doi:10.1093/brain/awm254 *Brain* (2008), **131**, 132–145

Improved sensory gating of urinary bladder afferents in Parkinson's disease following subthalamic stimulation

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In addition to motor symptoms, patients with Parkinson's disease (PD) show deficits in sensory processing. These deficits are thought to result from deficient gating of sensory information due to basal ganglia dysfunction in PD. Deep brain stimulation of the subthalamic nucleus (STN-DBS) has been shown to improve sensory deficits in PD, e.g. STN-DBS normalizes the perception of urinary bladder filling in patients with PD. This study aimed at investigating how STN-DBS modulates the processing of urinary bladder information to elucidate the (patho-)physiology of sensory gating mechanisms in PD.

Nine PD patients with bilateral STN-DBS switched on (STN-DBS ON) or off (STN-DBS OFF) were studied during dynamic bladder filling and an empty bladder condition (for control), while changes in regional cerebral blood flow (rCBF) were measured by PET. Urinary bladder filling led to an increased rCBF in the periaqueductal grey (PAG), the posterior thalamus, the insular cortex as well as in the right frontal cortex and the cerebellum bilaterally. A significant interaction between bladder condition and STN-DBS was observed in the posterior thalamus and the insular cortex, with enhanced modulation of these areas during STN-DBS ON compared to STN-DBS OFF. Furthermore, regression analyses revealed a modulation of the neural activity in the thalamus and the insular cortex by the PAG activity during STN-DBS ON only. Thus, STN-DBS led to a significant enhancement of afferent urinary bladder information processing. The data suggest that STN-DBS facilitates the discrimination of different bodily states by supporting sensory perception and the underlying neural mechanisms. Furthermore, this is the first imaging study, which shows an effect of STN-DBS on sensory gating in PD patients and its neural basis.

Keywords: deep brain stimulation; subthalamic nucleus; periaqueductal grey; visceral sensory processing; PET

Abbreviations: ACC = anterior cingulate cortex; DBS = deep brain stimulation; DLPFC = dorsolateral prefrontal cortex; GPi = internal globus pallidus; LFC = lateral frontal cortex; PAG = periaqueductal grey; PD = Parkinson's disease; rCBF = regional cerebral blood flow; ROI = region of interest; RT = reticular thalamus; SMA = supplementary motor area; SNr = substantia nigra pars reticulata; SPECT = single photon emission computerized tomography; SPM = statistical parametric mapping; STN = subthalamic nucleus; VA = ventral anterior nucleus; VL = ventral lateral nucleus

Received March 28, 2007. Revised September 18, 2007. Accepted September 24, 2007. Advance Access publication October 31, 2007

Introduction

Deficient perception of multimodal sensory information is a pathophysiological hallmark of Parkinson's disease (PD) (Kaji *et al.*, 2005) and results in disabling non-motor manifestations of PD (Snider *et al.*, 1976; Koller, 1984; Shulman *et al.*, 2001). Sensory deficits in PD patients are evident both in somatosensory pathways, e.g. coding for proprioception and kinaesthesia (Schneider *et al.*, 1986; Jobst *et al.*, 1997; Zia *et al.*, 2000; O'Suilleabhain *et al.*,

2001; Maschke *et al.*, 2003; Konczak *et al.*, 2007) as well as in visceral pathways, e.g. the monitoring of urinary bladder filling (Bonnet *et al.*, 1997; Araki *et al.*, 2000; Sakakibara *et al.*, 2001). A disturbed interaction between basal ganglia nuclei and the sensory systems has been suggested to underlie the sensory misperception in PD (Schwarz *et al.*, 1992). However, the neural mechanism of altered sensory gating in PD and, in particular, the link to the dysfunctional basal ganglia circuitry remain to be established.

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is an effective non-pharmacological approach to treat patients in advanced stages of PD (Deuschl *et al.*, 2006). Despite its clinical efficacy, the manifold physiological consequences of STN-DBS are to date poorly understood. It is known, however, that STN-DBS of PD patients does not only improve motor symptoms but also ameliorates deficient sensory processing (Maschke *et al.*, 2005; Shivitz *et al.*, 2006; Witjas *et al.*, 2007). Therefore, in addition to its well-established influence on motor circuitries (Limousin *et al.*, 1997; Ceballos-Baumann *et al.*, 1999; Thobois *et al.*, 2002; Strafella *et al.*, 2003), STN-DBS might modulate the processing of afferent information within cerebral sensory pathways. A recent electrophysiological study of afferent inhibition in PD patients supports this notion by showing that STN-DBS normalizes the central sensorimotor integration of peripheral sensory stimuli (Sailer *et al.*, 2007). However, the neural mechanisms by which STN-DBS interacts with disturbed sensory processing in PD remain elusive.

Accordingly, the current study aimed at investigating with the help of PET the modulation of sensory processes by STN-DBS in PD patients. In particular, we were interested in examining the neural mechanisms of disturbed sensory gating in PD and how STN-DBS, modulating the indirect basal ganglia pathway, may influence these processes.

We chose perception of urinary bladder filling as a model paradigm to elucidate the influence of STN-DBS on sensory processing in PD patients for the following reasons: First, misperception of bladder information within the storage phase of the urinary cycle causes bladder dysfunction in PD. Urodynamic studies show significantly earlier perception of bladder sensation in PD patients compared to healthy controls (Winge and Fowler, 2006). Second, deficient perception of sensory bladder information in PD is amenable to therapeutic intervention. Chronic stimulation of D1 and D2 receptors increases the volume at which PD patients recognize bladder filling (Brusa *et al.*, 2007). Furthermore, STN-DBS quickly normalizes urinary bladder sensations resulting in a delayed desire to void and an increased bladder capacity (Finazzi-Agro *et al.*, 2003; Seif *et al.*, 2004). Complementary, in an animal model of severe urinary over-activity due to intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), STN-DBS restores proper central processing of stretch information from the urinary bladder and, thereby, reduces the hypersensitivity to distension of the bladder wall (Dalmose *et al.*, 2004). Third, the principal anatomical organization of processing and integrating sensory bladder information corresponds to the somatosensory system with relay centres in the brainstem (periaquaeductal grey, PAG), thalamus (posterior portion) and primary sensory cortex (insula) (Carstens and Yokota, 1980; Matsuura *et al.*, 2002; Blok, 2002*b*). Therefore, investigating the perception of urinary bladder filling may have implications for the (patho-) physiology of sensory gating processes in general. Fourth, bladder filling represents a well-defined stimulus known to result in specific changes of the regional cerebral blood flow (rCBF) of brain centres involved in urinary bladder control (Kavia *et al.*, 2005).

Note, we here intended to investigate the impact of STN-DBS on the sensory processing of urinary bladder afferents rather than on the cortical control of the urge to void caused by a maximally filled bladder as in our previous study (Herzog *et al.*, 2006). Therefore, we measured changes in rCBF during the sensation of bladder filling caused by continuous moderate retrograde filling of the urinary bladder in PD patients. Using a modified version of a previously described perceptual rating scale (Athwal *et al.*, 2001), we ensured that none of the PD patients experienced an urge to void during the PET measurements. Additionally, an empty bladder condition was used for control. We predicted on the basis of previous studies in healthy subjects (Blok *et al.*, 1997, 1998; Nour *et al.*, 2000; Athwal *et al.*, 2001) that bladder filling would lead to enhanced activity in the neural pathway processing sensory bladder afferents involving the PAG, the thalamus and the insular cortex. In contrast to our previous study (Herzog *et al.*, 2006), we did not expect to find significant activations of the anterior cingulate cortex (ACC) or the left lateral frontal cortex (LFC) during bladder filling as these areas are involved in the cortical control of a filled urinary bladder in terms of suppressing the urge to void and maintaining continence. We hypothesised, based on the positive influence of STN-DBS on the perception of bladder information, that STN-DBS ON, but not STN-DBS OFF, would result in a significant modulation of neural activity in the cerebral areas processing sensory bladder afferents when comparing bladder filling with an empty bladder.

In summary, characterizing the effect of STN-DBS on the sensory processing of urinary bladder afferents may extend our understanding (i) how STN-DBS affects the processing of sensory information in PD, (ii) how the basal ganglia interact with sensory systems and (iii) how changes in sensory gating processes modify behavioural strategies.

Subjects and methods

Subjects

Nine patients (4 women and 5 men) suffering from Parkinson's disease, according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria, with a mean age of

Table 1 Patients' characteristics and responses to subthalamic deep brain stimulation

Patient number	Sex	Age	Disease duration (years)	Follow-up (months)	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	66	15	32	200 L-Dopa; 200 amantadine	59	28	3.0	2.0
2	M	66	15	54	300 L-Dopa, 300 amantadine	42	13	4.0	1.0
3	F	49	15	19	150 L-Dopa, 2 cabergoline; 150 amantadine	51	27	5.0	1.0
4	F	60	10	13	2 cabergoline	20	6	3.0	1.0
5	M	51	8	19	550 L-Dopa; 4 cabergoline	42	17	3.0	2.0
6	F	58	16	12	300 L-Dopa; 1 pramipexole	42	22	3.0	2.0
7	F	71	14	15	6 ropinirole	32	12	2.5	1.0
8	M	54	14	22	400 L-Dopa; 2 cabergoline; 300 amantadine	46	15	4.0	2.5
9	M	67	9	14	700 L-Dopa; 1 pramipexole; 150 amantadine	30	13	3.0	1.5
Mean ± SD		60.2 ± 7.8	12.9 ± 3.0	22.2 ± 13.4		40.4 ± 11.7	17.0 ± 7.3	3.4 ± 0.8	1.6 ± 0.6

60.2 ± 7.8 years (mean ± SD) and a disease duration of 12.9 ± 3.0 years were included in this study. All patients were treated by STN-DBS following bilateral implantation of quadripolar electrodes (model 3389, Medtronic, Minneapolis, MN). The surgical procedure has been described elsewhere in detail (Schrader *et al.*, 2002). The mean interval between operative implantation and PET examination was 22.2 ± 13.4 months. All patients showed a clinically relevant benefit by STN-DBS in the medication OFF condition (Table 1), with a significant reduction of the UPDRS motor part (UPDRS III, STN-DBS OFF: 40.4 ± 11.7, STN-DBS ON: 17.0 ± 7.3, $P < 0.001$, student's *t*-test) as well as the Hoehn and Yahr ratings (STN-DBS OFF: 3.4 ± 0.8, STN-DBS ON: 1.6 ± 0.6, $P < 0.001$). Patients were randomly selected for this study irrespective of clinical urinary dysfunction.

All patients gave informed consent. The study was approved by the Ethics Committee 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 antiparkinsonian medication. The experimental design was factorial, with the factors 'stimulation' (STN-DBS ON versus STN-DBS OFF) and 'bladder condition' (empty versus filling). Each of the resulting four conditions (ON-empty, ON-filling, OFF-empty, OFF-filling) was replicated three times per patient, giving a total of 108 observations (12 scans, 9 patients).

In each patient, the presence of a 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 veins for the administration of the radioactive tracer. Each patient's bladder was catheterized with a double lumen, fluid-filled pressure catheter (6F). A single lumen catheter was inserted into the rectum to monitor intraabdominal pressure and calculate intravesical pressure. For the empty bladder conditions, the bladder was emptied by the pressure catheter before the PET measurement.

For the filling-bladder conditions, the bladder was initially filled with isotonic saline solution at body temperature at an infusion velocity of 25–50 ml/min. The patients were asked to report bladder sensation on the basis of a modified, previously described rating scale (Athwal *et al.*, 2001):

0 = No bladder sensation. The patient might report the perception of the catheter positioned within the urethra.

1 = First, unspecific bladder sensation. Usually, the patients were not able to exactly describe these initial, unspecific sensations arising from the bladder, which, for example, might involve temperature sensations evoked by the instillation of the saline solution. These unspecific sensations could clearly be differentiated from the sensation of bladder filling by the PD patients.

2 = Sensation of bladder filling. Patients could easily report the filling of their bladder, which corresponded to the felt increase of bladder volume or to the felt distension of the bladder wall. It should be noted that the patients did not experience a desire or urge to void during this phase and that they could precisely differentiate between this filling phase and the following phase.

3 = Sensation of the desire to void. In this phase, the filled bladder caused the desire to void in the patients with PD. However, patients were still able to easily suppress the desire to void. In allegory, during a car drive, the patients would be able to withhold micturition until they would arrive at their destination and could use the toilet there.

4 = Urge to void. The strong desire to void has to be voluntarily suppressed with strong effort. Any activity of daily living would be discontinued as soon as possible to go to the bathroom. The bladder volume at the urge to void approximates bladder capacity.

Bladder volumes at sensation of bladder filling, desire to void and urge to void are presented in Table 2.

When the patient reported sensation of bladder filling (point 2 of the rating scale), infusion was continued at a lower infusion velocity (ml/min), corresponding to ~10% of the bladder volume associated with the sensation of bladder filling (Table 2).

Table 2 Stimulation parameters, mean bladder volume and filling velocity during PET measurement as well as mean bladder volume at desire to void and urge to void in STN-DBS OFF and ON

Patient Number	Stimulation parameters (V; μs; Hz)		Mean bladder volume (ml) [filling velocity (ml/min)] during PET measurement		Mean bladder volume (ml) at desire to void		Mean bladder volume (ml) at urge to void	
	Right electrode	Left electrode	STN-DBS OFF	STN-DBS ON	STN-DBS OFF	STN-DBS ON	STN-DBS OFF	STN-DBS ON
1	2.8; 60; 210	4.5; 60; 210	60 (5)	55 (5)	70	90	90	190
2	2.7; 60; 150	3.0; 60; 150	100 (10)	106 (10)	120	190	180	250
3	4.1; 60; 130	3.7; 60; 130	30 (5)	35 (5)	50	100	70	170
4	3.4; 60; 130	3.4; 60; 130	120 (10)	135 (10)	140	170	250	390
5	4.1; 60; 180	4.1; 60; 180	35 (5)	50 (5)	50	90	140	170
6	2.4; 60; 130	2.7; 60; 130	35 (3)	25 (3)	40	65	60	120
7	1.7; 60; 130	4.1; 60; 130	75 (10)	85 (10)	95	130	230	360
8	2.5; 60; 180	2.9; 60; 180	130 (10)	105 (10)	125	165	210	230
9	4.6; 60; 180	4.2; 60; 180	305 (25)	315 (25)	430	500	550	700
Mean ± SD			98.9 ± 85.8 (9.2 ± 6.6)	101.2 ± 88.1 (9.2 ± 6.6)	124.4 ± 120.2	166.6 ± 132.1	200.0 ± 159.6	286.7 ± 178.8

Simultaneously, a bolus of [^{15}O] water was intravenously injected, and the PET measurement was started (see below). No patient reported a desire to void (point 3 of the rating scale) during the PET measurements.

To allow adequate time for STN-DBS to become effective or ineffective, respectively, the order of conditions was counterbalanced across patients in the following way: In five patients, STN-DBS was switched OFF at least 20 min before the first PET scan and switched ON again directly after the sixth rCBF measurement. Before starting the seventh PET scan (after at least 20 min), effectiveness of STN-DBS was documented clinically. In these patients, STN-DBS remained ON during the subsequent six (seventh to twelfth) PET scans (and, of course, thereafter). In the other four patients, the first six PET scans 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 PET scan 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 PET scans was pseudo-randomized within patients.

PET scanning

Regional cerebral blood flow (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, USA), with a total axial field of view of 155 mm covering the whole brain. Data were acquired in three-dimensional mode with interdetector 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 were given intravenously as a bolus injection. Each patient was subjected to a radiation dose of 4.1 mSv (effective dose) during the entire course of the study (12 scans). Twelve consecutive PET scans were collected, each beginning when the brain activity exceeded a threshold of 5 kilo counts per second (kcps) above 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 the 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 × 128 pixels (size 2.0 × 2.0 mm^2) by two-dimensional 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, 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.*, 1995*a*). The resulting normalization parameter set was used to spatially normalize all PET images of the subject. 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.*, 1995*b*).

Table 3 Relative increases in neural activity associated with STN-DBS ON and OFF as well as with the bladder filling and empty bladder conditions and the interaction of the two factors

Region	Side	*x*	*y*	z	*T*-value
A. Main effect of STN-DBS ON: (ON-empty + ON-filling) > (OFF-empty + OFF-filling)					
STN	R	+14	−12	−14	5.82*
	L	−14	−6	−4	5.80*
B. Main effect of STN-DBS OFF: (OFF-empty + OFF-filling) > (ON-empty + ON-filling)					
Sensorimotor cortex	R	+36	−22	+58	6.29*
	L	−36	−22	+52	7.65*
SMA	M	−2	−10	56	6.73*
Cerebellum	R	+10	−56	−18	6.55*
	L	−4	−52	−6	5.36*
C. Main effect of bladder filling: (ON-filling + OFF-filling) > (ON-empty + OFF-empty)					
PAG	L	−4	−32	−20	4.04**
Thalamus	R	+4	−30	+6	4.20**
Insula	R	+34	+10	+6	3.00†
Frontal cortex	R	+52	+40	+26	3.40**
Cerebellum	R	+24	−48	−28	3.84**
	L	−16	−56	−28	3.63**
D. Interaction between STN-DBS and bladder condition: [(ON-filling > ON-empty) > (OFF-filling > OFF-empty)]					
Thalamus	R	+14	−28	+10	3.92**
Insula	R	+46	+8	+6	3.43**
E. Simple effect of bladder condition during STN-DBS ON: ON-filling > ON-empty					
PAG	L	−4	−30	−18	3.69**
Thalamus	R	+14	−30	+12	4.40**
Insula	R	+44	+6	+4	3.55**

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; PAG = periaqueductal grey.
*$P < 0.05$, corrected for multiple comparisons across the whole brain; **$P < 0.05$, corrected for region of interest (ROI)/small volume correction (SVC) using the following previously published co-ordinates: PAG +4, −24, −12 (Athwal *et al.*, 2001); thalamus +4, −24, +6 (Nour *et al.*, 2000); insula +40, +10, 0 (Nour *et al.*, 2000); right middle frontal gyrus +46, +48, +26 (Athwal *et al.*, 2001), left (−12, −48, −20) and right (+24, −52, −30) cerebellum (Athwal *et al.*, 2001).
†$P = 0.08$, corrected for region of interest (ROI)/small volume correction (SVC).

The resulting voxel size in stereotactic space was $2 \times 2 \times 2\,mm^3$. 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.*, 1995*b*). This removed systematic state-dependent differences in global blood flow associated with the different conditions that 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}). SPM{Z} statistics were interpreted in light of the theory of probabilistic behaviour of Gaussian random fields (Friston *et al.*, 1995*b*). 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 (Nour *et al.*, 2000; Athwal *et al.*, 2001) 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 Athwal *et al.* (2001) for the periaqueductal grey (PAG; 4, −24, −12) and of Nour *et al.* (2000) for the posterior thalamus (4, −24, 6) and the insular cortex (40, 10, 0). These three areas constitute the main areas in the known pathway processing visceral sensory information from the bladder (Griffiths, 2004). Additional ROI analyses were performed for the areas known to be involved in monitoring changes in bladder volume and micturition in healthy subjects (Nour *et al.*, 2000; Athwal *et al.*, 2001): pons (4, −22, −32), cingulate cortex (−2, 18, 22), middle frontal gyrus (left: −36, 38, 44; right: 46, 48, 26), parietal cortex (left: −56, −48, 52; right: 58, −28, 56) and cerebellum (left: −12, −48, −20; right: 24, −52, −30). We used ROI analyses to verify that the anterior cingulate cortex (ACC; −6, 36, 22) and the left lateral frontal cortex (LFC; −16, 36, 32), previously activated when patients with PD suppressed the urge to void caused by a filled bladder (Herzog *et al.*, 2006), were not activated during the current bladder filling conditions.

Finally, to characterize the putative modulation of the neural activity in the posterior thalamus and the insular cortex by the neural activity of the PAG in the conditions of STN-DBS ON and OFF, respectively, we performed regression analyses (Weiss *et al.*, 2003) that model the influence of the PAG on the posterior thalamus and the insular cortex, using all data points acquired during STN-DBS ON and STN-DBS OFF, respectively, from representative voxels in the PAG (−4, −32, −20), the posterior thalamus (+4, −30, +6), and the insular cortex (+34, +10, +6, see Table 3C). If the PAG influences activity in the posterior thalamus and the insular cortex, the regression slopes should be significantly different from zero; that is, the variance in the measured signal in the posterior thalamus and the insular cortex is predictable by the variance of the measured signal in the PAG.

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 SPMs maps on the single subject MRI template (in MNI space) provided by SPM2.

Results

Urodynamic data

The mean bladder volume at which the PET measurements were started was similar in STN-DBS OFF and ON (STN-DBS OFF: 98.9 ± 85.8 ml, STN-DBS ON: 101.2 ± 88.1 ml, $P = 0.613$, see Table 2). However, the mean bladder volumes at the desire and the urge to void (points 3 and 4 of the rating scale, respectively) increased significantly ($P < 0.001$) during STN-DBS ON compared to STN-DBS OFF (Table 2). The volume at the desire to void was 59% of that at the urge to void (which represents the bladder capacity). Thus, the relationship between these two bladder volumes was comparable to that in our previous study [62%, (Herzog *et al.*, 2006)]. Furthermore, the increase of bladder capacity (mean volume at the urge to void) by STN-DBS ON was similar to that observed previously [43 and 48%, respectively (Herzog *et al.*, 2006)].

Neural activations measured by PET

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

As in our previous study (Herzog *et al.*, 2006), STN-DBS ON (relative to STN-DBS OFF) led to significantly increased neural activity in the subthalamic nucleus bilaterally ($P < 0.05$, corrected for whole brain), independent of bladder state (Table 3).

STN-DBS OFF (relative to STN-DBS ON, see Table 3) increased neural activity bilaterally in the sensorimotor cortex (predominantly left-sided), the SMA and (predominately right-sided) the cerebellum ($P < 0.05$, corrected for whole brain).

Main effect of bladder condition: bladder filling versus empty bladder and vice versa

At the predefined threshold ($P < 0.05$, corrected for the whole brain), no significant increases of neural activity were observed for bladder filling in relation to empty bladder and vice versa. However, based on previous studies (Nour *et al.*, 2000; Athwal *et al.*, 2001), we hypothesized that dynamic changes of bladder volume would lead to changes of neural activity in areas processing afferent sensory bladder information, i.e. PAG, the posterior thalamus and the insular cortex. As expected, the hypothesis-driven ROI-analyses on the contrast bladder filling versus empty bladder (independent of STN-DBS) yielded increased neural activity in the PAG (−4, −32, −20; $p_{svc} < 0.05$), the posterior thalamus (+4, −30, +6; $p_{svc} < 0.05$) and the insular cortex (+34, +10, +6, $p_{svc} = 0.08$). Additional ROI analyses of the areas previously shown to be involved in monitoring changes in bladder volume and micturition in healthy subjects (Nour *et al.*, 2000; Athwal *et al.*, 2001) revealed a significant increase of neural activity in the right frontal cortex (+52, +40, +26; $p_{svc} < 0.05$) and in the cerebellum bilaterally (right: +24, −48, −28; left: −16, −56, −28; both $p_{svc} < 0.05$, see Table 3C). However, for the main effect of bladder filling, no significant activation could be detected in the ACC or the left LFC (Herzog *et al.*, 2006). Note, all the areas significantly activated in the ROI analyses also survived the threshold of $P < 0.001$, uncorrected, for the whole brain, a threshold previously adopted by four PET studies investigating the neural mechanisms of micturition in healthy subjects (Blok *et al.*, 1997, 1998; Nour *et al.*, 2000; Athwal *et al.*, 2001).

The reverse contrast (empty bladder > bladder filling) did not reveal any significant changes in neural activity in the ROI analyses.

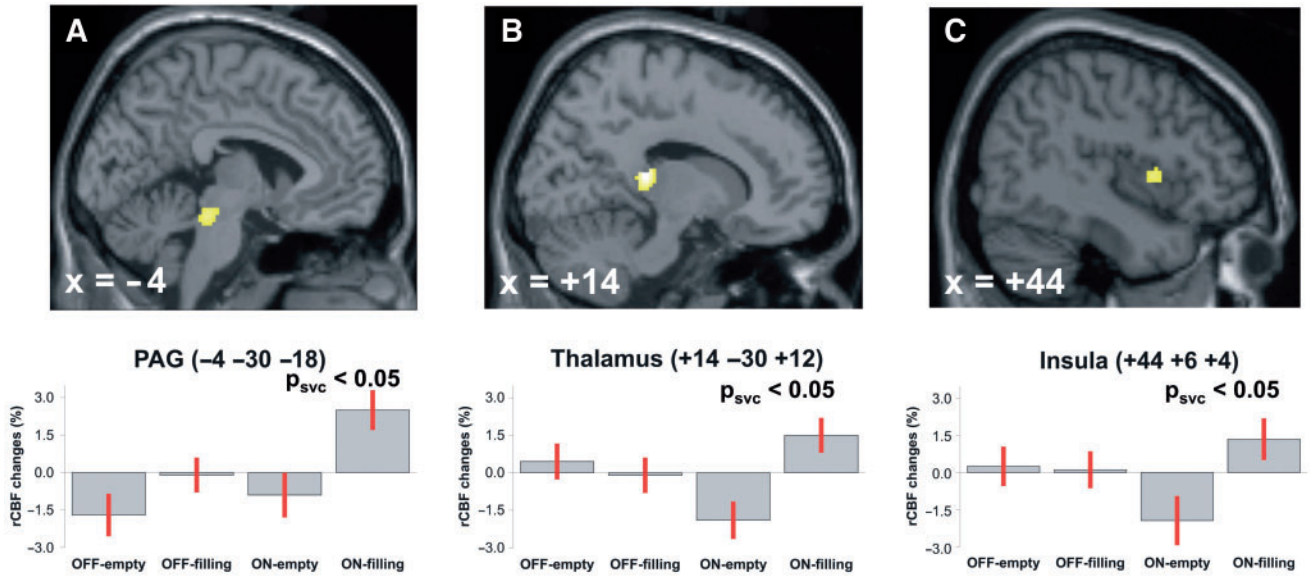

Fig. 1 Modulation of visceral sensory gating mechanisms by bilateral STN-DBS. Upper row: the simple effect of bladder condition during STN-DBS ON (ON-filling > ON-empty) yields significant activations in the periaqueductal grey (PAG, **A**), the posterior thalamus (**B**) and the insula (**C**, all $p_{svc} < 0.05$). The activation clusters are shown superimposed on sagittal slices at $x = -4$ mm for the PAG (A), $x = +14$ mm for the thalamus (**B**), and $x = +44$ mm for the insula (**C**) of the standard spm2 single subject MRI template in MNI space. For display purposes only, the threshold was set to $P < 0.001$, uncorrected, for all figures. Lower row: plots of the relative rCBF changes for the four experimental conditions (OFF-empty, OFF-filling, ON-empty and ON-filling) in the maximally activated voxels within the periaqueductal grey (PAG, **A**), the posterior thalamus (**B**) and the insula (**C**). Note the significantly stronger modulation of rCBF by bladder filling during STN-DBS ON—especially for the thalamus and the insula—compared to STN-DBS OFF. The zero line in the bar graphs represents the study-specific normalized mean rCBF value.

Interactions between STN-DBS and bladder condition

For the neural activations in the posterior thalamus and the insular cortex, a significant interaction ($p_{svc} < 0.05$, Table 3) of the factors STN-DBS and bladder condition was observed when assessing the term [(ON-filling > ON-empty) > (OFF-filling > OFF-empty)]. This interaction was mainly due to a differential increase of neural activity in the posterior thalamus and the insular cortex when bladder filling was contrasted with an empty bladder for the stimulation ON condition compared to stimulation OFF condition. No significant activation of the right frontal cortex, the cerebellum, the ACC, or the left LFC could be detected by the corresponding ROI analyses applied to the interaction term.

Furthermore, the reverse interaction term [(OFF-filling > OFF-empty) > (ON-filling > ON-empty)] did not reveal any significant changes in neural activity.

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

Bladder filling (compared to an empty bladder) was associated with significant neural activation ($p_{svc} < 0.05$) in the posterior thalamus and the insular cortex as well as the PAG under STN-DBS ON (ON-filling > ON-empty, Table 3 and Fig. 1). In contrast, under STN-DBS OFF, the bladder filling condition (in contrast to the empty bladder condition, OFF filling > OFF-empty) did not yield significant increases in neural activity. However, a ROI analysis revealed a sub-threshold activation of the PAG with a local maximum at the coordinates −2, −32, −18 for the simple effect of bladder condition during STN-DBS OFF ($p_{SVC} = 0.36$, corrected; $p_{SVC} = 0.02$, uncorrected).

Regression analyses

Regression analyses of the influence of the PAG activity on the neural activity in the posterior thalamus and the insular cortex during STN-DBS ON revealed that there was a significant correlation between the PAG activity and the neural activity in the posterior thalamus (Y[posterior thalamus] = 0.386 * X[PAG] − 0.216; $r = 0.408$, $P = 0.002$) and in the insular cortex (Y[insular cortex] = 0.327 * X[PAG] − 0.275; $r = 0.314$, $P = 0.02$), respectively. However, no significant correlation was found during STN-DBS OFF: Y[posterior thalamus] = 0.001 * X[PAG] − 0.02; $r = -0.001$, $P = 0.99$ and Y[insular cortex] = 0.065 * X[PAG] − 0.117; $r = 0.079$, $P = 0.57$ (Fig. 2).

Possible medication effects

PET examinations were performed in the medication OFF condition at least 12 h after withdrawal of antiparkinsonian medication. It should be noted that 12 h of drug withdrawal could possibly not be sufficient to completely wash out

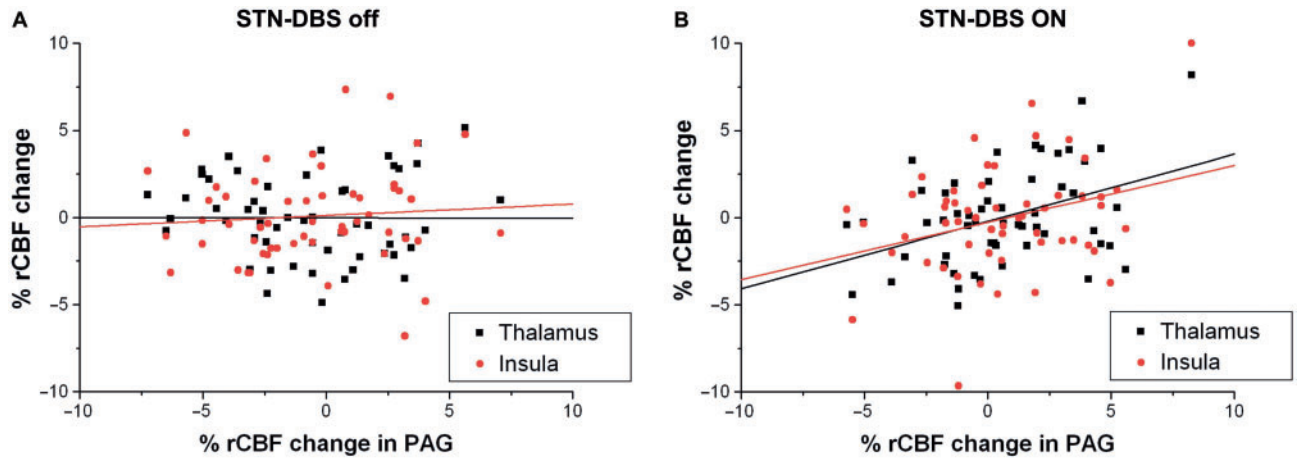

Fig. 2 Modulation of the correlation between the neural activity in the periaqueductal grey (PAG) and the (posterior) thalamus as well as the insular cortex by STN-DBS as revealed by regression analyses using a least square method ($Y = a * X + b$). (**A**) During STN-DBS OFF, no influence of the PAG activity on the neural activity in the thalamus (black symbols) and the insula (red symbols) was discernable: Y[thalamus] = −0.001 * X[PAG]−0.02; $r = -0.001$, $P = 0.99$ and Y[insula] = 0.065 * X[PAG]−0.117; $r = 0.079$, $P = 0.57$. (**B**) In contrast, during STN-DBS ON, the regression slopes between PAG and the thalamus and the insula were significantly different from zero (Y[thalamus] = 0.386 * X[PAG]−0.216; $r = 0.408$, $P = 0.002$ and Y[insula] = 0.327 * X[PAG]−0.275; $r = 0.314$, $P = 0.02$); that is, the variance in the measured signal in the thalamus and the insula was predictable by the variance of the measured signal in the PAG. Thus, neural activity in the PAG influences activity in the thalamus and the insula during STN-DBS ON only. The zero value in the graphs represents the study-specific normalized mean rCBF value.

dopamine agonists due to their pharmacokinetic characteristics. Therefore, to examine the effect of the potentially remaining dopamine agonists on our findings, we performed a further analysis, in which the individual dopamine equivalent dose of each patient, i.e. the sum of dopamine medication and dopamine agonists, was entered as an additional regressor. This analysis yielded identical results. Thus, there was no significant effect of the antiparkinsonian medication on the observed CBF changes.

Discussion

In this PET study, we demonstrate a profound influence of STN-DBS in patients with PD on brain areas involved in the processing of visceral urinary bladder afferent information. We show that the modulation of neural activity in the thalamus and the insular cortex was only present in the STN-DBS ON condition. In contrast, in the STN-DBS OFF condition, we did not find a relevant modulation of these two areas by the urinary bladder state. Furthermore, regression analyses revealed a significant correlation of the neural activity in the thalamus and the insular cortex with the neural activity in the PAG during STN-DBS ON only. Hence, this is the first imaging study to show that partially restoring basal ganglia function (by STN-DBS) significantly improves sensory gating processes within brain areas primarily involved in the processing of visceral afferents.

Methodological considerations

Cerebral activations in response to urinary bladder stimulation and control of voiding behaviour involve a complex and dynamically organized network. Thus, some methodological aspects have to be considered when interpreting the present data.

First, in this study, we aimed at investigating the brain areas dedicated to convey afferent bladder information. Previous studies identified the PAG, the posterior thalamus and the insular cortex as the primary sensory areas most effectively responding to dynamic changes of the bladder state, including increases of bladder volume by anterograde and retrograde filling (Athwal *et al.*, 2001; Matsuura *et al.*, 2002) or decreases of bladder volume by micturition (Nour *et al.*, 2000). Consistent with these findings, we found increased rCBF in the PAG, the posterior thalamus, and the insular cortex associated with bladder filling to an extent, which did not lead to the sensation of an urge to void. Importantly, we did not observe significant activations of the left LFC and ACC known to be involved in monitoring and controlling the storage phase of the urinary cycle (Blok, 2002*a*) and associated with an urge to void, withholding urine, or the onset of micturition (Blok *et al.*, 1997, 1998; Athwal *et al.*, 2001; Dasgupta *et al.*, 2005; Kuhtz-Buschbeck *et al.*, 2005; Herzog *et al.*, 2006). Rather, the present study revealed the neural network involved in processing afferent sensory information during the filling phase of the urinary bladder. As the applied bladder volumes did not cause a desire or urge to void in our PD patients, the super ordinate mechanisms of the storage phase controlling continence maintenance or appropriateness of micturition were not recruited.

Second, STN-DBS is known to change the subjective perception of bladder filling with a consecutive increase in bladder volume (Finazzi-Agro *et al.*, 2003; Seif *et al.*, 2004).

Therefore, STN-DBS itself may alter the physical conditions of our experimental setting due to differences in absolute bladder volumes during STN-DBS OFF and ON: Different bladder volumes may influence cerebral activation patterns independently from the state of STN-DBS. To circumvent this problem, we ensured comparable experimental conditions during STN-DBS OFF and ON through the use of identical subjective ratings as well as similar intra-individual bladder volumes and relative filling rates (Table 2). Remarkably, the bladder volumes at the sensation of bladder filling (point 2 on the perceptual rating scale) in the current study were somewhat higher than the volumes at which a different group of PD patients reported a desire to void (point 3 on the perceptual rating scale) in our previous study (Herzog *et al.*, 2006). However, this discrepancy is most likely due to differences in the urological characteristics of both PD patient groups as can be shown by the results of the concurrent urodynamic examinations (Table 2). It is well known that urological parameters, like absolute bladder capacity, strongly depend on the patients' characteristics, e.g. gender, age, body weight, etc. Thus, due to a larger bladder capacity, the mean bladder volume at the desire to void was absolutely larger in the present than in the previous patient group, but well comparable in terms of relative bladder volume (59 versus 62% of bladder capacity). Note, that there was a comparable (relative) increase of the bladder capacity by STN-DBS in both patient groups (previous group: 135–200 ml, i.e. 65 ml = 48%; current group: 200–286 ml, i.e. 86 ml = 43%). These data confirm that STN-DBS had a similar effect on the urodynamic parameters in both patient groups. Although urodynamic measurements with retrograde bladder filling cannot resemble physiological anterograde bladder filling, we chose this method to provide reproducible urinary bladder states in each of the 12 PET scans. Furthermore, previous imaging studies found a comparable network of cortical and subcortical areas involved in urinary bladder control, irrespective of using physiological anterograde bladder filling by water drinking (Blok *et al.*, 1997, 1998; Dasgupta *et al.*, 2005; Kuhtz-Buschbeck *et al.*, 2005) or retrograde urodynamic filling (Nour *et al.*, 2000; Matsuura *et al.*, 2002; Herzog *et al.*, 2006).

Third, a distinct group of PD patients in an advanced stage of the disease treated by STN-DBS was enrolled in the current study. It might be argued that this fact limits the relevance of the current findings. However, according to questionnaire-based studies focussing on the prevalence of urinary disturbances in PD patients, ~40% of all PD patients (Araki and Kuno, 2000; Campos-Sousa *et al.*, 2003) suffer from bladder dysfunction. The frequency of bladder dysfunction seems to increase concomitantly with disease progression (Porter and Bors, 1971; Murnaghan and Millard, 1984; Hattori *et al.*, 1992; Araki and Kuno, 2000; Lemack *et al.*, 2000; Schneider *et al.*, 1978). Thus, urinary dysfunction is not only a problem in patients with advanced PD, but also seems to be present already early in the course of the disease. The early onset of urinary dysfunction in PD and the concomitant increase of urological and other (e.g. motor) symptoms during disease progression clearly suggest that urinary dysfunction is part of the pathophysiology of PD, which can be effectively modulated by STN-DBS.

Cerebral areas involved in the sensory processing of urinary bladder afferents

The PAG, according to anatomical and electrophysiological animal studies, receives strong afferent projections from the sacral cord (Blok *et al.*, 1995; Vanderhorst *et al.*, 1996; Mouton and Holstege, 2000), supporting its role as a central relay centre for afferent sensory information from pelvic organs. More specifically, the peripheral fibres of the dorsal root ganglion neurones of the pelvic nerve innervate the bladder wall mechanoreceptors (de Groat *et al.*, 1981; Mallory *et al.*, 1989), whereas their proximal fibres terminate within spinal Rexed's laminae I, V, VII and X of the lumbosacral cord at segments L4- S2 (Morgan *et al.*, 1981). Stimulation of the pelvic nerve, which mainly transfers information about bladder filling, elicited short latency potentials in the PAG (Noto *et al.*, 1991). Similarly, micturition in cats led to an increased discharge frequency in the PAG neurons, which is caused by changes in afferent input from the lumbosacral cord due to alteration in bladder wall distension (Liu *et al.*, 2004). It has been suggested that the PAG, due to its response to bladder stretch receptor activity, may predominantly monitor changes in bladder volume (Blok, 2002*b*; Holstege and Mouton, 2003). Functional imaging provides evidence that PAG may also process other visceral interoceptive sensations. For example, the analysis of neural activations measured by fMRI caused by pneumatic balloon dilatation of the anal canal (Eickhoff *et al.*, 2006) or distal stomach (Ladabaum *et al.*, 2001) showed mesencephalic activations in close vicinity to the current PAG activation. Therefore, our data is consistent with the notion of a common mesencephalic processing of visceral afferents based on an organ-specific activation within the human PAG (Carrive, 1993).

The posterior thalamus represents the second major subcortical relay structure which has been previously shown to be essential in processing afferent urinary bladder information and which exhibits increased activation during both bladder filling and micturition (Nour *et al.*, 2000; Matsuura *et al.*, 2002). Again, a nearly identical local maximum of activation was found within the posterior thalamus during rectal distension (Eickhoff *et al.*, 2006). Animal studies revealed significant neuronal responses within the posterior thalamic complex due to the distension of the urinary bladder (Carstens and Yokota, 1980; Chandler *et al.*, 1992; Horn *et al.*, 1999) as well as pelvic nerve stimulation (Bruggemann *et al.*, 1994). The current posterior thalamic activation probably corresponds to the

posterior portion of the ventral medial nucleus (VMpo), the posterior nucleus (Po), and the basal portion of the ventral medial nucleus (VMb) (Blomqvist *et al.*, 2000). This group of thalamic nuclei has been shown to relay physiological information from different visceral tissues (Craig *et al.*, 1994).

The insular cortex is considered to be a major target area of thalamocortical projections from the posterior thalamic complex (Allen *et al.*, 1991; Clasca *et al.*, 1997). Consistent with our findings, previous studies revealed significant insular activations in association with bladder filling and micturition (Nour *et al.*, 2000; Matsuura *et al.*, 2002). Based on human and animal studies, the insula is well recognized as the viscerosensory cortex and as a crucial structure for the integration of interoceptive information (Critchley, 2005). In good accordance with this notion, insular activation has also been observed following gastrointestinal stimulation: Insular activations due to rectal and anal (Eickhoff *et al.*, 2006), oesophageal (Aziz *et al.*, 2000), and gastric stimulation (Ladabaum *et al.*, 2001) have been demonstrated in close vicinity to the activations found in our and other functional imaging studies on urinary visceral representations, with a tendency for a more posterior and dorsal local maximum.

In addition to PAG, posterior thalamus, and insular cortex, we found that the right frontal cortex and the cerebellum bilaterally were activated by the main effect of bladder filling independent of STN-DBS. These findings are consistent with the suggestion that 'the cerebellum processes sensory information from the bladder during urine storage' (Athwal *et al.*, 2001). In addition, animal studies revealed that stimulation or lesions of the cerebellum can affect urine storage and micturition (Bradley and Teague, 1969; Nishizawa *et al.*, 1989). Furthermore, the current findings support the known role of the frontal lobes in the cortical control of bladder function (Andrew and Nathan, 1964). Interestingly, our current and previous results suggest that the activity of the left frontal cortex is modulated by STN-DBS during urge control (Herzog *et al.*, 2006; Kuhtz-Buschbeck *et al.*, 2005), while the right frontal cortex is involved in monitoring sensory bladder afferents independent of STN-DBS.

Impact of STN-DBS on sensory gating of urinary bladder afferents

Several studies found significant impairments in PD patients when processing multimodal sensory information that is critical for the perceptual discrimination between stimuli. Deficits in processing proprioceptive information included difficulties in determining limb position (Zia *et al.*, 2000) and mandibular joint movements (Schneider *et al.*, 1986), as well as disturbed sensory scaling of kinaesthesia (Jobst *et al.*, 1997; O'Suilleabhain *et al.*, 2001; Maschke *et al.*, 2003; Konczak *et al.*, 2007). Additionally, the processing of tactile information has been shown to be disturbed in PD patients with, e.g. difficulties in dissolving the resolution of different gratings (Sathian *et al.*, 1997; Shin *et al.*, 2005) and increased thresholds for two-point discrimination (Schneider *et al.*, 1987). PD patients also exhibit deficits in visual (Bandini *et al.*, 2001; Muller *et al.*, 2002) and auditory perception (Philipova *et al.*, 1997; Pekkonen *et al.*, 1998). Examining by PET, the sensory processing of vibratory stimuli applied to the hand revealed that PD patients, compared to controls, showed alterations in the cerebral activation pattern, with significantly decreased rCBF of the contralateral sensory cortex and increased rCBF of ipsilateral sensory cortical areas (Boecker *et al.*, 1999). Consequently, both psycho-physical and imaging data of PD patients have been interpreted as indicative for profound alterations in central focussing and gating of sensory impulses due to dysfunction within the basal ganglia circuitry (Abbruzzese and Berardelli, 2003).

Interestingly, a partial reversal of basal ganglia dysfunction by chronic dopaminergic medication or STN-DBS has been shown to be associated with normalization of sensory disturbances. For example, following 3–10 months of anti-parkinsonian therapy in de-novo PD patients, there was a significant improvement of tactile spatial acuity compared to the pre-therapeutic condition without medication (Shin *et al.*, 2005). Likewise, STN-DBS ON leads acutely to a significant improvement of perception of kinaesthesia in passive upper limb movements [compared to the STN-DBS OFF condition (Maschke *et al.*, 2005)]. Despite clear evidence of an improvement of sensory gating in PD patients by therapeutic interventions targeting at basal ganglia dysfunction, a physiological explanation for this effect has yet been elusive.

Parallel to the findings in the domain of somatosensory perception, studies in PD patients and animal studies have demonstrated an influence of STN-DBS on the visceral sensation of bladder filling with a normalization of the perception of the urge to void and bladder capacity (Finazzi-Agro *et al.*, 2003; Seif *et al.*, 2004). Therefore, the observation of a significant improvement of urodynamic measures may result from an altered central processing of afferent urinary bladder information by STN-DBS. Our data suggest a STN-DBS-dependent modulation of cerebral areas involved in the primary sensory urinary pathway, and thereby, provide an explanation for the benefit of STN-DBS ON on bladder control in PD. STN-DBS ON was characterized by increased activation of PAG, the posterior thalamus, and the insular cortex in the filling condition. In contrast, during STN-DBS OFF, there was a non-significant modulation of the PAG only, but no discernable rCBF change of downstream areas (thalamus and insular cortex). Furthermore, with the help of regression analyses we demonstrated a modulation of the neural activity in the thalamus and the insular cortex by the PAG activity during STN-DBS ON only. In contrast, during STN-DBS OFF, the variance in the measured signal in the thalamus and the insular cortex could not be predicted by the variance of

the signal in the PAG. The data thus suggest that STN-DBS profoundly influences the gain of urinary afferents by increasing or decreasing the relative activation of primary sensory areas as a function of afferent bladder information. This neural mechanism may espouse discrimination of two opposite sensory conditions and facilitate differential representation of bodily states within the cerebral sensory network.

The present results complement our previous finding that a STN-DBS related modulation of frontal centres involved in the cortical control of the urinary bladder occurs during withholding urine (Herzog *et al.*, 2006). In that study, we showed an increase of rCBF in the ACC and an additional activation of the LFC during STN-DBS OFF and withholding urine which we suggested to result from streams of undifferentiated sensory information to these cortical centres. The ACC as an essential integrator of afferent bodily information (Critchley *et al.*, 2003) could possibly no longer be in a position to reliably classify bladder information and, subsequently, as a compensatory mechanism, LFC activation might be induced for maintenance of urinary continence (Andrew and Nathan, 1964; Kuhtz-Buschbeck *et al.*, 2005; Herzog *et al.*, 2006). In contrast, STN-DBS ON may enable appropriate appraisal of bladder information within the frontal network due to its focussing effect on upstream sensory areas, as corroborated by our current findings.

The neural basis for the interaction between restored basal ganglia function by STN-DBS and modulated activation of the PAG, the thalamus, and the insular cortex remains speculative. However, an influential suggestion is that the reticular nucleus of the thalamus plays a crucial role in gating sensory information (Yingling and Skinner, 1976). The reticular nucleus receives unidirectional projections from the cortex and has bidirectional connections with all thalamic nuclei and is, thus, in a strategic position to modulate the flow of information between the thalamus and the cortex (Pinault, 2004). Correspondingly, alteration of the feedback system within the reticular thalamus has been shown to impact upon the focussing of activation within thalamocortical projections (Le Masson *et al.*, 2002). At the same time, the reticular nucleus is also targeted by collaterals of the efferents from the internal globus pallidus (GPi) to the ventrolateral thalamus and, thus, may constitute a structure through which the basal ganglia select sensory information relevant for the initiation of behaviour (Schwarz *et al.*, 1992). Partial restoration of the basal ganglia function by STN-DBS may therefore recondition the physiological interaction between the pallidal outflow and the modulatory impact of the thalamic reticular system, resulting in a more focussed processing of sensory information (Fig. 3). Alternatively, the process of sensory gating might be related to modulation of sensory information within a frontal-cortical network (Pleger *et al.*, 2001). However, the lack of a differential influence of STN-DBS on frontal cortical areas in the presence of a significant modulation of neural activity at the thalamic level by STN-DBS in our current paradigm does not support the latter hypothesis.

That there was a (albeit non-significant) modulation of the PAG activity through STN-DBS may be due to its central position within the network for the processing of visceral afferents (Shelley and Trimble, 2004). There are both large afferent projections from the insular cortex to the PAG (Bragin *et al.*, 1984; Herrero *et al.*, 1991) and reciprocal connections between the thalamus and the PAG (Krout and Loewy, 2000). Thus, changes of the activation state within the thalamo-insular loop may consecutively impact upon activity within the PAG due to the strong interconnectivity between these centres. Alternatively, electrophysiological evidence exists for a direct influence of efferents from the GPi/substantia nigra pars reticulata (SNr) complex on centres of the brainstem including the pedunculopontine nucleus (Potter *et al.*, 2004). Referring to anatomical evidence for connections to the PAG (Meller and Dennis, 1986; Shammah-Lagnado *et al.*, 1996), STN-DBS may therefore lead to a release of the pathological inhibitory tone of GPi/SNr on the PAG and, thereby, promote the transfer of sensory information to subsequent areas in the sensory processing chain. To date, experimental support for either hypothesis is lacking.

The current finding that restoring basal ganglia function in PD via STN-DBS positively influences the perception of bladder filling triggers the question whether bladder filling and the resulting desire to void may negatively influence motor symptoms of PD or may reduce the effect of dopaminergic medication. From clinical experience, it is well known that the motor state of PD patients can acutely worsen due to infectious diseases, trauma, surgery or gastrointestinal disease—even without any change in dopaminergic medication. Furthermore, the affected PD patients may become (temporarily) refractory to dopaminergic rescue medication (Thomas *et al.*, 2003; Onofrj and Thomas, 2005). Similarly, pain and visceral discomfort can lead to an acute exacerbation of motor symptoms, e.g. an increase in tremor amplitude. To our knowledge, however, no systematic investigation on the mechanisms underlying this interaction has yet been performed. In particular, studies which systematically examine different degrees of bladder filling and, thereby, the influence of an increasing desire to void upon PD motor symptoms are lacking. Our data suggest that this interesting topic warrants further clinical studies.

Conclusion

In conclusion, we demonstrate that STN-DBS profoundly modulates sensory processing of urinary bladder information within the primary sensory pathway of visceral afferents. Hence, this is the first study, which reveals the neural mechanisms underlying the effects of STN-DBS on sensory gating in PD patients. Future studies may show

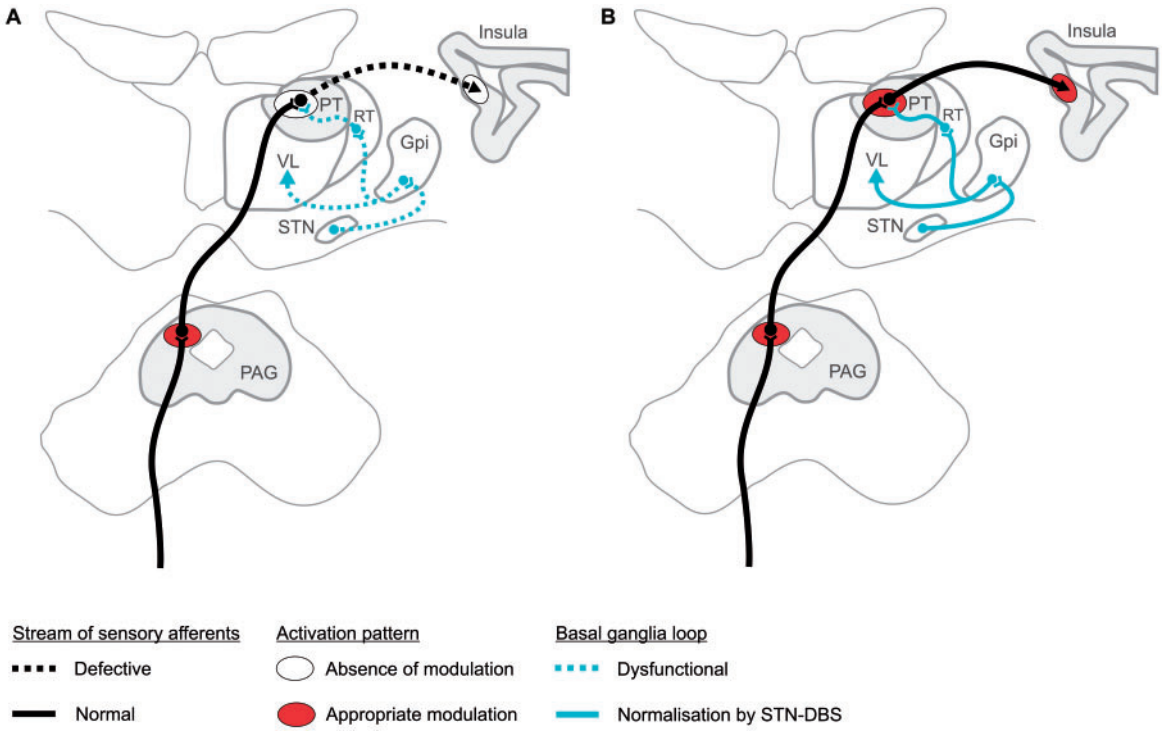

Fig. 3 Possible mechanisms underlying the influence of STN-DBS on cerebral areas involved in the processing of afferent urinary bladder information in the stimulation OFF (**A**) and stimulation ON (**B**) conditions. Urinary afferent bladder information is conveyed by the periaqueductal grey (PAG) and the posterior thalamus (PT) to the insula. Efferents from the internal globus pallidus (GPi) to the ventrolateral thalamus (VL) send collaterals to the reticular thalamus (RT), which modulates the flow of information between the thalamus and the cortex. In the stimulation OFF condition, the dysfunctional basal ganglia state leads to an insufficient activation of the RT, which results in aberrant or absent modulation of thalamic and insular areas. In the ON condition, stimulation of the subthalamic nucleus (STN) partially restores the basal ganglia circuit and eventually normalizes the modulation of the thalamo-cortical sensory projections by the RT.

whether the present results exemplify a general principle of the effect of STN-DBS on sensory information processing irrespective of the sensory modality or whether they are specific to the autonomic nervous system.

Acknowledgements

Supported by the Deutsche Forschungsgemeinschaft (G.R.F.: DFG-KFO 112; P.H.W.: We 2857/2-1) and the Kompetenznetz Parkinson (BMBF FK01GI0201). We are grateful to our colleagues from the PET group at the Institute of Medicine for expert help during scanning.

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