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SELECTIVE FRONTAL BRAIN RESPONSE IN CORRELATION TO BLADDER FILLING IN PARKINSON'S PATIENTS UNDER DEEP-BRAIN-STIMULATION. AN URODYNAMIC CONTROLLED PET-SCAN STUDY.

Hypothesis / aims of study

In addition to motor symptoms the overactive bladder syndrome (OAB) is a common complaint in patients suffering from advanced idiopathic Parkinson`s disease (PD). Urodynamic (UD) evaluation in these patients revealed increased bladder sensitivity, reduced functional bladder capacity and an early desire to void. Deep brain stimulation of the subthalamic nucleus (STN-DBS) has been established as a through-breaking therapeutic approach for alleviating the leading motor symptoms in these patients. Experimental data from urodynamic testing in men and animal models demonstrated an additional relief of OAB- symptoms under STN-DBS by delaying the first desire to void and increasing bladder capacity. The neural basis of the modulating influence on urinary function under STN-DBS remains unclear. We therefore performed a positron emission tomography (PET) scan of the brain to elucidate the topography of cortical areas that are active during stimulation conditions while monitoring the bladderfunction simultaniously by urodynamics.

Study design, materials and methods

The study included 11 patients (six women and five men) with idiopathic Parkinson's disease. The mean age of patients was 57.7 ± 10.9 years (mean ± standard deviation). The examinations and concomitant urodynamic measurements were performed in a medication OFF condition at least 12 hours after withdrawal of antiparkinsonian medication. The urodynamic investigation was conducted according to the International Continence Society. The bladder was filled until the patients reported a strong desire to void and emptied by a syringe between the measurements. The experimental design was factorial with the factors "stimulation" (ON versus OFF) and 'bladder state' (empty vs. filled). The distribution of the regional cerebral blood flow (rCBF) after bolus injection of ^{15}O water was used simultaneously as an indirect measure of cerebral activation. PET scans were performed during the following four conditions: ON-empty, ON-filled, OFF-empty, OFF-filled. Every condition was replicated three times per patient, giving a total of 132 observations (12 scans, 11 patients). The order of conditions was counterbalanced within and across patients. Only activations that exceeded a statistical threshold of $p < 0.05$ (corrected for multiple comparisons, corresponding to T=4.79) were considered significant("**main effects"**). Due to differences in effect size, region-of-interest (ROI) analyses based on previous findings were applied. Here the statistical threshold was set at $p < 0.05$ (small-volume correction)("**interaction**" and "**simple effects**").

Results

The UD investigation showed the following mean values: first desire to void at a volume of 140ml in stimulation *on* condition compared to 78,9ml in *off* condition; second desire (strong urge) to void 199,5ml (*on*) compared to 135,5ml (*off*). These changes were all significant (p<0,05). Detrusor overactivities (DO) appeared in 4/11 patients. The mean volume when DO appeared delayed to higher volumes in *on vs. off* conditions (mean 169ml to 112ml). Significant changes in regional blood flow according to the PET-scan are displayed in table 1 and 2. Beside the main effects of STN-DBS that are due to the stimulation itself (basalganglia in ON condition vs. sensorimotor cortex in OFF condition) the main effect of bladder state turned out to be an increased rCBF in the anterior cingulate gyrus (ACC). This significant increase of neural activity in the ACC was closely associated with the sensation of urge and was even more pronounced when STN-DBS was switched OFF. A significant increase of neural activation in the left lateral frontal cortex (LFC) was mainly due to the contrast between the filled and empty bladder states when STN-DBS was switched OFF.

Interpretation of results

We propose that the modulation of frontal brain activities reflects a facilitated processing of afferent bladder information by STN-DBS. As a conceptual model, we propose that the activation of LFC in the stimulation OFF condition may be regarded as a compensatory strategy guided by ACC for maintenance of continence. The precise identification of the anatomical cerebral structures involved in micturition can contribute to a better understanding of the control of micturition and the development of therapeutic models.

Concluding message

The present study demonstrates, for the first time, that STN-DBS specifically modulates forebrain cortical centres involved in urinary bladder control.

Table 1:

main effects stimulator OFF:(eOFF+fOFF)>(eON+fON)		
region	hemisphere	T-value
sensorimotor cortex	right	10,13*
	left	6,76*
cerebellum	right	5,99*
	left	6,08*
main effects stimulator ON: (eON+fON)>(eOFF+fOFF)		
basal ganglia	right	8,03*
	left	9,54*
main effects of filled bladder: (fON+fOFF)>(eON+fON)		
anterior cingulate cortex		4,99*
e = empty Bladder; f = filled Bladder *** P < 0.05, corrected for multiple comparisons across the whole brain**		

Table 2:

interaction stimulator and bladder state:[(fOFF>eOFF)>(fON>eON)]	
region	T-value
lateral frontal cortex	3,95**
simple effects on bladder state during stimulator: fON>eON	
anterior cingulate cortex	4,05#
simple effects on bladder state during stimulator off: fOFF>eOFF	
anterior cingulate cortex	3,95**
lateral frontal cortex	3,96**
e = empty Bladder; f = filled Bladder **** P < 0.05, corrected for region of interest (ROI)/ small volume correction (SVC)** **# P < 0.001, uncorrected**	

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