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Roy H[1], Roy C[1], Griffiths D[2], Menke R[3], Zrinzo L[4], Foltynie T[4], Akram H[4], FitzGerald J[5], Aziz T[5], Green A[5]
1. *Oxford University Hospital Trust,* ***2.*** *University of Pittsburgh, retired,* ***3.*** *FMRIB centre, Oxford,* ***4.*** *UCL,* ***5.*** *Functional Neurosurgery, Oxford*

NOVEL INSIGHTS INTO THE ROLE OF THE BRAINSTEM IN BLADDER CONTROL FROM A NEUROMODULATION STUDY

Hypothesis / aims of study
Deep brain stimulation (DBS) within the brainstem pedunculopontine nucleus (PPN) has been reported in a single case to produce self-resolving urinary incontinence [Aviles-Olmos et al 2011]. This effect may have been a result of an effect of stimulation at the pontine micturition centre (PMC) or pontine continence centre (PCC). The aim of this study was to test the effect on PPN stimulation on urodynamic bladder filling parameters and to evaluate the urodynamic response to stimulation in the light of electrode proximity to the proposed locations of the PMC and PCC.

Study design, materials and methods
7 subjects with PPN DBS electrodes inserted for the control of movement disorder (Parkinson's disease) symptoms were recruited. Subjects underwent bladder catheteriseation with a dual lumen catheter (8 Fr), and a rectal cather (4.5 Fr) was inserted to measure abdominal pressure. The bladder was infused with a sterile solution of isotonic saline at an average rate of 30 ml min^{-1}. During infusion of saline into the bladder, participants were asked to report when they first experienced the following sensations; 1. Initial sensation of bladder filling, 2. Initial desire to void, 3. Normal desire to void, 4. Strong desire to void, 5. Maximal capacity (point at which they could tolerate no further filling). When the patient reported reaching maximal capacity, the saline infusion was stopped immediately. For each patient, bladder filling was carried out twice with PPN DBS turned 'ON' and twice with PPN DBS turned 'OFF'.

In order to determine the proximity between PPN electrodes and the proposed locations of the PMC and PCC, we referred to Blok et al's 1997 PET study [Blok et al 1997]. The voxel of maximal activation assumed to be the PCC in this study was converted from Talairach to MNI space using GingerALE (http://brainmap.org/). As the region identified in Blok's study was on the right side only, whereas the PCC is expected to be a bilateral area based on animal studies, we calculated the left sided equivalent by inverting the co-ordinate in the X dimension. A similar conversion was used to generate an approximate location of the pontine micturition centre.

All patients gave consent to participate and for their data to be used for research purposes. All parts of this study were carried out in accordance with the Declaration of Helsinki and received approval from the Oxfordshire Research Ethics Committee B (study 09/H0605/62).

Results
All seven subjects in the brain stimulation group were male. Six had DBS electrodes targeted bilaterally to the pedunculopontine nucleus, and one patient (patient 1) had a right-sided PPN electrode only. One patient (patient 3) had bilateral subthalamic nucleus DBS electrodes in addition to the bilateral PPN electrodes- the subthalamic nucleus electrodes were switched off throughout testing.

Five subjects (subjects 3-7) had increased bladder capacity with PPN DBS ON vs PPN DBS OFF, and statistical analysis showed that DBS significantly increased bladder capacity in this group (OFF DBS: 131 mls (range 39-230); ON DBS: 199 mls (range 103-440), $p < 0.05$, Wilcoxon test). Two subjects (subject 1 and 2) had a reduced bladder capacity with PPN DBS turned ON (OFF DBS: 137 mls (range 39-254), ON DBS: 188 mls (range 40-441)), however this change was not statistically significant due to the small group size (Figure 1). There was no effect of PPN DBS on detrusor overactivity in either group.

Assessment of electrode location revealed that the electrode locations for the five subjects whose bladder capacity increased with DBS were closest to the PCC. For the two subjects in whom DBS reduced bladder capacity, their electrode locations were either in the vicinity of the PMC (subject 1) or distant from both the PMC or the PCC (subject 2). For electrode locations, see table 1.

Interpretation of results
Our results show that the effect of PPN DBS on bladder function may vary depending on the precise location of the electrodes. At a given superior-inferior (Z) and left-right (X) co-ordinate within the brainstem, the more ventral electrodes are more likely to produce an increase in bladder capacity (as demonstrated by the increased bladder capacity in subjects 3-7), possibly due to proximity to the PCC. A more dorsally placed electrode may be more likely to produce reduced bladder capacity or incontinence due to proximity to the PMC.

Concluding message
The brainstem is known to be the site of important brain centres for bladder control, including the PMC and the PCC. Great care about the effects on bladder function should be taken when inserting DBS electrodes into this region. Furthermore, it is possible that with further detailed study, targeting the PCC may be a useful means for bringing about improved continence in patients with intractable incontinence syndromes.

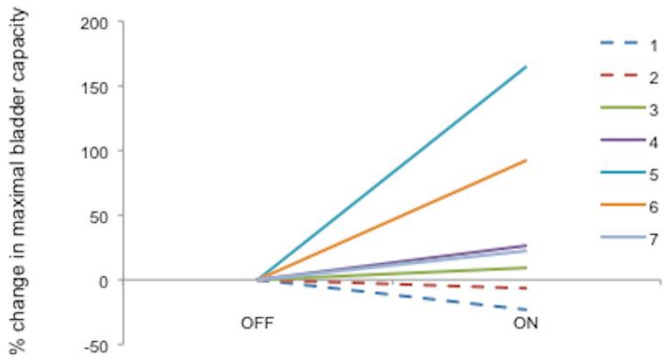

Figure 1: Percentage change in bladder capacity for each subject with PPN DBS OFF/ON

	Side	MNI Co-ordinates		
		X	Y	Z
Pontine micturition centre	L	-8	-44	-28
	R	8	-44	-28
Pontine continence centre	**L**	**-8**	**-29**	**-30**
	R	**8**	**-29**	**-30**
Subject 1 DBS electrodes	L	-	-	-
	R	5	-36	-28
Subject 2 DBS electrodes	L	-7	-23	-11
	R	9	-23	-11
Subject 3 DBS electrodes	L	-10	-28	-23
	R	10	-28	-23
Subject 4 DBS electrodes	L	-7	-31	-30
	R	9	-28	-24
Subject 5 DBS electrodes	L	-7	-29	-23
	R	6	-32	-23
Subject 6 DBS electrodes	L	-10	-28	-19
	R	12	-30	-27
Subject 7 DBS electrodes	L	-5	-29	-18
	R	7	-29	-16

Table 1: MNI co-ordinates for PMC, PCC and PPN electrodes

References

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