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NOVEL INSIGHTS INTO THE NEURAL BASIS OF LOWER URINARY TRACT SYMPTOMS IN PARKINSON'S DISEASE: A STRUCTURAL MRI STUDY

Hypothesis / aims of study

Parkinson's disease (PD) is a neurodegenerative condition that commonly leads to lower urinary tract symptoms. A number of important nuclei involved in the neural control of the bladder exist within the brainstem [1], however, the involvment of brainstem regions in the development of bladder symptoms in PD has not been determined. The primary aim of this study was to test the hypothesis that a relationship exists between the degree of microstructural degeneration within brainstem bladder centres and the severity of bladder symptoms in PD. Given the emerging role of deep brain stimulation (DBS) for Parkinson's disease and the recent reports that DBS at brainstem sites can alter bladder function [2,3], a secondary aim of this project was to assess whether stimulation of degenerating tracts identified in the first part of the study could restore bladder function.

Study design, materials and methods

17 patients with PD undergoing DBS to control their movement disorder symptoms were included in this study. Prior to DBS surgery, all patients had a diffusion-weighted MRI scan and a T1-weighted MRI scan. They also reported the severity of 4 urinary symptoms; urinary frequency, urinary urgency, urge incontinence and nocturia. These scores were combined to create a composite bladder symptom severity score. Tract based spatial statistics (TBSS) was used to create an average white matter map representing all brains of subjects included. Right and left brainstem masks of the white matter tracts were created using the Juelich Histological Atlas and applied to the mean TBSS skeleton mask. Correlations between bladder score and TBSS metrics were determined using permutation-based non-parametric testing applied to voxel-wise general linear model, carried out using the whole brain white matter skeleton and the brainstem mask, with age as a covariate of no interest. Results were considered significant for $p < 0.05$, after correction for multiple comparisons (family wise error, FWE), within each region of interest using the threshold-free cluster enhancement (TFCE) approach. We ran probabilistic tractography for all subjects in MNI space from the significant positively correlated MD values (right and left brainstem, see results section), thresholded each individual tractography output at 10% of the maximum value, binarised the thresholded output, and then averaged these for all subjects to create left and right group masks. 2 patients underwent DBS of the pedunculopontine nucleus and had long term follow-up to determine post-operative changes in lower urinary tract symptoms. Tractography was performed using the electrode contacts as seed regions to investigate the white matter tracts associated with the contacts.

Results

There were 13 male and 4 female subjects and the mean age at the time of MRI scan was 67.34 ± 5.97 years (range 54-75). The mean bladder score was 8.12 ± 3.38 (range 4-16). There was no significant correlation between bladder score and age or bladder score and pre-operative Unified Parkinson's Disease Rating Scale (UPDRS) values. TBSS using the entire white matter skeleton did not show any significant correlation between bladder scores and DTI measures of white matter microstructural integrity. However, using the intersection between the right and left brainstem masks with the skeleton as regions-of-interest, there were areas of significantly increased mean diffusivity (MD) bilaterally, that correlated positively with bladder score (Figure 1). Tractography using the significant MD voxels as seed regions produced group maps for the right and left hemisphere which included tracts passing through the ventrolateral pons, cerebellum and internal capsule (Figure 2). There was also a small area of significant negative correlation between bladder score and MD on the left. (Figure 1).

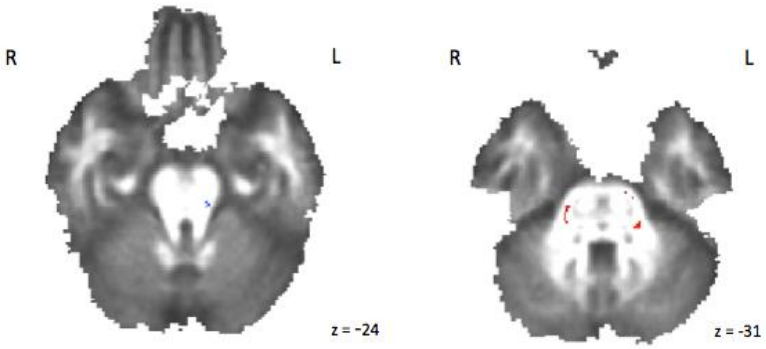

Figure 1: *Left: voxels in which increased MD correlated significantly with better bladder symptoms (blue) Right: voxels in which increased MD correlated significantly with worse bladder symptoms*

Of the 2 pedunculopontine nucleus DBS patients, patient 1 reported improved bladder symptoms 6 months after DBS implantation, with reduced frequency and nocturia (score improved from 12 to 8). Patient 2 reported worse bladder symptoms overall 6 months after surgery, with increased frequency, nocturia and urgency but improved urge incontinence (score worsened from 8 to 10). Tractography seeded from patient 1's electrode contacts showed considerable overlap with the group tractography map produced by seeding from the voxels identified in the first part of the study whose MD values correlated positively with bladder score, whereas tractography run from patient 2's electrode contacts had little overlap in the brainstem with these same tracts (Figure 2).

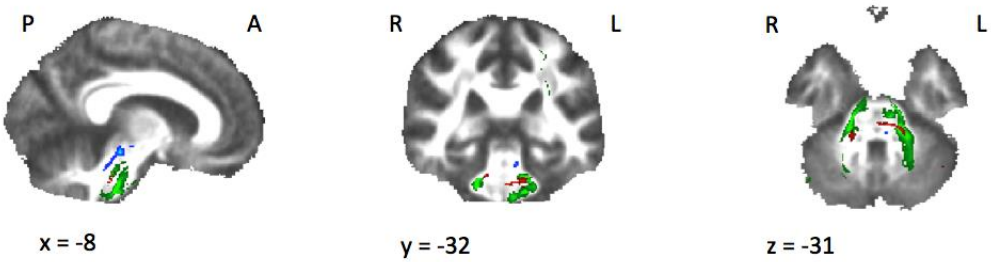

Figure 2: *Green: group tractography map produced by running tractography from significant TBSS MD results (positive correlation) Red: tractography map produced by seeding from DBS contacts of patient 1, Blue: tractography map produced by seeding from DBS contacts of patient 2*

Interpretation of results

There is significant brainstem microstructural degeneration associated with lower urinary tract storage symptoms in patients with Parkinson's disease. The main region of change is close to the vicinity of the pontine L region, an area thought to be important for maintaining continence. Our analysis also revealed an area which is significantly more structurally organised in patients with worse bladder symptoms. This area may be a compensatory region which is used to maintain continence in patients with degeneration within standard bladder control nuclei; its increased use in this situation producing a higher level of organisation.
Tractography from electrode contacts of a patient whose bladder symptoms improved after pedunculopontine nucleus DBS revealed tracts which overlapped with white matter tracts seeded from the region of degeneration identified in the TBSS study. This was not the case for tracts seeded from the electrode contacts of a patients whose symptoms worsened after DBS. This suggests that urinary storage symptoms may be ameliorated by neuromodulation of specific tracts within the brainstem, which are associated with degeneration in PD. However, more subjects need to be tested to confirm this hypothesis.

Concluding message

As far as we are aware, this is the first study that has attempted to demonstrate white matter structural correlates of bladder symptoms in PD. Brainstem structural changes that are associated with worse lower urinary tract symptoms in PD have been identified and may represent targets for neuromodulation.

References

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