berardelli A. Sensorimotor integration in movement disorders. *Mov Disord* 2003; 18: 231–40.
- Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; 21: 167–78.
- Andrew J, Nathan PW. Lesions on the anterior frontal lobes and disturbances of micturition and defaecation. *Brain* 1964; 87: 233–62.
- Andrew J, Nathan PW, Spanos NC. Disturbances of micturition and defaecation due to aneurysms of anterior communicating or anterior cerebral arteries. *J Neurosurg* 1966; 24: 1–10.
- Arnsten AF, Goldman-Rakic PS. Selective prefrontal cortical projections to the region of the locus coeruleus and raphe nuclei in the rhesus monkey. *Brain Res* 1984; 306: 9–18.
- Athwal BS, Berkley KJ, Hussain I, Brennan A, Craggs M, Sakakibara R, et al. Brain responses to changes in bladder volume and urge to void in healthy men. *Brain* 2001; 124: 369–77.
- Aziz Q, Schnitzler A, Enck P. Functional neuroimaging of visceral sensation. *J Clin Neurophysiol* 2000; 17: 604–12.
- Barbas H, Henion TH, Dermon CR. Diverse thalamic projections to the prefrontal cortex in the rhesus monkey. *J Comp Neurol* 1991; 313: 65–94.
- Baroni A, Benvenuti F, Fantini L, Pantaleo T, Urbani F. Human ballistic arm abduction movements: effects of L-dopa treatment in Parkinson's disease. *Neurology* 1984; 34: 868–76.
- Beckstead RM. An autoradiographic examination of corticocortical and subcortical projections of the mediodorsal-projection (prefrontal) cortex in the rat. *J Comp Neurol* 1979; 184: 43–62.
- Blok BF. Brain control of the lower urinary tract. *Scand J Urol Nephrol Suppl* 2002; p. 11–5.
- Blok BF, Holstege G. Direct projections from the periaqueductal gray to the pontine micturition center (M-region). An anterograde and retrograde tracing study in the cat. *Neurosci Lett* 1994; 166: 93–6.
- Blok BF, Willemsen AT, Holstege G. A PET study on brain control of micturition in humans. *Brain* 1997; 120: 111–21.
- Blok BF, Sturms LM, Holstege G. Brain activation during micturition in women. *Brain* 1998; 121: 2033–42.
- Buchel C, Bornhoved K, Quante M, Glauche V, Bromm B, Weiller C. Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study. *J Neurosci* 2002; 22: 970–6.
- Ceballos-Baumann AO, Boecker H, Bartenstein P, von Falkenhayn I, Riescher H, Conrad B, et al. A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson disease: enhanced movement-related activity of motor-association cortex and decreased motor cortex resting activity. *Arch Neurol* 1999; 56: 997–1003.
- Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *J Physiol* 2000; 523: 259–70.
- Critchley HD, Mathias CJ, Josephs O, O'Doherty J, Zanini S, Dewar BK, et al. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain* 2003; 126: 2139–52.
- Dalmo AL, Bjarkam CR, Sorensen JC, Djurhuus JC, Jorgensen TM. Effects of high frequency deep brain stimulation on urine storage and voiding function in conscious minipigs. *Neurourol Urodyn* 2004; 23: 265–72.
- Dasgupta R, Critchley HD, Dolan RJ, Fowler CJ. Changes in brain activity following sacral neuromodulation for urinary retention. *J Urol* 2005; 174: 2268–72.
- DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 1990; 13: 281–5.
- DeVito JL, Anderson ME. An autoradiographic study of efferent connections of the globus pallidus in *Macaca mulatta*. *Exp Brain Res* 1982; 46: 107–17.
- Devos D, Labyt E, Cassim F, Bourriez J, Reyns N, Touzet G, et al. Subthalamic stimulation influences postmovement cortical somatosensory processing in Parkinson's disease. *Eur J Neurosci* 2003; 18: 1884–8.
- Duffau H, Capelle L. Incontinence after brain glioma surgery: new insights into the cortical control of micturition and continence. Case report. *J Neurosurg* 2005; 102: 148–51.
- Evans A, Kamber M, Collins D, MacDonald D. An MRI-based probabilistic atlas of neuroanatomy. In: Shorvton S, Fish D, Andersmann F, Bydder G, Stefan H, editors. *Magnetic resonance scanning and epilepsy*. New York: Plenum Press; 1994. p. 263–74.
- Finazzi-Agro E, Peppe A, D'Amico A, Petta F, Mazzone P, Stanzione P, et al. Effects of subthalamic nucleus stimulation on urodynamic findings in patients with Parkinson's disease. *J Urol* 2003; 169: 1388–91.
- Fink GR, Marshall JC, Halligan PW, Frith CD, Driver J, Frackowiak RS, et al. The neural consequences of conflict between intention and the senses. *Brain* 1999; 122: 497–512.
- Flowers KA. Visual “closed-loop” and “open-loop” characteristics of voluntary movement in patients with Parkinsonism and intention tremor. *Brain* 1976; 99: 269–310.
- Friston K, Ashburner J, Frith C, Poline J, Heather K, Frackowiak R. Spatial registration and normalization of images. *Hum Brain Mapp* 1995a; 3: 165–89.
- Friston K, Holmes A, Worsley K, Poline J, Frith C, Frackowiak R. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp* 1995b; 2: 189–210.
- Friston KJ. Testing for anatomically specified regional effects. *Hum Brain Mapp* 1997; 5: 133–6.
- Gerschlag W, Alesch F, Cunningham R, Deecke L, Dirnberger G, Endl W, et al. Bilateral subthalamic nucleus stimulation improves frontal cortex function in Parkinson's disease. An electrophysiological study of the contingent negative variation. *Brain* 1999; 122: 2365–73.

- Hershey T, Revilla FJ, Wernle AR, McGee-Minnich L, Antenor JV, Videen TO, et al. Cortical and subcortical blood flow effects of subthalamic nucleus stimulation in PD. *Neurology* 2003; 61: 816–21.
- Holstege G. Some anatomical observations on the projections from the hypothalamus to brainstem and spinal cord: an HRP and autoradiographic tracing study in the cat. *J Comp Neurol* 1987; 260: 98–126.
- Ilinsky IA, Jouandet ML, Goldman-Rakic PS. Organization of the nigrothalamocortical system in the rhesus monkey. *J Comp Neurol* 1985; 236: 315–30.
- Inase M, Tokuno H, Nambu A, Akazawa T, Takada M. Origin of thalamocortical projections to the presupplementary motor area (pre-SMA) in the macaque monkey. *Neurosci Res* 1996; 25: 217–27.
- Kaji R, Murase N. Sensory function of basal ganglia. *Mov Disord* 2001; 16: 593–4.
- Kita H, Oomura Y. Reciprocal connections between the lateral hypothalamus and the frontal complex in the rat: electrophysiological and anatomical observations. *Brain Res* 1981; 213: 1–16.
- Koechlin E, Ody C, Kouneiher F. The architecture of cognitive control in the human prefrontal cortex. *Science* 2003; 302: 1181–5.
- Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. [see comment]. *N Engl J Med* 2003; 349: 1925–34.
- Kuhtz-Buschbeck JP, van der Horst C, Pott C, Wolff S, Nabavi A, Jansen O, et al. Cortical representation of the urge to void: a functional magnetic resonance imaging study. *J Urol* 2005; 174: 1477–81.
- Lang EW, Chesnut RM, Hennerici M. Urinary retention and space-occupying lesions of the frontal cortex. *Eur Neurol* 1996; 36: 43–7.
- Lemack GE, Dewey RB Jr, Roehrborn CG, O'Suilleabhain PE, Zimmern PE. Questionnaire-based assessment of bladder dysfunction in patients with mild to moderate Parkinson's disease. *Urology* 2000; 56: 250–4.
- Limousin P, Greene J, Pollak P, Rothwell J, Benabid AL, Frackowiak R. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. *Ann Neurol* 1997; 42: 283–91.
- Liotti M, Brannan S, Egan G, Shade R, Madden L, Abplanalp B, et al. Brain responses associated with consciousness of breathlessness (air hunger). *Proc Natl Acad Sci USA* 2001; 98: 2035–40.
- Lynd-Balta E, Haber SN. Primate striatonigral projections: a comparison of the sensorimotor-related striatum and the ventral striatum. *J Comp Neurol* 1994; 345: 562–78.
- Matsuura S, Kakizaki H, Mitsui T, Shiga T, Tamaki N, Koyanagi T. Human brain region response to distention or cold stimulation of the bladder: a positron emission tomography study. *J Urol* 2002; 168: 2035–9.
- Nour S, Svarer C, Kristensen JK, Paulson OB, Law I. Cerebral activation during micturition in normal men. *Brain* 2000; 123: 781–9.
- Ongur D, An X, Price JL. Prefrontal cortical projections to the hypothalamus in macaque monkeys. *J Comp Neurol* 1998; 401: 480–505.
- Parent A, Hazrati LN. Multiple striatal representation in primate substantia nigra. *J Comp Neurol* 1994; 344: 305–20.
- Parent A, Mackey A, Smith Y, Boucher R. The output organization of the substantia nigra in primate as revealed by a retrograde double labeling method. *Brain Res Bull* 1983; 10: 529–37.
- Parent A, Smith Y, Filion M, Dumas J. Distinct afferents to internal and external pallidal segments in the squirrel monkey. *Neurosci Lett* 1989; 96: 140–4.
- Rorden C, Brett M. Stereotaxic display of brain lesions. *Behav Neurol* 2000; 12: 191–200.
- Sakakibara R, Hattori T, Yasuda K, Yamanishi T. Micturitional disturbance after acute hemispheric stroke: analysis of the lesion site by CT and MRI. *J Neurol Sci* 1996; 137: 47–56.
- Schrader B, Hamel W, Weinert D, Mehdorn HM. Documentation of electrode localization. *Mov Disord* 2002; 17: S167–74.
- Schroeder U, Kuehler A, Haslinger B, Erhard P, Fogel W, Tronnier VM, et al. Subthalamic nucleus stimulation affects striato-anterior cingulate cortex circuit in a response conflict task: a PET study. *Brain* 2002; 125: 1995–2004.
- Schroeder U, Kuehler A, Lange KW, Haslinger B, Tronnier VM, Krause M, et al. Subthalamic nucleus stimulation affects a frontotemporal network: a PET study. *Ann Neurol* 2003; 54: 445–50.
- Seif C, Herzog J, van der Horst C, Schrader B, Volkmann J, Deuschl G, et al. Effect of subthalamic deep brain stimulation on the function of the urinary bladder. *Ann Neurol* 2004; 55: 118–20.
- Sekido N, Akaza H. Neurogenic bladder may be a side effect of focus resection in an epileptic patient. *Int J Urol* 1997; 4: 101–3.
- Sesack SR, Deutch AY, Roth RH, Bunney BS. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. *J Comp Neurol* 1989; 290: 213–42.
- Stephan KE, Marshall JC, Friston KJ, Rowe JB, Ritzl A, Zilles K, et al. Lateralized cognitive processes and lateralized task control in the human brain. *Science* 2003; 301: 384–6.
- Strafella AP, Dagher A, Sadikot AF. Cerebral blood flow changes induced by subthalamic stimulation in Parkinson's disease. *Neurology* 2003; 60: 1039–42.
- Thobois S, Dominey P, Fraix V, Mertens P, Guenot M, Zimmer L, et al. Effects of subthalamic nucleus stimulation on actual and imagined movement in Parkinson's disease: a PET study. *J Neurol* 2002; 249: 1689–98.
- Worsley K, Marret S, Neelin P, Vandal A, Friston K, Evans A. A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp* 1996; 4: 58–73.
- Yelnik J, Francois C, Percheron G, Tande D. A spatial and quantitative study of the striatopallidal connection in the monkey. *Neuroreport* 1996; 7: 985–8.