Chronic pedunculopontine nucleus stimulation restores functional connectivity

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The mechanisms of deep brain stimulation (DBS) are poorly understood. Earlier, high-frequency DBS has been thought to represent a depolarization block of the target area and low-frequency stimulation has been thought to 'drive' neuronal activity. We investigated the long-term effect of low-frequency DBS in a longitudinal imaging study of a patient who received bilateral pedunculopontine nucleus stimulation. We used the diffusion tensor imaging techniques including probabilistic tractography and topographic mapping to analyze long-term changes in connectivity with low-frequency DBS. Post-DBS connectivity analysis suggested a normalization of pathological pedunculopontine nucleus connectivity with DBS therapy. These findings may help elucidate the mechanisms of DBS, suggesting neuroplasticity involving a reorganization of target connectivity long term. This is the first reported case showing neuroimaging evidence of neuroplasticity after low-frequency DBS. ***NeuroReport*** **21:1065–1068 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The mechanisms of deep brain stimulation (DBS) are poorly understood. Earlier, high-frequency DBS has been thought to represent a depolarization block of the target area similar to a 'reversible lesion' [1]. On the other hand, low-frequency stimulation is thought to 'drive' the neuronal activity. However, it is likely that the effect of DBS is more complex than this. For example, clinical effect may be because of stimulation of the target area driving plastic reorganization. Low-frequency DBS of the pedunculopontine nucleus (PPN) is a new therapy for the treatment of gait dysfunction in Parkinson's disease (PD), in particular gait 'freezing' [2]. We investigated the long-term effect of low-frequency stimulation in a longitudinal imaging study of a patient who received bilateral PPN stimulation. Diffusion tensor imaging (DTI) allows the study of white matter connectivity, by obtaining the fractional anisotropy (FA) of neuronal tissue. We used pre-DBS and post-DBS DTI to investigate the effects of chronic low-frequency PPN stimulation using the probabilistic tractography and topographic mapping.

Case report and methods

We present a 56-year-old male patient with PD. The patient suffered significant on-state freezing of gait (FOG). [Preoperative freezing of gait questionnaire (FOG-Q) score: 14; gait and falls questionnaire score: 38] [3]. The patient proceeded to bilateral stereotactic implantation of Medtronic (Minnesota, USA) 3387 DBS electrodes into the PPN. PPN targeting was performed with the aid of DTI FA mapping of the PPN region [4] where the fibers of the medial lemnisci and the superior cerebellar decussation were identified and targeting planned accordingly. The patient postoperatively improved with gait and falls questionnaire improvement of 42% and FOG-Q score improvement of 14%. Twelve months post-stimulation the patient underwent further neuroimaging acquisition.

Neuroimaging acquisition pre and post-DBS

The patient was enrolled for acquisition of diffusion-weighted data on a Philips Achieva 1.5 Tesla Magnet using the echo planar imaging. DTI images used 32 directions of diffusion weightings ($b_{max} = 1200\,s/mm^2$) and two non-diffusion weighted volumes; echo time 65 ms; repetition time 9390 ms; reconstructed matrix = $128 \times 128 \times 45$; reconstructed voxel size $2.5\,mm \times 2.5\,mm \times 2.5\,mm$. The patient underwent further diffusion weighted data acquisition using the same protocol 12 months post-stimulation.

Data analysis

Diffusion data was processed using FMRIB's (Oxford centre for functional MRI of the brain) diffusion toolbox [5]. After correction of the eddy current distortion, FA images were generated by fitting a tensor model to the diffusion data, and then brain extracted [6]. The Bayesian estimation of diffusion parameters was carried out using the

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Markov Chain Monte Carlo sampling to build up distributions on diffusion parameters at each voxel. Probabilistic tractography was performed using the PPN as seed voxels. Post-operative computed tomography imaging was acquired to confirm electrode localization. The computed tomography data and MRI structural and diffusion data was co-registered using linear and nonlinear registration. Each electrode contact was then mapped into stereotactic space and the clinically effective centroid (centre of mass) of stimulation of each electrode was used as seed from which to conduct probabilistic tractography. We characterized PPN connectivity pre and post-stimulation. We then performed connectivity-based topographic mapping by taking the entire brainstem and computing each brainstem voxel's probabilistic connectivity with 96 predefined cortical target areas. The dominant connectivity pattern of each voxel is then computed to create a topographic map of dominant connectivity patterns of the brainstem including the pedunculopontine region.

Results

Pre-stimulation PPN connectivity

The pre-stimulation PPN connectivity profile was altered from that of non-FOG PD patients and healthy control individuals (Schweder *et al.* [7]). FOG patients, including our current case study, showed absence of connectivity with the cerebellum, and increased connectivity to the anterior pons at the level of the mid-section of the fourth ventricle, not shown in non-FOG PD patients or healthy control individuals. Pre-stimulation PPN cortical connectivity was shown with the motor cortex, especially the lower extremity representation of the cortical homunculus.

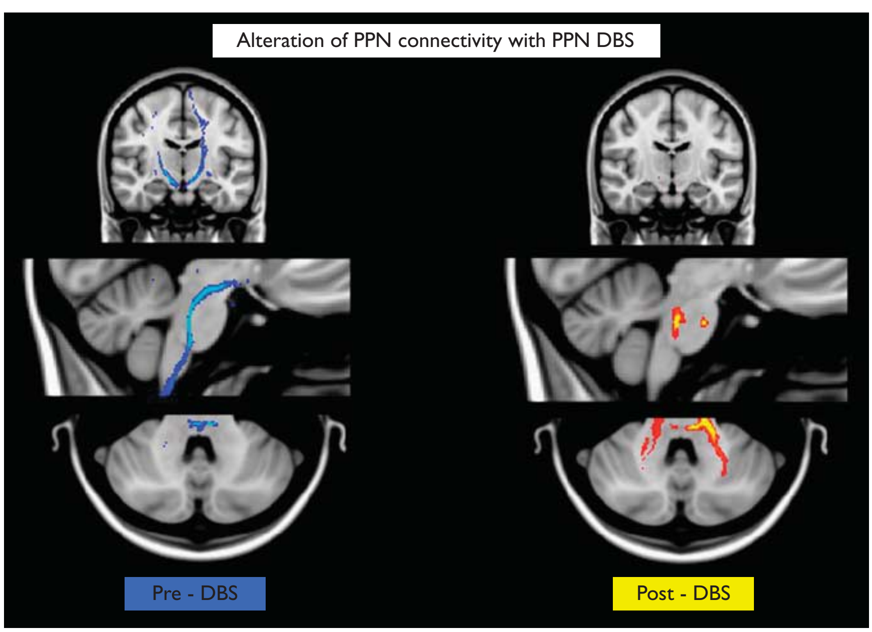
Post-stimulation PPN connectivity

Post-stimulation cortical and brainstem connectivity was significantly reduced. Previously absent cerebellar connectivity was now evident to post-stimulation (Fig. 1). The post-stimulation cerebellar connectivity was qualitatively more similar to that of normal control individuals. (Schweder *et al.* [7]).

Post-stimulation brainstem topography

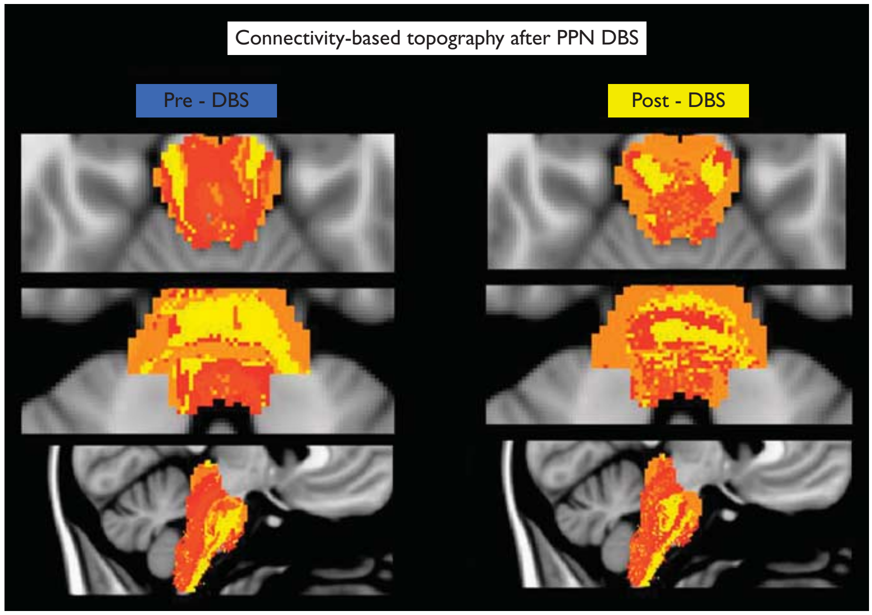
Using probabilistic tractography, we mapped each brainstem voxel's connectivity with 96-predefined cortical areas. The highest probability was then used to create a map of dominant cortical connectivity of the brainstem. Each color represents a separate cortical target area (Fig. 2). Pre-stimulation, at the level of the pons where we have earlier shown an increased connectivity profile of the PPN in FOG patients, we showed a similar area with dominant connectivity to primary motor cortex (yellow).

Fig. 1



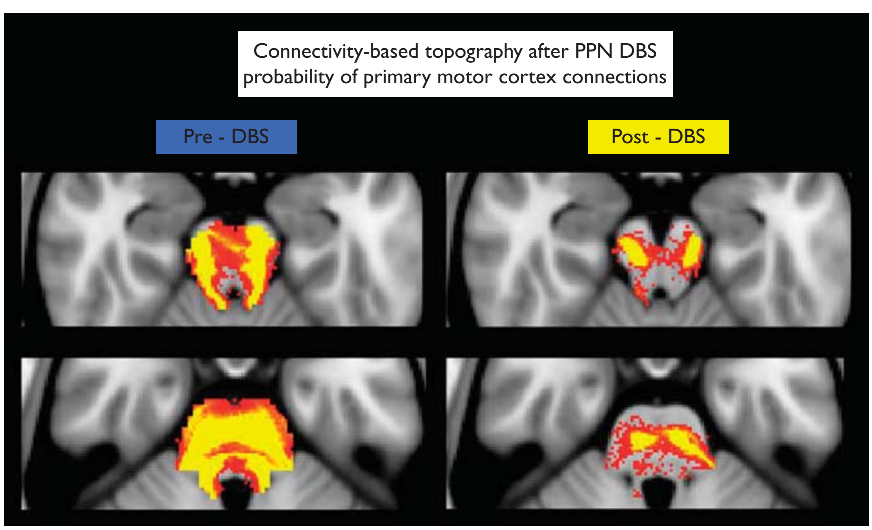
Probabilistic tractography analysis of the pedunculopontine nucleus (PPN). Using the effective centroid of stimulation, left and right seed voxels were placed. Results of probabilistic tractography were registered to the MNI152 brain and thresholded for significance. Left: connectivity profile of the PPN pre-stimulation. Cortical connectivity is shown (top), with the motor cortex, especially the lower extremity representation of the cortical homunculus. Brainstem pathways are shown and notably an absence of connectivity with the cerebellum. Right: connectivity profile of the PPN post-stimulation. Cortical and brainstem connectivity is significantly reduced. Previously absent cerebellar connectivity is now visualized post-stimulation. DBS, deep brain stimulation.

Fig. 2



Connectivity-based topography of the brainstem pre-stimulation and post-stimulation. Left: topographic map of the brainstem pre-stimulation. Top: axial section at the level of the pedunculopontine nucleus (PPN). Each color represents a cortical area with which that voxel shows its dominant connectivity. Middle: axial section at the level of the mid-pons. Yellow representing those voxels with dominant connectivity with primary motor cortex. The 'overactive' anterior pontine dominant connectivity is shown where the corticopontine fibers decussate. Right: topographic map of the brainstem post-stimulation. Middle: the dominant connectivity pattern with primary motor cortex has changed post-stimulation. Voxels in the anterior pontine decussation of corticopontine fibres now show dominant connectivity with other cortical areas including parietal and prefrontal cortex. DBS, deep brain stimulation.

Fig. 3



Probabilistic representation of motor cortex connectivity. Left: pre-stimulation. Large parts of the mesencephalon and pons show connectivity with the motor cortex (red–yellow probability map; yellow highest probability). Right: post-stimulation. Connectivity pattern is reduced in volume and voxels representing normal motor pathways are shown to have primary motor cortex connectivity. DBS, deep brain stimulation; PPN, pedunculopontine nucleus.

This 'overactive' anterior pontine-dominant connectivity is shown where the corticopontine fibres decussate. Post-stimulation, this abnormal connectivity pattern was significantly reduced. Instead, the connectivity had changed such that the dominant connectivity was with other cortical areas including pre-frontal cortical areas.

We further characterized the brainstem-motor cortex connectivity by visualizing the probability map of connectivity of each voxel with the motor cortex (Fig. 3). This showed that the probability map of connectivity is markedly reduced in area and volume post-stimulation.

Discussion

Probabilistic tractography analysis showed a connectivity loss of the PPN with the cerebellum in gait freezing. The patient exhibited increased PPN connectivity with the decussation of corticopontine fibers in the anterior pons. Post-stimulation connectivity analysis showed a restoration of PPN connectivity with the cerebellum. Corticopontine fibre tracts that were pronounced pre-stimulation were less prominent post-stimulation. In addition the brainstem topographic mapping revealed a re-organization of connectivity-based topography post-stimulation. Our results suggest that loss of pre-stimulation cerebellar connectivity is partially restored post-stimulation and corticopontine 'over-activity' pre-stimulation is reduced post-DBS. It is unclear exactly how low-frequency and high-frequency DBS affect target structures and how stimulation frequency affects the mechanism of action of DBS. It has been earlier shown that high-frequency subthalamic nucleus DBS generates an excitatory effect on axons around the electrode [8–10] and it has been hypothesized that high frequency stimulation overrides abnormal neural activity [11]. Neuroplasticity has been raised as a possible mechanism of the clinical effect of DBS in dystonia [12]. Our patient showed neuroimaging evidence of neuroplastic reorganization with low-frequency DBS. Evidence of the role of the cerebellum after PPN DBS has been described, where changes in cerebral blood flow to subcortical areas, including the cerebellum, were evident with stimulation [13].

Conclusion

This is the first reported case of imaging evidence of neuroplasticity after low-frequency DBS. Tractographic analyses of the PPN highlight the role of the corticopontine-cerebellar pathways in the pathophysiology of gait freezing. Reduced cerebellar connectivity pre-stimulation was partially restored after stimulation. Over-activity of corticopontine fibres pre-stimulation was reduced after chronic DBS. Post-DBS connectivity analysis suggested a normalization of pathological PPN connectivity with DBS therapy. These findings may help elucidate the mechanisms of DBS, suggesting neuroplasticity involving a reorganization of target connectivity long-term.

Acknowledgement

There are no conflicts of interest.

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